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MINIREVIEWS

Frailty, sarcopenia and cachexia in heart failure patients: Different clinical entities of the same painting

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Abstract

Heart Failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome. Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. However, these co-factors often remain unaddressed, resulting in poor quality-of-life, prolonged physical disability and exercise intolerance and finally with higher rehospitalization rates and mortality. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, angiotensin-converting enzyme inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

Key Words: Heart failure; Sarcopenia; Cachexia; Frailty; Terapheutic implication; Comorbidities

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Core Tip: The last heart failure (HF) guidelines of the European Society of Cardiology dedicate a chapter each for cachexia, sarcopenia and frailty and several studies

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regarding these topics are coming up. This wealth of information highlights the importance of these co-factors in HF management and are each uniquely relevant to evaluate older patients with HF. It is time to routinely assess cachexia, sarcopenia and frailty that could help in personalized care plan, improve outcomes and reduce hospitalization and institutionalization. However, definitions, pathophysiology and treatment of all these conditions still remain unclear and we briefly summarize the most recent knowledge available in literature.

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INTRODUCTION

Heart failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome[1]. HF syndrome shows a significant impact on the health-care resources and its occurrence is ever increasing in the elderly[2]. Recently there are discussion regarding frailty and the common problems affecting skeletal muscle, both sarcopenia and cachexia. These comorbidities are crucial issue to plan health care resources for older patient with HF. After hospitalization for acute HF, these co-factors often remain unaddressed resulting in prolonged physical disability, poor quality-of-life, exercise intolerance and finally with higher rehospitalization rates and mortality. Besides, HF hospitalization independently and significantly increased the risk of limitations of Basic and Instrumental Activities of Daily Living (IADL)[3]. The complex relationship between frailty, muscle wasting and cachexia can coexist and different strategies and interventions need to be deeply investigated to improve outcome, quality of life and HF-related re-admissions. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

FRAILTY IN HF

Frailty recognize a biologic basis and it is characterized by a loss of strength and physical ability with a progressive decline of cognitive function. Incorrect definition includes this syndrome as a comorbidity or a disability, but comorbidity is a risk factor and disability is an outcome of frailty state[4]. Frailty patients show a strong susceptibility to several endogenous and exogenous stressors. This vulnerability state contributes to risk of falls, hospitalization and death. Frailty is a common finding in HF patients and the prevalence is higher in older age and correlates significantly with HF severity, however frailty must not be considered only in older individuals and all patients with HF deserve a frailty assessment[5]. FRAIL-HF study reveal the presence of frailty state in 70% of patients with HF and ≥ 80 years old. On the other hand frail patients show an higher risk to develop HF[6]. Several frailty score and pre-fail status assessment are now available; Clinical Frailty Scale, gait speed test, PRISMA/7 questionnaire, Fried Score, FRAIL Score and Short Physical Performance Battery (SPPB) are routinely used in clinical practice with good agreement between methods[7-9]. Recently the HF Association/European Society of Cardiology establish a new frailty score that is the first elaborated in HF setting. This new score consider a 4-domain framework such as clinical, functional, cognitive-psychological and social variables, extremely useful and practical to diagnose frailty in HF patients[10] (Table 1). Nowadays an overall geriatric assessment that consider not only the frailty state but also depression, cognitive impairment and muscle wasting are each uniquely relevant to evaluate older patients with HF and significantly impact prognosis and treatment success (*i.e.*, transcatheter or surgical Aortic Valve Replacement)[11,12]. The SPPB is a set of objective measures of physical performance, highly predictive of disability, hospitalization, institutionalization, and mortality in community-dwelling older

Table 1 Current definitions of frailty, cachexia and sarcopenia

Institution/authors, journal, year	Frailty	Institution/authors, journal, year	Cachexia	Institution/authors, journal, year	Sarcopenia
British Geriatrics Society, Age UK and Royal College of General Practitioners Report[7]. *Age Aging* 2014	(1) A gait speed < 0.8 m/s; (2) Timed-up-and-go test > 10 s; (3) Score of ≥ 3 on the PRISMA 7 questionnaire. Falls, delirium and sudden immobility can used to indicate the presence of frailty	Argilés *et al*[19]. Consensus on cachexia definitions. *J Am Med Dir Assoc* 2010	Weight loss > 5% of body weight (or BMI < 20 kg/m^2) in ≤ 1 year in presence of chronic illness and three of five of these criteria. (1) Decreased muscle strength; (2) Fatigue; (3) Anorexia; (4) Low fat free mass index; (5) Anaemia (< 120 g/L), low serum albumin (< 32 g/L) and CRP > 5 mg/L, IL-6 > 4 pg/mL	Revised European consensus on definition and diagnosis[36]. *Age Aging* 2019	(1) Low muscle strength; (2) Evidence of low muscle quantity or quality; (3) Detection of low physical performance. The combination of three represent severe sarcopenia
Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure[10]. *Eur J Heart Fail* 2019	The frailty score in HF patients were built with the following variables: (1) Clinical: Comorbidities, weight loss, falls; (2) Psycho-cognitive: Cognitive impairment, dementia, depression; (3) Functional: ADL/IADL, mobility, balance; (4) Social: Living alone, no social support, institutionalisation	International Consensus on Cancer Cachexia Classification[65]. *Lancet* 2003	The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI < 20 kg/m^2) or skeletal muscle mass reduction	Society of Sarcopenia, Cachexia and Wasting Disorders[37]. *J Am Med Dir Assoc* 2011	Muscle loss with (1) walking speed equal or less than 1 m/s; (2) walks less than 400 m during a 6-minute walk. Appendicular lean mass/height2 > 2 SD below the mean mass of a healthy person (aged 20–30 yr)
Fried *et al*[4]. *J Gerontol A Biol Sci Med Sci* 2001	Frailty was defined with three or more of the following criteria: (1) Unintentional weight loss (4, 5 kgs in past year); (2) Self-reported exhaustion; (3) Weakness (reduced grip strength); (4) Slow walking speed; (5) Low physical activity. A pre-frail status is accordingly whit one or two criteria	SCRINIO working group[66]. *JPEN J Parenter Enteral Nutr* 2009	The patients were divided in 4 groups based on combinations of body weight loss < 10% in precachexia and ≥ 10% in cachexia; associated to the presence/absence of at least 1 symptom of anorexia, fatigue or early satiation	International working group on sarcopenia[39]. *J Am Med Dir Assoc* 2011	Gait speed of less than 1 ms (-1) and low muscle mass (appendicular mass relative to ht (2) that is ≤ 7.23 kg/m^2 in men and ≤ 5.67 kg/m^2 in women)
Canadian Study of Health and Aging[9]. *CMAJ* 2005	Clinical frailty scale is based on IADL, activity, mobility, energy, and symptoms all associated with clinical judgement			Special Interest Groups "Cachexia-Anorexia in Chronic wasting diseases" and "Nutrition in Geriatrics"[21]. *Clin Nutr* 2008	Reduced muscle mass, strength and function (low handgrip strength (men < 26 kg, women < 16 kg), gait speed ≤ 0.8 m/s, low appendicular lean mass/BMI)

BMI: Body mass index; IL-6: Interleukin-6; hg: Height; kgs: Kilograms; CRP: C-reactive protein; IADL: Instrumental activities of daily living.

individuals[13,14]. The prognostic potential of the instrument has been proven in patients hospitalized for HF, pneumonia, chronic obstructive pulmonary disease (COPD) and minor stroke[15]. Furthermore, in a cohort of hospitalized elderly HF patients, a low physical performance status, as evaluated with SPPB, predicted mortality even after adjustment for left ventricle ejection fraction (LVEF), New York Heart Association (NYHA) Class and comorbidities[16]. Moreover, handgrip strength, serum albumin and IADL status are all associated with health outcome in elderly patients hospitalized for HF. Moreover, the pre-frailty state, a condition that is potentially reversible, identified by slow gait speed, exhaustion and low energy expenditure, is in the same way an independent predictor of new cardiovascular events in older adults[17]. For all these reasons closer follow up by HF team is highly necessary in frail patients. This approach could monitor HF symptoms, adjust medications and address reversible causes leading to worsening of frailty score and consequent HF decompensation.

CARDIAC CACHEXIA IN HF

Cachexia is a serious but underrecognized consequence of many chronic diseases such as cancers, COPD, malnutrition state, neurological disease, rheumatoid arthritis and kidney disease. It is considered a wasting process at multiorgan levels (skeletal muscle, fat and bone tissue)[18]. Cachexia is defined by a weight loss > 5% of body weight [or body mass index (BMI) < 20 kg/m^2] in ≤ 1 year in presence of chronic illness and three of five of these criteria (1) decreased muscle strength; (2) fatigue; (3) anorexia; (4) low fat free mass index; and (5) abnormal biochemistry [anaemia (< 120 g/L), low serum albumin (< 32 g/L), increased inflammatory markers (C-reactive protein > 5 mg/L), interleukin-6 (IL-6) > 4 pg/mL][19] (Table 1). The overall prevalence in Western World is still growing and affects around 1% of patients population[20,21]. Cachexia is more frequently common in end-stage HF, its prevalence ranges from 5%-15%[22], but surprisingly it is not clear a close relationship with LVEF, in particular the prevalence of the disease is the same in various HF phenotype[23]. In a prospective study that enrolled outpatients with LVEF ≤ 40%, 18% are cachectic and cardiac cachexia is associated with intestinal congestion irrespective of HF stage and cardiac function. Inflammation state, gastrointestinal discomfort, appetite loss provide probable mechanisms, by which intestinal congestion may trigger cardiac cachexia[24]. Instead right ventricular dysfunction and weight loss may have a pathophysiological linked (venous congestion, malabsorption, anorexia, gut bacteria translocation)[25]; improvement of right ventricular function may delay the occurrence of cachexia. Moreover, tricuspid regurgitation and pulmonary hypertension are associated with low BMI and they are accentuating risk factor for cachexia, together with hypoalbuminemia and hyponatremia due to protein-losing enteropathy[26,27].

Cachectic patients show an impaired functional capacity, more severe symptoms and low quality of life[28]. This serious complication is associated with frequent hospitalization increased length of in hospital stay and health care cost[29]. Weight loss displays an additional prognostic information beyond clinical features of HF severity with significant association with morbidity and mortality[30]. Wasting disorders is and independent risk factor for impaired survival in chronic HF patients (adjusting for age, sex, NYHA class, LVEF, and VO2 consumption); mortality at 18 months of followup is around 50% in patients with cachexia[31]. In hospitalized HF patients with cardiac cachexia factors such renal function, age, and haemoglobin are pivotal prognostic markers[32].

As opposite, obesity is an independent risk factor associated with HF, but recently it is well demonstrated that obesity in patients that have already developed HF (across a wide range of BMI) is related to lower mortality; highlighting the concept of "obesity paradox" also common in other chronic disease[33]. However, BMI does not reflect the body composition regarding the percentage of fat mass, fat-free mass and lean mass. Inside this different large spectrum of body composition, patients with preserved skeletal muscle mass show a better prognosis compared with patients with reduced lean mass due to increased stroke volume and consequent better tissue perfusion[34]. Thus, fat mass loss but not lean mass has a prognostic impact and it is a good indicator of enhanced catabolism and has a role of cardioprotection in advanced HF.

SARCOPENIA IN HF

Recently the 12th Cachexia Conference held in Berlin in December 2019 highlights preclinical and clinical studies in the field of wasting disorders[35]. The definition of sarcopenia remains a matter of discussion, however for the first time it is recognized that strength is better than mass to evaluate adverse outcomes and actually the European consensus on definition and diagnosis Sarcopenia define the disease with three criterion: (1) Low muscle strength, that is considered the most accurate parameter to evaluate sarcopenia; (2) Evidence of low muscle quantity or quality; and (3) The detection of low physical performance (Table 1). The presence of all three criteria permit to define ad advance sarcopenia status. Several tests and different tools are widely described to assess sarcopenia in practice and in research with specific description of each method used[36-39]. Sarcopenia is age related and old muscle mass is reduced by 1%-2% annually after 50 years old with a contemporary decline in muscle strength by about 1.5%[40]. Its prevalence increases around 3% annually after the 60 years old[41]. For the first time the European Society of Cardiology in the guidelines of 2016 dedicate a chapter to cachexia and sarcopenia recognizing as important comorbidities of HF[42]. The prevalence of sarcopenia is around 20% in HF with

reduced ejection fraction (HFrEF) and HF with preserved ejection fraction patients without clear difference in prevalence across different HF phenotype. A monotonic association existed between increasing sarcopenia prevalence and other comorbidities, in particular sarcopenia correlates with the decline of glomerular filtration rate[43,44]. Six-minutes-walk test and spiroergometry show lower Vitamin E/VCO2 (VO2) and shorter exercise time in sarcopenic HF patients, highlighting the impact of muscle wasting in lower muscle strength and lower physical performance in HF population. Bekfani *et al*[45] find better quality of life in patients with higher values of muscle strength/muscle mass ratio (evaluated by Visual Analogue Scale derived from the EQ-5D)[45]. Emami *et al*[46] demonstrate a percentage of overlap (6.7% in HF population studied) of both sarcopenia and cachexia. The lowest values of muscle strength and function, as assessed by handgrip and quadriceps strength, 6 min walking test, SPPB score and peak VO2, are observed only in sarcopenic groups[46]. Moreover, sarcopenia significantly impact the functional capacity of HF patients; and it is associated with increased likelihood of adverse events including falls, fractures, worst neurocognitive profile and low physical performance that may precipitate a relative clinical HF stable condition. In older patients low physical activity is strictly related with the occurrence of sarcopenia and it is an independent factor in prolonging hospital stay among patients admitted to hospital care[47]. However, muscle wasting might be present also in younger patients with HF and non-ischemic dilated cardiomyopathy, particularly in those with advance clinical status[48]. In literature, some discordant opinions are evident regarding the recovery of skeletal muscle after heart transplantation (HT) or left ventricle assistant device implantation[49]. Skeletal muscle impairment seems to persist after months from HT and contribute to the impaired exercise capacity[50], however a recent study demonstrates the recovery of muscle mass and strength after 1.5-3 years of follow up after HT. Moreover, HT and ventricular assist device therapy lead to an improvement in frailty score during follow up highlighting that sarcopenia and frailty are both dynamic and not a fixed entity[51].

BASIC PATHOPHYSIOLOGICAL OVERVIEW

Cardiac cachexia, sarcopenia and frailty in HF patients recognize similar pathophysiological features (Figure 1). Systemic inflammation and hypermetabolism play a pivotal role; cachectic patients display an increased cortisol/dehydroepiandrosterone ratio and higher cytokine levels such as tumor necrosis factor (TNF)-alpha, soluble TNF-receptor 1 and IL-6. Higher levels of hormones and cytokines activities are both associated with muscle wasting, reduced fat tissue and bone mass. Few hormones are implicated in the pathophysiology in cachexia and sarcopenia. Growth hormone, insulin resistance and insulin-like growth factor-1 levels are all associated with muscle mass loss and consequently with a significant reduction of physical performance[52]. Triiodothyronine in cachectic oncologic patients is increased compared to non-cachectic cancer patients and it is also normal in patients with benign weight loss. Ghrelin significantly inhibits the production of cytokines with inflammatory pathway and exhibits anti-cachectic activity both with growth hormone dependent and independent mechanisms. Low testosterone levels are usually common in all HF patients and contribute to the progression of cardiac cachexia, sarcopenia and frailty through altered peripheral vascular resistance, increased cardiac afterload, and decreased cardiac output. Nutritional alterations and gastrointestinal malabsorption lead to an abnormal calorie uptake, protein balance and insulin resistance[53]. Advanced HF status is linked to gastroenteropathy secondary to intestinal edema that result in protein losing enteropathy which causes malabsorption and anorexia[54]. Catabolic/anabolic imbalance change the substrate utilization in tissues. Moreover, cachexia in HF is associated with an increase in adiponectin concentration strictly related to type B natriuretic peptide levels[55]. All these reasons exacerbate the wasting process and muscle cells apoptosis, and therefore result in muscle atrophy and lower muscular strength favoring the occurrence of frailty[56].

TERAPHEUTIC IMPLICATION

Physical inactivity due to the progression of HF syndrome are common in frailty patients. Sarcopenic, cachectic and frailty patients show impaired exercise capacity and limitations in common activity such as food preparation and eating, contributing to disability and muscle loss. Skeletal muscle improvement after exercise training

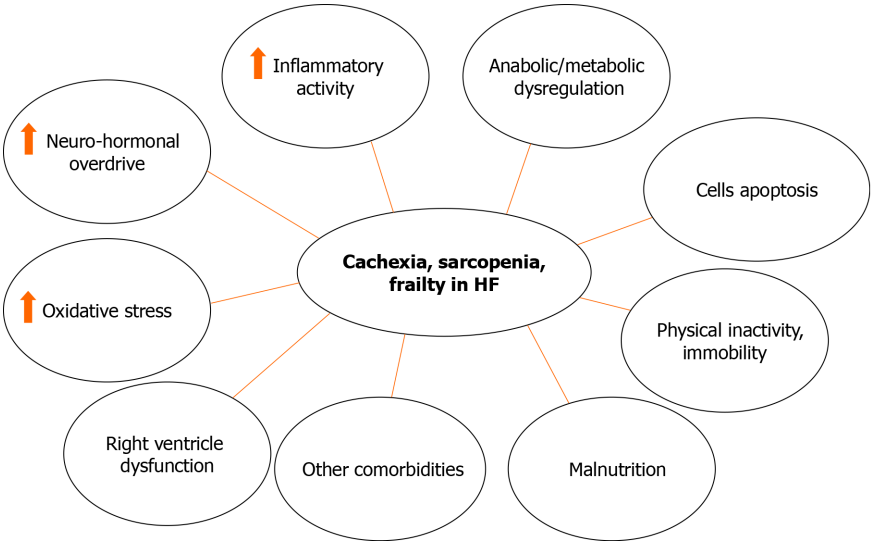


Figure 1 Pathophysiological mechanism and contributing factors leading to cachexia, sarcopenia and frailty in heart failure. HF: Heart failure.

explain the reduction of maximal oxygen consumption demonstrating how physical activity is the major treatment of these patients[57]. Physical exercise program and nutritional supplementation are more effective in individuals with low functional level and increased number of frailty criteria[58]. Growing evidence show a potential benefit from oral supplementation in terms of protein and energy intake in HF patients with the aim to avoid the loss of lean mass[59,60], this personalized dietary intervention results in a potential benefit with significant impact in reducing mortality and hospital readmission. In sarcopenic patients potential treatments may include appetite stimulants and anabolic agents, including testosterone, in combination with the application of nutritional supplements and anti-catabolic interventions, although none is of proven benefit and their safety is unknown[61]. However, scientific data are scarce and the quality of the evidence is low, and no strong recommendations can be currently made in HF setting[62].

In patients with HFrEF and sinus rhythm, b-blockers significantly improve the outcome due its effect on weight gain counterpoising the sympathetic activation that it is an important determinant of cardiac cachexia[63]. Moreover treatment with an angiotensin-converting enzyme (ACE) inhibitor (enalapril) reduces the risk of weight loss in patients with HFrEF[64-66].

CONCLUSION

Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. All these conditions are serious complications in HF patients and are associated with increasing hospitalization and mortality rates[1]. It is time to produce an important effort to include a routinely assessment in clinical practice of cachexia, sarcopenia and frailty for HF patients that could help in earlier therapeutic decision, personalized care plan, improve outcomes and reduce hospitalization and institutionalization. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, ACE inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting.

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes in patients with native valve infective endocarditis and diabetes mellitus

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Abstract

BACKGROUND

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

AIM

To investigate (1) trends in the prevalence of DM among patients with NVIE; and (2) the impact of DM on NVIE outcomes.

METHODS

We identified 76385 with NVIE from the 2004 to 2014 National Inpatient Sample, of which 22284 (28%) had DM. We assessed trends in DM from 2004 to 2014 using the Cochrane Armitage test. We compared baseline comorbidities, microorganisms, and in-patients procedures between those with *vs* without DM. Propensity match analysis and multivariate logistic regression were used to investigate study outcomes in in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block.

RESULTS

database in the United States. Informed patient consent is not required.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Data sharing statement: Data that support the findings of this study are publicly available at https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp.

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Crude rates of DM increased from in 22% in 2004 to 30% in 2014. There were significant differences in demographics, comorbidities and NVIE risk factors between the two groups. Staphylococcus aureus was the most common organism identified with higher rates in patients with DM (33.1% *vs* 35.6%; $P < 0.0001$). After propensity matching, in-hospital mortality (11.1% *vs* 11.9%; $P < 0.0001$), stroke (2.3% *vs* 3.0%; $P < 0.0001$), acute heart failure (4.6% *vs* 6.5%; $P = 0.001$), cardiogenic shock (1.5% *vs* 1.9%; $P < 0.0001$), septic shock (7.2% *vs* 9.6%; $P < 0.0001$), and atrioventricular block (1.5% *vs* 2.4%; $P < 0.0001$), were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

CONCLUSION

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes. Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

Key Words: Infective endocarditis; Native valve infective endocarditis; Diabetes mellitus; Valvular heart disease; Cardiovascular disease; National Inpatient Sample

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Core Tip: In this observational study, we found increasing prevalence rates for diabetes mellitus (DM) among patients with native valve infective endocarditis (NVIE) from 2004–2014. There were significant differences in risk factors, microbiology, and in-patient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

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INTRODUCTION

Despite advancements in management strategies, infective endocarditis (IE) is associated with high mortality rates ranging from 10%-26% and an estimated five-year survival rate of 60%-70%[1-4]. Also, IE carries a significant long term morbidity risk with high rates of stroke (24%), and heart failure (49%)[1-4]. One of the challenges associated with IE management is identifying patients at increased risk of complications. While current guidelines recommend active surveillance, early stratification can help identify patients who may benefit from further intervention.

We have seen an increase in hospitalization from native valve infective endocarditis (NVIE) in the United States [from 155151 (2002-2006) to 195300 (2012-2016)][5]. This is likely related to increased risk factors such as drug abuse, advanced age, and diabetes mellitus (DM)[5-9]. There is a paucity of data on the outcomes of NVIE in DM patients. Previous studies looking at DM and IE have been limited by single-center experiences, sample size and analyses that combine NVIE and prosthetic valve infective endocarditis (PVIE)[9-16]. In this study, using a well-characterized database, we investigated trends in the prevalence of DM among patients with NVIE; and the impact of DM on in-hospital mortality, acute heart failure, stroke, septic shock, cardiogenic shock, and atrioventricular block.

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MATERIALS AND METHODS

Study design

Our data source was the National In-patient Sample (NIS) 2004–2014, a subset of the Healthcare Cost Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ)[17,18]. Briefly, NIS and HCUP are the largest all-payer inpatient database in the United States. The database contains a 20% stratified sample of all discharges from United States hospitals representing the United States population and accounts for 90% of all hospitalizations[18]. It includes information on demographics, hospital characteristics, up to 25 diagnostic and procedure codes based on the International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM), and outcomes based on patient discharge records.

Study population, variables and outcomes

We queried NIS 2004–2014 using ICD-9-CM codes to identify patients age 18 and above, who were hospitalized with the primary diagnosis of acute or subacute IE. To limit the sample to NVIE, we excluded patients with a prior history of valve replacement and cardiac devices (Figure 1). The algorithm has been validated[5]. The cohort was then divided into those with and without DM. Demographics associated with each diagnosis were identified from NIS, and associated comorbidities were extracted from AHRQ[17,18]. This allows the identification of comorbidities that were present before admission. Other variables that could impact study outcomes, such as the type of organism and inpatient procedures, were included in the analysis. The primary endpoint was to investigate the impact of DM on in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock and atrioventricular block in those with NVIE. All clinical characteristics were defined using ICD-9-CM codes (Supplementary Table 1).

Statistical analysis

IBM SPSS V.25 was used for statistical analysis. Statistical significance was defined as $P < 0.05$. We compared baseline characteristics, organisms involved, and inpatient procedures between patients with DM compared to those without DM. Chi-square was used for categorical variables, while an independent student *t*-test was used for continuous variables. We performed trend analysis using the Cochrane-Armitage test to evaluate the temporal trends in the prevalence of DM in patients with NVIE.

We compared the incidence of in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block. Descriptive statistics were reported in frequencies with percentages for categorical variables, while continuous variables were reported in mean, standard deviation, median, and 25th and 75th percentiles. To limit selection bias, we employed propensity score methodology to match hospitalizations with NVIE patients who had DM *vs* those without any DM at a 1:1 ratio. The nearest neighbor technique was adopted to match each case to control, which is closest to the calculated propensity score, with a caliper width of 0.1. The propensity score was calculated from the following 26 matching variables: Age, sex, race, atrial fibrillation, tobacco use disorder, valvular heart disease, hypothyroidism, chronic kidney disease, obesity, hypertension, congestive heart failure, chronic lung disease, hyperlipidemia, hemodialysis, chronic liver disease, peripheral artery disease, coronary artery disease, drug abuse, pulmonary hypertension, human immunodeficiency virus, congenital heart disease, history of cardiac transplant, rheumatic heart disease, staphylococcus aureus, other staphylococcus, viridians, streptococci, enterococci, group A streptococci, group B streptococci, group G streptococci, and gram-negative bacteremia. Multivariate logistic regression was then used to estimate the adjusted odds ratio of the study outcome in those with DM compared to those without DM.

Binomial regression was used to identify variables in the demographics, comorbidities, and microbiology that were associated with mortality. All significant variables were then incorporated into a multivariate logistic regression model to determine the predictors of in-hospital mortality.

RESULTS

We identified 76385 patients with NVIE. Among these patients, 21284 (28%) had DM. The mean age of patients with DM was significantly higher (63.4 ± 14 *vs* 58.2 ± 19; $P < 0.0001$). The most predominant race was White American, and they were less likely to

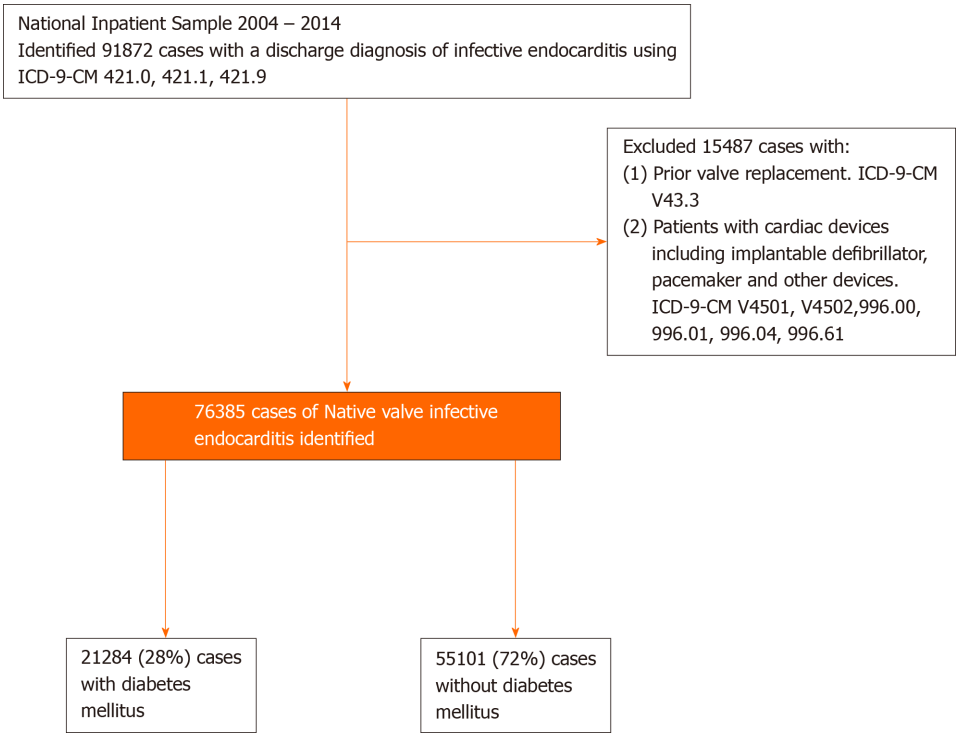


Figure 1 Flow chart of our study design. ICD-9-CM: International Classification of Diseases 9th revision, Clinical Modification.

have DM compared to African, Hispanics, Asians, and Native Americans (Table 1). Patients with DM had higher rates of comorbidities, including hypertension, congestive heart failure, dyslipidemia, obesity, coronary artery disease, and pulmonary hypertension compared to those without DM (Table 1). The crude rates of DM in patients with NVIE significantly increased from 22% in 2004 to 30% in 2014; $P < 0.0001$ (Figure 2).

In terms of the infective organism involved, patients with DM had higher rates of staphylococcus aureus (35.6% *vs* 33.1%; $P < 0.0001$), other staphylococcus organisms (6.7% *vs* 5.4%; $P < 0.0001$), enterococci (7.6% *vs* 6.5%; $P < 0.0001$), group B streptococci (1.6% *vs* 1.3%; $P < 0.0001$), and gram-negative organisms (4.8 *vs* 3.8; $P < 0.0001$) (Table 2). For inpatient procedures, DM patients were less likely to undergo surgical valve replacement (8.2% *vs* 10.6%; $P < 0.0001$) (Table 3).

After propensity matching rates of stroke (2.4% *vs* 1.5%; $P < 0.0001$), acute heart failure (6.5% *vs* 4.6%; $P = 0.001$), atrioventricular block (6.5% *vs* 4.6%; $P < 0.0001$), septic shock (9.6% *vs* 7.2%; $P < 0.0001$), cardiogenic shock (1.9% *vs* 1.5%; $P < 0.0001$), and in-hospital mortality (11.9% *vs* 11.1%; $P < 0.0001$), were significantly higher in patients with DM and NVIE, compared to those with NVIE alone. The multivariate logistic regression followed similar trends (Table 4). Predictors of in-hospital mortality in patients with NVIE and DM included hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age (Table 5).

DISCUSSION

In this observational study, we found increasing prevalence rates for DM among patients with NVIE from 2004–2014. There were significant differences in risk factors, microbiology, and in-patient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age. Compared to other studies that have investigated the clinical outcomes of DM in IE patients[9-16]. We had a robust sample size. Also, the analyses in these studies combined NVIE and PVIE. It is essential to stratify because the clinical course, management, and outcomes significantly differ[19-21]. Lastly, we identified the independent predictors of mortality.

The overall prevalence of DM was 28%, and the crude rates of DM significantly

Table 1 Baseline characteristics of primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

Demographics and Co-morbidities	NVIE		
	No DM (%)	DM (%)	*P* value
Age (yr), mean (SD)	58.2 ± 19	63.37 ± 14	< 0.0001
Gender			< 0.0001
Male	58.4	55.6	
Female	41.6	44.4	
Race			< 0.0001
White	71.9	62.5	
Black	15.9	20.0	
Hispanic	7.1	11.2	
Asian	1.8	2.4	
Native Americans	0.6	1.0	
Other	2.7	2.9	
Co-morbidities			
Tobacco abuse	14.8	9.0	< 0.0001
Hypothyroidism	6.2	9.6	< 0.0001
Hyperlipidemia	11.5	25.1	< 0.0001
Valvular heart diseases	21.6	19.0	< 0.0001
Chronic kidney disease	3.8	7.9	< 0.0001
Obesity	1.8	7.2	< 0.0001
Congestive heart failure	26.2	34.2	< 0.0001
Chronic liver disease	9.3	12.4	< 0.0001
Hypertension	39.1	64.8	< 0.0001
HIV	2.6	0.9	< 0.0001
Atrial fibrillation	18.9	22.4	< 0.0001
Pulmonary hypertension	5.8	6.5	< 0.0001
Coronary artery disease	14.2	29.7	< 0.0001
Peripheral artery disease	2.4	5.5	< 0.0001
Hemodialysis	15.0	27.8	< 0.0001
History of cardiac arrest	0.0	0.1	0.011
History of drug abuse	11.9	3.8	< 0.0001
Congenital heart disease	1.8	0.8	< 0.0001
Rheumatic heart disease	11.8	9.6	< 0.0001

DM: Diabetes mellitus; HIV: Human immunodeficiency virus; SD: Standard deviation; NVIE: Native valve infective endocarditis.

increased from 2004–2014. It should be mentioned that there has been a parallel increase in the prevalence of DM in the United States, which had been attributed to increased risk factors such as obesity, sedentary lifestyle, enhanced detection, and increased longevity[22,23]. A study demonstrated an increased prevalence from 7.7% in 1999-2000 to 13.3% in 2015-2016 among United States adults[24]. In another study using the national health and nutrition examination survey, the prevalence increased from 9.8% in 1988–1994 to 12.4% in 2011–2012, across all age, sex, and racial groups[25].

The clinical profile of NVIE patients with DM was different compared to those without DM. DM patients had higher rates of comorbidities, and IE risk factors such as

Table 2 Infective organisms identified in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

Infective organisms	NVIE		
	No DM (%)	DM (%)	*P* value
Staphylococcus aureus	33.1	35.6	< 0.001
Other staphylococcus	5.4	6.7	< 0.001
Viridans streptococci	18.6	15.5	< 0.001
Enterococci	6.5	7.6	< 0.001
Pneumococcus	0.5	0.4	0.11
Group A streptococci	0.7	0.5	0.003
Group B streptococci	1.3	1.6	< 0.001
Group C streptococci	0.1	0.1	0.44
Group G streptococci	0.2	0.2	0.87
Gram negative	3.8	4.8	< 0.001
Anaerobes	0.4	0.3	0.82
Fungemia	0.2	0.2	0.81

DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

Table 3 Inpatient procedures in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

NVIE			
Inpatient procedures	No DM (%)	DM (%)	*P* value
Surgical valve replacement	12.3	9.2	< 0.001
Aortic valve replacement	6.5	5.1	< 0.001
Mitral valve replacement	5.0	3.7	< 0.001
Tricuspid valve replacement	0.1	0.1	0.43
Pulmonary valve replacement	0.7	0.3	< 0.001

Surgical valve replacement, included aortic valve replacement, mitral valve replacement, tricuspid valve replacement and pulmonary valve replacement.
DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

older age, and hemodialysis. They were less likely to have structural heart disease (valvular heart disease and congenital heart disease) and intravenous drug abuse (Table 1). Several other studies have reported similar findings[8,10,12-14]. We also found significant differences in the organisms involved. DM patients had higher rates of staphylococcus species, enterococci, and gram-negative microorganisms. This is also consistent with prior studies and likely due to increased health care utilization in DM patients, exposing them to nosocomial infections and immune dysfunctions, rendering them more susceptible to skin and soft tissue infections[16,26].

There are a couple of explanations for the poor outcomes among NVIE patients with DM. First, they are more likely to have staphylococcus aureus infections. Staphylococcus aureus tends to stick and multiply on heart valves, promoting vegetation, abscess formation, mechanical complications, and mortality[27-29]. Secondly, IE is characterized by an immunologic response that leads to immune complex formation; the exaggerated immunologic response in DM patients likely contributed to poor outcomes noted in this study[30]. Finally, lower rates of life-saving procedures such a surgical valve replacement, as demonstrated in this study, and higher rates of comorbidities in DM patients are other explanations.

Current IE management strategies center around presumed patient mortality risk. Generally, low-risk patients can be safely managed with antibiotics. At the same time,

Table 4 Association between diabetes mellitus and outcomes of hospitalizations for native valve infective endocarditis after propensity matching

NVIE						
	No DM (%)	DM (%)	aOR	Lower CI	Upper CI	*P* value
In-hospital mortality	11.1	11.9	1.2	1.1	1.4	< 0.0001
Acute heart failure	4.6	6.5	1.2	1.1	1.3	0.001
Stroke	2.3	3.0	1.3	1.1	1.5	< 0.0001
Atrioventricular block	1.5	2.4	1.5	1.3	1.5	< 0.0001
Septic shock	7.2	9.6	1.2	1.1	1.3	< 0.0001
Cardiogenic shock	1.5	1.9	1.4	1.2	1.6	< 0.0001

aOR: Adjusted odds ratio; CI: Confidence interval; DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

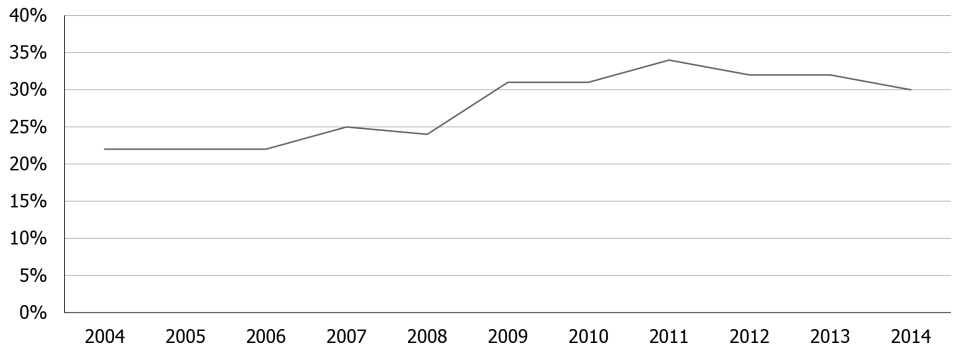
Table 5 Logistic regression analysis for predictors of in hospital mortality among patients with native valve infective endocarditis and diabetes mellitus

	95%CI			
	OR	Lower	Upper	*P* value
Age (yr)				
18-65	REF	REF	REF	REF
> 65	1.02	1.02	1.02	< 0.001
Hypertension	0.56	0.50	0.62	< 0.0001
Atrial fibrillation	1.17	1.05	1.31	0.006
Tobacco abuse	0.74	0.61	0.90	0.003
Hyperlipidemia	0.69	0.61	0.78	< 0.0001
Congestive heart failure	1.34	1.22	1.48	< 0.0001
Chronic liver disease	1.51	1.19	1.92	0.001
Staphylococcus aureus	1.25	1.13	1.39	< 0.0001
Hemodialysis	2.04	1.83	2.27	< 0.0001

CI: Confidence interval; OR: Odds ratio; REF: Reference.

aggressive intervention such as valve replacement is recommended for those at high risk of mortality, suffering from, acute heart failure, large vegetation, and mechanical complications such as valvular dysfunction, and perivalvular abscess[31-34]. These recommendations stem from observational studies demonstrating mortality benefit[31-34]. In this study, odds for in-hospital mortality was 20% higher in DM patients compared to those without DM. Staphylococcus aureus was highly prevalent among patients with DM, and it was significantly associated with mortality. Several other studies have linked staphylococcus aureus to death, likely due to severe valvular damage and complications[4,27,28,34]. Early surgery should be considered in NVIE secondary to staphylococcus aureus, especially in DM patients, due to severe valve destruction and increased mortality.

Other predictors of mortality among DM patients in this study include congestive heart failure, hemodialysis, and atrial fibrillation. This suggests that prevention and aggressive management of comorbid conditions in DM patients could potentially decrease associated NVIE mortality. NVIE is characterized by bacteremia, bacteria colonization, adhesion on cardiac valves and vegetation formation[35]. Immune dysfunction, micro- and macro-angiopathies, and decreased bactericidal activity of the gastrointestinal and genitourinary system make DM patients more susceptible to infections[36]. Tight glycemic control, vaccination, and adequate skin care will help reduce bacteremia and NVIE in DM patients.



Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Diabetes mellitus	22%	22%	22%	25%	24%	31%	31%	34%	32%	32%	30%

Figure 2 Trends in the prevalence of diabetes mellitus among patients with infective endocarditis. $P < 0.0001$.

Some limitations of our study should also be noted. First, data on glycemic control and management of DM were not available. It is well known that strict glycemic control can improve the clinical outcome in patients with DM[4]. Secondly, the study lacked information on clinical variables such as echocardiographic features, vegetation size, and antimicrobials therapy, all of which might impact clinical outcomes[4].

CONCLUSION

Among patients with NVIE, DM is associated with increased mortality and complications. This is likely due to higher rates of staphylococcus bacteremia, underlying comorbidities, and immune dysfunction. Further studies should focus on prevention and management strategies among DM patients with NVIE.

ARTICLE HIGHLIGHTS

Research background

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

Research motivation

Previous studies looking at DM and infective endocarditis (IE) have included analyses that combine NVIE and prosthetic valve IE.

Research objectives

In this study, aim to investigate the temporal trends in the prevalence of DM in NVIE and investigate the impact of DM on NVIE outcomes.

Research methods

The National Inpatient Sample 2004–2014 was queried. Cochrane Armitage test was used for trend analysis. Propensity match scoring and multivariate logistic regression were used to investigate study outcomes (Supplementary Table 2).

Research results

We identified 76385 patients with NVIE, of which 21284 (28%) had DM. Patients with DM had more comorbidities, were more likely to have staphylococcus infection, and less likely to undergo surgical valve replacement. In-hospital mortality, and IE related complications such as stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block, were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

Research conclusions

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes.

Research perspectives

Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

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CASE REPORT

Myasthenic crisis-induced Takotsubo cardiomyopathy in an elderly man: A case report of an underestimated but deadly combination

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Abstract

BACKGROUND

Patients with myasthenia gravis (MG) are at a higher risk of developing Takotsubo cardiomyopathy (TTC), particularly during a myasthenic crisis. Myasthenic crisis-associated TTC occurs predominantly in women. In this case report, we present a man with metastasized prostate carcinoma who developed TTC after new-onset MG.

CASE SUMMARY

An 81-year-old man with non-insulin dependent diabetes mellitus and metastasized prostate carcinoma presented with dyspnea. During primary assessment examination at the emergency department, there was evident blepharoptosis of his right eye. His electrocardiograms were suggestive of an acute anterior wall myocardial infarction, for which he underwent emergency coronary angiography. No obstructive coronary artery disease was found. During the coronary angiography, the patient developed respiratory failure and was admitted to the Intensive Care Unit for non-invasive respiratory support. The following day, diagnostic neostigmine test revealed a myasthenic crisis. Bedside echocardiography revealed left ventricular apical ballooning with a typical appearance of TTC. Despite the potentially reversible character of both MG and TTC, the patient and family requested an end of support in the Intensive Care Unit due to age and chronic malignancy with reduced quality of life in recent months after non-chemo-responding prostate carcinoma. The patient died soon after treatment withdrawal.

CONCLUSION

Elderly men should be carefully evaluated for TTC when new-onset MG is

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Core Tip: An elderly man presented with dyspnea and neurological symptoms, including blepharoptosis. Simultaneously, the patient had signs of an acute myocardial infarction, but obstructive coronary artery disease was ruled out by coronary angiogram. Due to respiratory failure, the patient was admitted to the Intensive Care Unit for non-invasive support. The next day, bedside echocardiography revealed left ventricular apical ballooning, typical for Takotsubo cardiomyopathy. Meanwhile, second consultation by the neurologist performing a diagnostic neostigmine test confirmed a myasthenic crisis. Altogether, the patient was diagnosed with a new-onset myasthenic crisis-induced Takotsubo cardiomyopathy. Unfortunately, in this elderly man, this combination was fatal.

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INTRODUCTION

Takotsubo cardiomyopathy (TTC) is a transient cardiac syndrome that typically causes mid-ventricular circumferential and apical hypokinesis mimicking an acute coronary syndrome. In TTC, acute coronary or microvascular spasms can result in stunning of the myocardium with left ventricular dysfunction caused by catecholamine release due to emotion or physical stress[1]. Until 2009, only two cases of patients who had developed TTC after plasmapheresis for a myasthenic crisis were reported[2]. A myasthenic crisis if often the first manifestation of myasthenia gravis (MG). MG is a neuromuscular disease in which autoantibodies are formed against the acetylcholine receptors in the neuromuscular junction, causing severe muscular weakness[2]. The pathophysiology of MG-associated TTC is not exactly clear. A myasthenic crisis can induce severe stress, resulting in excessive catecholamine release. Guaricci *et al*[3] describe a neurogenic/catecholaminergic hypothesis: Supraphysiological levels of epinephrine can paradoxically lead to negative inotropic effects by reducing myofilament contractility, therefore leading to myocardial stunning[3]. Women are 9-times more likely to develop TTC then men. Post-menopausal women are especially prone to TTC[1,4].

Diabetes mellitus is a common comorbidity. When TTC develops during myasthenic crisis, the risk of respiratory failure, intubation and mechanical ventilation (81%) and death (25%) are significant[4,5]. In patients with TTC, respiratory failure is caused by a manifestation of pulmonary edema due to acute heart failure. In MG, however, respiratory distress and failure can be explained by severe skeletal muscle weakness which can lead to hypercapnic failure[6]. However, non-invasive ventilation can successfully stabilize approximately one-third of patients suffering from each of these types of respiratory failure[7,8]. This weakens the awareness that both syndromes can arise during a serious physical and/or emotional stress event. Suspicion of MG with development of pulmonary lung edema should prompt evaluation for TTC. Awareness of the possibility that both MG and TTC may cause respiratory failure, and that an association exists between these conditions, may lead to early recognition, adequate diagnostic work-up and timely treatment.

In this case report, we sought to describe an elderly man with dyspnea who was diagnosed with new-onset MG and TTC.

CASE PRESENTATION

Chief complaints

An 81-year-old man with a medical history of non-insulin dependent diabetes and metastasized prostate carcinoma was referred to our emergency department (ED) by his general practitioner, with complaint of dyspnea and generalized muscle weakness.

History of present illness

The patient had developed walking difficulties, balance impairment and ptosis of his right eye over the past few days, and developed progressive dyspnea in the last few hours before presentation to clinic. The ptosis of the right eye, as well as generalized muscle weakness, were apparent on primary examination in the ED.

History of past illness

The patient was known to have ongoing non-insulin dependent diabetes and metastasized prostate carcinoma.

Physical examination

At the ED, the patient's temperature was 36.5 °C, heart rate was 95 beats per min, respiratory rate 26 was breaths per min, blood pressure was 190/110 mmHg, and oxygen saturation with 3 L O_2 was 96%. The initial neurological examination showed a blepharoptosis, general muscular weakness, and disbalance. As such, our differential diagnosis included peripheral neuromuscular disease related to diabetes mellitus, with considerations for further diagnosis to rule out metastatic disease or paraneoplastic neurological disease. In relation to the patient's complaint of progressive dyspnea, his electrocardiogram (ECG) showed signs of acute coronary syndrome.

Laboratory examinations

Serial ECGs revealed signs of acute anterior wall myocardial infarct, although the patient had no typical symptoms of an acute coronary syndrome (Figure 1). This finding was accompanied by raised serum high-sensitivity troponin levels (maximum 0.814 μg/L; normal range: 0-0.014 μg/L).

Imaging examinations

A conventional X-ray and computed tomography angiography of the chest showed no pulmonary embolism or parenchymal abnormalities, except for atelectasis of both lower lung fields. An emergency coronary angiography showed no obstructive coronary lesions (Figure 2).

Further diagnostic work-up

The patient's respiratory condition quickly deteriorated and he was admitted to the intensive care unit (ICU) with hypercapnic failure, where he was successfully stabilized with non-invasive ventilation (bilevel pressure support). The following day, the typical combination of ptosis and generalized weakness progressing to respiratory failure prompted re-consultation with the neurologist.

MULTIDISCIPLINARY EXPERT CONSULTATION

Ruud Keunen, MD, PhD, Department of Neurology, Haga Teaching Hospital, The Hague, The Netherlands

"The patient should start with mestinon and immunoglobulins treatment if the neostigmine test is positive. Further consideration of steroids has been advised."

Sakir Akin, MD, PhD, Cardiologist-Intensivist, Department of Intensive Care, Haga Teaching Hospital, The Hague, The Netherlands

"The patient should continue inotropic support during continuing acute heart failure. Beside this, there should be ongoing respiratory bilevel non-invasive support to prevent further respiratory complications, accompanied by hypokinetic diaphragm, of myasthenic crisis on top of pulmonary edema by cardiac dysfunction."

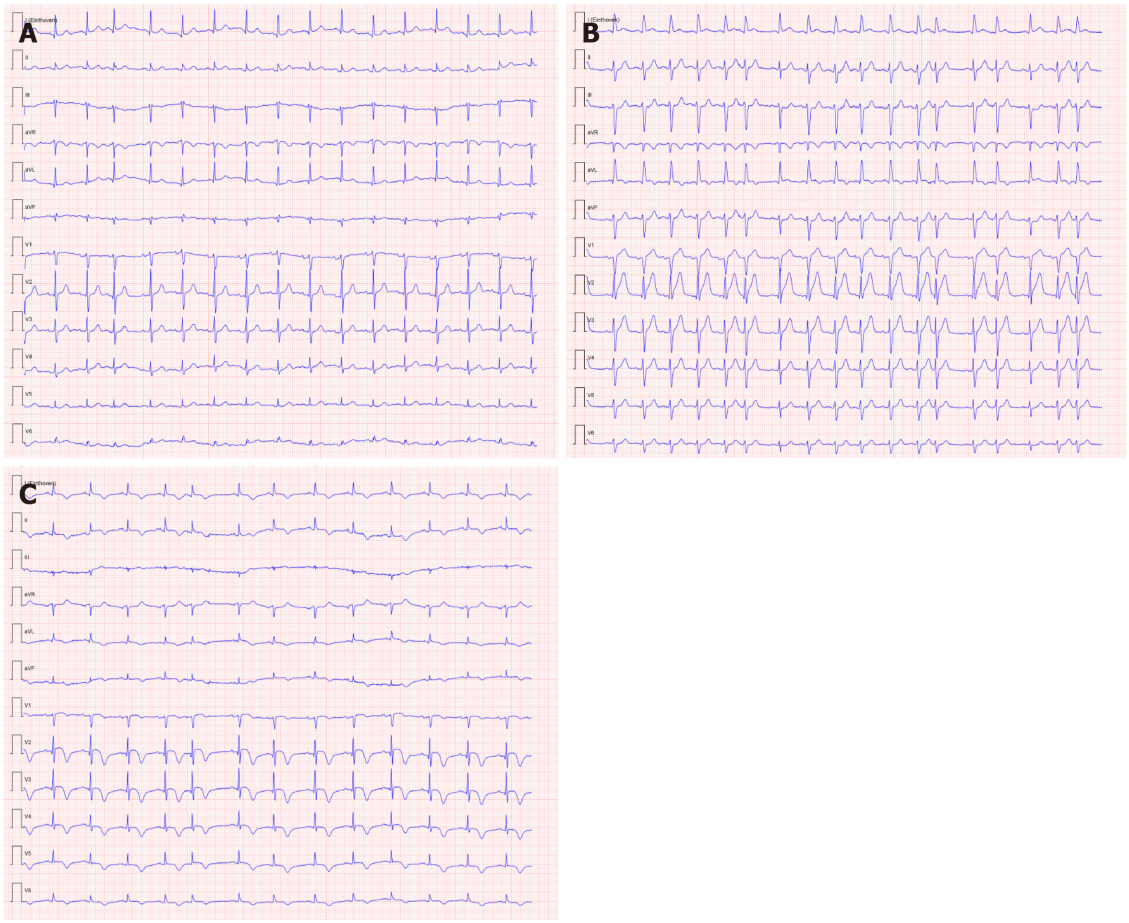


Figure 1 Comparison of electrocardiograms during the myasthenic crisis. A: The electrocardiogram (ECG) was taken upon presentation in the emergency department and showed normal sinus rhythm, with no signs of pathology; B: The second ECG was taken at 4 h after presentation and showed ST-elevation in anterior leads (V1-V4) and lateral leads (I and aVL), with minimal reciprocal depressions in inferior leads (II and aVF) and new T-wave inversion in aVL; C: The third ECG was taken 1 d after presentation to the emergency department and showed evolving ST-elevations in anterior leads, with biphasic T-waves and new inverted T-waves in I, II, aVL and aVF.

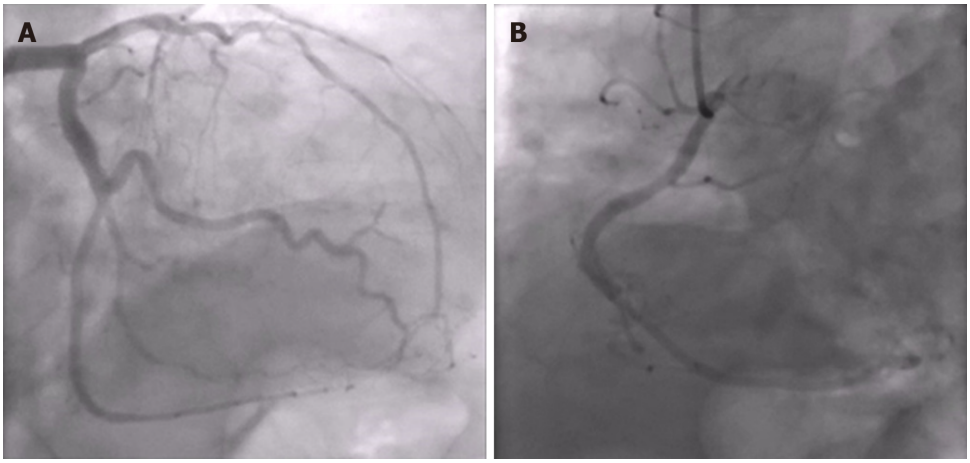


Figure 2 Coronary angiography showed no significant coronary obstruction. A: Left anterior descending artery; B: Right coronary artery.

FINAL DIAGNOSIS

A diagnostic neostigmine test confirmed the diagnosis of myasthenic crisis with new-onset MG. The acetylcholine receptor (known as AChR) antibody was also positive. During his treatment in the ICU, the patient showed signs of progressive hemodynamic instability, requiring inotropic support with dobutamine. Although follow-up ECGs showed a persistent and evolving anterior wall myocardial infarction,

the patient never developed chest pain (Figure 1). Troponin levels also decreased spontaneously. A repeat transthoracic echocardiogram showed apical ballooning of the left ventricle (resembling a Japanese octopus trap) with hypokinesia of the anterior wall, whilst the right ventricle was hyperdynamic but normal in size (Figures 3 and 4). Compared with the quick-look echo carried out in the ED, there was the same morphologic abnormality of the left ventricle. This was suggestive of stress-induced cardiomyopathy, also known as TTC. Theoretically, the myasthenic crisis may have provoked this rare cardiac complication due to excessive catecholamine release. Both MG and TTC are potentially reversible conditions. However, in this specific case of a patient of advanced age and frail physical condition due to chemotherapy-resistant metastasized prostate carcinoma, the clinical condition deteriorated quickly before the effect of intravenous immunoglobulin could occur.

TREATMENT

The patient was supported for neuromuscular failure by non-invasive ventilation and by dobutamin to address the acute heart failure. Despite these treatments, there was ongoing deterioration of his end-organ functions.

OUTCOME AND FOLLOW-UP

On day 3 of ICU treatment, the patient no longer tolerated non-invasive ventilation and became agitated. The patient and his family requested withdrawal of supportive ICU treatment considering the patient's medical history and significantly reduced quality of life in the past few months. After careful evaluation of the patient's wishes, medical history and rapid clinical deterioration, supportive ICU treatments were withdrawn. The patient was given treatment to relieve symptoms and died quickly after withdrawal of supportive therapies.

DISCUSSION

MG is a rare disease in men and even more rarely leads to TTC[4,9]. Symptoms of respiratory failure, blepharoptosis, dysphagia and overall muscle weakness are present in more than half of the patients[5]. In MG patients, women have a higher risk of developing TTC than men, but men have a poorer prognosis. MG-associated TTC may present differently in men and women[1].

In recent years, large cohort studies have attempted to explain the association between MG and TTC. Myasthenic crisis may result in physiologic stress-induced cardiomyopathy, although direct cardiac involvement of MG cannot be ruled out. The golden standard to rule out acute coronary disease is to perform a coronary angiography (CAG). However, this is a relatively invasive and prolonged procedure in which complications can occur, as in our case where the patient became respiratory insufficient during the CAG. An alternative could have been a computed tomography angiography, which is faster and safer as no arterial access is needed, and gives reliable assessment of the coronaries[10]. Although CAG is the golden standard to distinguish acute coronary syndrome from TTC, non-invasive imaging modalities are becoming useful for TTC assessment. Even in emergent situations, echocardiography can provide a good evaluation of TTC. However, poor echo windows could still influence the visibility of ventricular walls. More accurate non-invasive cardiac imaging modalities known from the field of complex congenital anomalies could help to delineate the ventricular walls and refine the diagnosis[11].

MG-associated TTC triggered by a myasthenic crisis is rare. No more than 20 cases are described in depth in the published literature. In a Dutch national representative dataset, we found 175 cases with MC-associated TTC[4,5]. However, the case we present here is unique because of the patient's age, male sex and comorbid malignancy. Triggers of myasthenic crisis and development of TTC seem to be heterogeneous. This rare condition should be suspected even in patients without a prior diagnosis of MG, as is demonstrated in the case we present here.

The number of cases describing the combination of these two diseases are increasing. Although, in many of them, development of TTC is a result of the treatment of MG[12,13]. In our case, there was no relation with the treatment of MG since

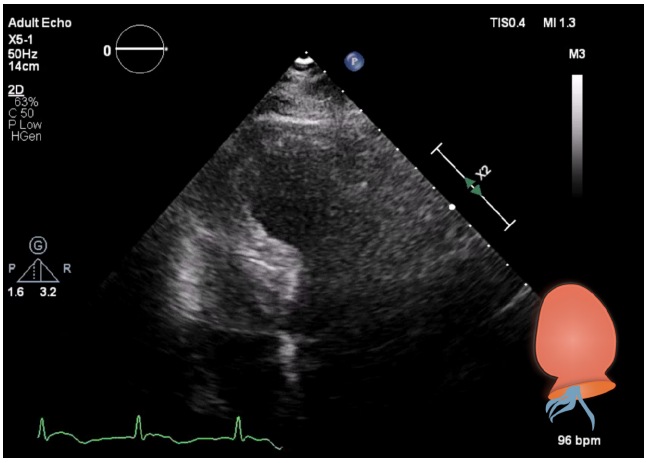


Figure 3 Transthoracic echocardiography in four-chamber view. Apical to mid-ventricular segment ballooning was present at end-systole. Please note the endomyocardial board in end systolic contraction forming apical ballooning of the left ventricle, like a Japanese octopus trap (Takotsubo; see inset illustration), and normal right ventricle size.



Figure 4 Japanese octopus traps, also known as Takotsubo. The shape of Takotsubo resembles apical ballooning.

the patient presented with ventricular dysfunction in the ED where the diagnosis of MG was not yet known. We do not consider it likely that the myasthenic crisis in our patient was related to medication use. The patient had been treated with gosereline injections every 3 mo for an extended period uneventfully.

Based on the literature, our collective experiences and experience with the case that we present as an illustration, we propose that patients with neurological symptoms together with ST-elevation myocardial infarction on the ECG without obstructive coronary lesions should be evaluated with left ventricle angiogram during coronary angiography to exclude TTC. Early initiation of a diagnostic neostigmine test can lead to more awareness of possible new-onset MG in cases of unusual presentation of circulatory instability.

CONCLUSION

We conclude there is a high need for continuous reporting of similar atypical cases to help improve the understanding of this rare entity. Further studies are needed to evaluate possible direct associations between MG and stress-induced TTC.

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CASE REPORT

Anthracycline-induced cardiotoxicity: A case report and review of literature

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Abstract

BACKGROUND

Doxorubicin and other anthracycline derivatives inhibit topoisomerase II and is an important class of cytotoxic chemotherapy in cancer treatment. The use of anthracycline is limited by dose-dependent cardiotoxicity, which may manifest initially as asymptomatic cardiac dysfunction with subsequent progression to congestive heart failure. Despite baseline assessment and periodic monitoring of cardiac function for patients receiving anthracycline agents, there are unmet needs in prediction and prevention of anthracycline-induced cardiotoxicity (AIC).

CASE SUMMARY

A 35-year-old African American female was found to have a 9-cm high-grade osteosarcoma of right femur and normal baseline cardiac function with left ventricular ejection fraction of approximately 60%-70% determined by transthoracic and dobutamine stress echocardiogram. She underwent perioperative doxorubicin and cisplatin chemotherapy with 3 cycles before surgery and 3 cycles after surgery, and received a total of 450 mg/m^2 doxorubicin at the end of her treatment course. She was evaluated regularly during chemotherapy without any cardiac or respiratory symptoms. Approximately two months after her last chemotherapy, the patient presented to the emergency

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department with dyspnea for one week and was intubated for acute hypoxic respiratory failure. Echocardiogram showed an ejection fraction of 5%-10% with severe biventricular failure. Despite attempts to optimize cardiac function, the patient's hemodynamic status continued to decline, and resuscitation was not successful on the seventh day of hospitalization. The autopsy showed no evidence of osteosarcoma, and the likely cause of death was cardiac failure with the evidence of pulmonary congestion, liver congestion, and multiple body cavity effusions.

CONCLUSION
We present a case of 35-year-old African American female developing cardiogenic shock shortly after receiving a cumulative dose of 450 mg/m^2 doxorubicin over 9 mo. Cardiac monitoring and management of patients receiving anthracycline chemotherapy have been an area of intense research since introduction of these agents in clinical practice. We have reviewed literature and recent advances in the prediction and prevention of AIC. Although risk factors currently identified can help stratify patients who need closer monitoring, there are limitations to our current understanding and further research is needed in this field.

Key Words: Anthracycline; Cardiotoxicity; Doxorubicin; Troponin; Brain natriuretic peptide; Case report

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Core Tip: Anthracyclines may exert a direct toxic effect on cardiac myocytes, precipitating symptomatic heart failure. The case presented demonstrates an example of acute heart failure in a well-compensated young adult who did not at first glance warrant greater than routine cardiac surveillance during doxorubicin treatment course. Utilization of cardioprotective agents and cardiac strain markers such as troponin and brain natriuretic peptide may help to prevent and identify cardiac dysfunction in asymptomatic patients. Prevention of anthracycline-induced cardiotoxicity and cardiovascular toxicities of other anti-cancer therapy requires multidisciplinary approaches such as modification of cardiovascular risk factors, active management of comorbidities, and pharmacologic therapy in selected patients.

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INTRODUCTION

Anthracycline is a class of commonly used agents for the treatment of solid and hematologic cancers. Cardiotoxicity is a well-documented side effect of anthracycline, likely due to free radical damage and DNA strand breakage in cardiomyocytes[1]. Anthracycline-induced cardiotoxicity (AIC) accounts for greater than 30% of cardiotoxicity from cancer-related therapy[2]. When symptoms and signs of cardiotoxicity such as congestive heart failure are identified early, discontinuation of anthracycline, initiating appropriate medical management followed by frequent monitoring of cardiac function can help to alleviate further decline of cardiac function. When a patient is asymptomatic, it is difficult to predict adverse outcomes or plan appropriate frequency of cardiac monitoring.

Here we present a case of an unusual course of AIC in a 35-year-old African American female who received a cumulative dose of 450 mg/m^2 doxorubicin over 9 mo. We also discuss measures and methods that have been reported for early identification and prevention of deterioration of cardiac function.

CASE PRESENTATION

Chief complaints

A 35-year-old African American female without significant past medical history presented to the orthopedic clinic for evaluation of a right knee mass measuring about 5 cm × 9 cm × 6 cm at distal thigh that had been growing in size over the past six months.

History of present illness

A magnetic resonance imaging (MRI) of the knee showed a 5.6 cm × 9.1 cm × 6.0 cm tumor of the distal right femur, and biopsy revealed high-grade osteoblastic osteosarcoma. Further imaging studies including (18)F-fluorodeoxyglucose positron emission tomography/computed tomography (CT) did not indicate distant metastatic disease, and she was referred to medical oncology clinic for pre-operative chemotherapy. At the time of her pre-treatment evaluation, the patient had no chronic medical issues and was not taking any medications. There was no cancer or cardiovascular disease in her family. She had normal complete blood count and comprehensive metabolic panel results. CT scan of chest showed no evidence of pulmonary metastasis, and baseline transthoracic and dobutamine stress echocardiogram showed normal cardiac function with normal right ventricular systolic function and left ventricular ejection fraction (LVEF) 60%-70%.

The patient underwent three cycles of cisplatin and doxorubicin before undergoing resection of the tumor and a total right knee replacement. She had a follow-up echocardiogram after 2 cycles of chemotherapy which again showed normal cardiac function with LVEF 70%. Additionally, she had serial blood tests done for troponin and brain natriuretic peptide (BNP) during hospitalization for neutropenic infection with respiratory symptoms after cycle 2 chemotherapy, and dehydration with hypokalemia after cycle 3 chemotherapy; all the troponin levels were within normal limit except transient increase in BNP with subsequent normalization was noted after cycle 3 chemotherapy. Surgical pathology showed 5% tumor necrosis, and restaging CT and bone scan after surgery showed no evidence of metastatic disease. The patient subsequently completed three more cycles of cisplatin and doxorubicin with good tolerance. While on chemotherapy treatment, she experienced fatigue, nausea, alopecia, and neutropenic infection despite using granulocyte colony stimulating factor, prophylactic antibiotics, and other supportive care measures. She was evaluated every 3-4 wk with history and physical examination, as well as routine laboratory tests.

Approximately two months after her last chemotherapy, she was seen in the medical oncology clinic with an unremarkable history and physical examination. One week later, she presented to the emergency department with complaints of sudden onset of dyspnea, palpitations, and left-sided chest pain. CT angiography of chest showed no pulmonary embolism, but found new right lower lobe indeterminate nodules, measuring up to 7 mm, a small focus of airspace disease in the peripheral right lower lobe, and mild interstitial pulmonary edema. Echocardiogram showed LVEF 5%-10% with severe decrease in right ventricular systolic function. Her serial serum troponin levels were significantly and persistently elevated.

History of past illness

No significant past medical history.

Personal and family history

No cancer or cardiovascular disease in her family.

Physical examination

A 5 cm × 9 cm × 6 cm tumor was noted at the distal right thigh.

Laboratory examinations

Normal complete blood count and comprehensive metabolic panel results.

Imaging examinations

An MRI of the knee showed a 5.6 cm × 9.1 cm × 6.0 cm tumor of the distal right femur, and biopsy revealed high-grade osteoblastic osteosarcoma. Further imaging studies including (18)F-fluorodeoxyglucose positron emission tomography/CT did not indicate distant metastatic disease, and she was referred to medical oncology clinic for

pre-operative chemotherapy. At the time of her pre-treatment evaluation, the patient had no chronic medical issues and was not taking any medications. CT scan of chest showed no evidence of pulmonary metastasis, and baseline transthoracic and dobutamine stress echocardiogram showed normal cardiac function with normal right ventricular systolic function and LVEF 60%-70%.

FINAL DIAGNOSIS

A subsequent autopsy showed no evidence of cancer, and microscopic evaluation of the myocardium was significant for prominent interstitial edema, minimally thinned myocytes, and very focal, minimal interstitial fibrosis (Figure 1).

TREATMENT

She was intubated for acute hypoxic respiratory failure due to cardiogenic shock and started on inotropic and vasopressor support. She subsequently developed cardiorenal syndrome. Due to history of malignancy, she was not a candidate for cardiac transplant. An Impella ventricular assist device was placed emergently through the right femoral artery to increase cardiac output on the seventh day of hospitalization.

OUTCOME AND FOLLOW-UP

After placement of ventricular assist device, she became hemodynamically unstable and unresponsive to fluid resuscitation. A hematoma was noted at right femoral access site with drop in hemoglobin from 8.0 g/dL to 6.3 g/dL. Emergent transfusions were ordered, but the patient decompensated and was found to be pulseless. Advanced cardiac life support was initiated, and bedside echocardiogram showed a pericardial effusion with concern for a cardiac tamponade, so an emergent pericardiocentesis was performed at bedside. Unfortunately, restoration of spontaneous circulation was unable to be obtained and the patient expired.

DISCUSSION

While the rapid onset of the patient's symptoms presented a broad differential diagnosis for her acute heart failure, the lack of evidence for obvious infection, intracardiac malignancy, prior history of coronary artery disease, or cardiac risk factors prompted suspicion for a diagnosis of anthracycline induced cardiotoxicity. This patient had an initial ejection fraction of 70%, which was reduced to 10% in nine months. The echocardiogram did not show apical ballooning, which would be typical for stress or Takutsubo cardiomyopathy. Therefore, patient's cause of death is likely from AIC which may manifest either as early side effect with transient cardiac arrhythmia occurring immediately after first dose, or late side effect with cardiomyopathy occurring 2-3 mo or years after therapy. Most AIC develops within one year after completion of treatment[3]. Early AIC does not lead to subsequent development of cardiomyopathy, and therefore is not considered as an indication to stop anthracycline treatment once cardiac arrhythmia is controlled. The estimated risk of impaired cardiac function is about 1% to 2% at a cumulative dose of 300 mg/m^2 of doxorubicin, and this risk increases significantly to more than 5% when the cumulative dose of doxorubicin exceeds 450 mg/m^2[4].

Retrospective studies and meta-analyses have identified risk factors associated with AIC including: Cumulative dose, administration schedule, duration of infusion, age (> 65 years or < 18 years), female gender, African-American race, history of chest irradiation, use of other cardiac toxic agents such as trastuzumab, existing cardiovascular disease such as coronary artery disease, hypertension and metabolic syndrome[5-7]. Increased risks for AIC have also been associated with genetic polymorphisms in ATP-binding cassette transporter, TOP2 regulator gene *RARG*, uridine diphosphate glucuronosyltransferase 1A6 glucuronidation gene *UGT1A6*, carbonyl reductase genes that reduce anthracyclines to cardiotoxic alcohol metabolites, the myofilament splice variant gene *CELF4*, the hyaluronic acid gene *HAS3*, and

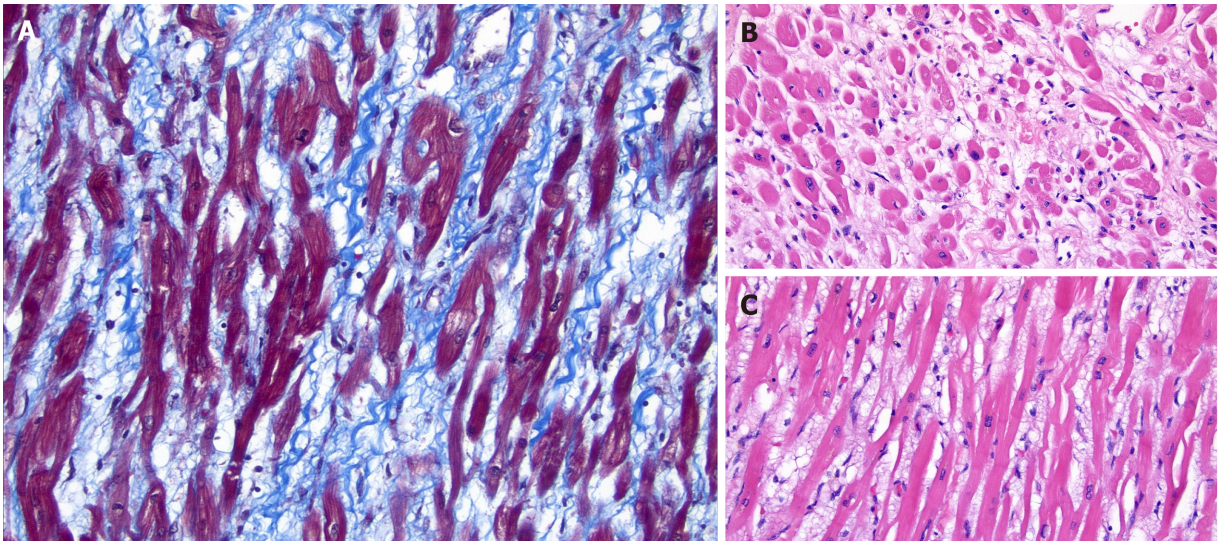


Figure 1 Pathology of myocardium with various stains. A: Trichrome stain showing minimal collagen deposition; B: Cross section of myocardium showing decreased diameter and prominent interstitial edema; C: Hematoxylin and eosin stain showing mildly thinned myocardiocytes with prominent interstitial edema.

rs28714259 from chromosome 15[8-10]. Early identification of patients at risk of AIC is key to preventing cardiotoxicity[11]. We have outlined strategies to mitigate selected modifiable risk factors associated with AIC in Table 1.

Dexrazoxane (ICRF-187) was approved by the United States Food and Drug Administration in 1995 as a cardioprotectant for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy[12]. In randomized studies, 3% of patients treated with dexrazoxane developed CHF compared with 22% of patients who did not receive dexrazoxane. Its mechanisms of action include reduction of cardiotoxic reactive oxygen species, iron chelation, and catalytic inhibitor of topoisomerase II[13]. It should be noted that there have been some concerns in utilizing this agent due to its side effect of secondary malignancy and decreased antitumor effect of anthracycline[14]. Alterations in infusion schedule and the use of pegylated formulation have also shown to reduce the risk of AIC[15]. A study in pediatric population suggested that infusions greater than 6 h reduce the risk of clinical heart failure when compared to those that received IV pushes[16].

Cardiac monitoring and management of patients receiving anthracyclines have been an area of active research since introduction of these agents in clinical practice and are summarized in Table 2[17-21]. In 2017, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines for the prevention and monitoring of cardiac dysfunction in adult cancer survivors[21]. The ASCO guidelines recommend comprehensive assessment in patients with cancer that includes a history and physical examination, screening for cardiovascular disease risk factors, and an echocardiogram before initiation of anthracycline and other cardiotoxic therapies. Echocardiogram may be performed during cardiotoxic cancer treatment and between 6 mo to 12 mo after completion of therapy in asymptomatic patients considered to be at increased risk for cardiac dysfunction. Patients found to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist for further assessment and management.

It is well known that monitoring LVEF alone during anthracycline treatment is insufficient to detect subclinical changes or predict early declines in cardiac function[22]. Studies have shown that persistent elevation of cardiac biomarkers such as troponin and BNP during anthracycline treatment is a harbinger of subsequent LVEF reduction[23,24]. Guidelines from ASCO, European Society for Medical Oncology (ESMO) and Italian Society of Cardiology support periodic measurements of troponin and BNP during anthracycline therapy in patients with risk factors for AIC[18,20,21]. Cardiology consultation and initiation of heart failure therapy with neurohormonal inhibitor such as angiotensin converting enzyme inhibitor (ACE-I) are recommended when cardiac biomarkers are persistently elevated. In addition, these guidelines recommend dexrazoxane treatment, continuous infusion and switching to liposomal formulation in patients planning to receive high-dose anthracyclines (doxorubicin ≥

Table 1 Strategies to mitigate selected modifiable risk factors associated with anthracycline-induced cardiotoxicity

Risk factor	Risk-reduction strategy
Hypertension	Lifestyle modification and pharmacologic control
Diabetes	Lifestyle modification and pharmacologic control
Dyslipidemia	Lifestyle modification and pharmacologic control
Smoking	Smoking cessation
Coronary artery disease	Lifestyle modification and pharmacologic control
Obesity	Lifestyle modification and weight management

Table 2 Monitoring and prevention strategies for anthracycline-induced cardiotoxicity

Method	Description
Biomarkers	Serial measurement of troponin and brain natriuretic peptide
Imaging studies	Regular monitoring of left ventricular function with echocardiogram or cardiac MRI
Pharmacologic agents	Concurrent use of dexrazoxane (for patients receiving doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2)
Administration strategies	Limiting total dose of anthracycline therapy
	Continuous infusion
	Divided doses
	Liposomal formulation

MRI: Magnetic resonance imaging.

250 mg/m^2 or epirubicin ≥ 600 mg/m^2).

Neurohormonal blocking agents such as beta-blockers (BB), ACE-I, angiotensin receptor blockers (ARB), and aldosterone antagonists have been investigated as prevention and treatment of AIC. In preclinical studies, these agents have shown to suppress neurohormonal activation, reduce left ventricular remodeling, and prevent or delay the onset of cardiac symptoms[25]. However, clinical studies have shown mixed results in using neurohormonal inhibitors at the time of chemotherapy to prevent AIC.

The Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity (CECCY; ClinicalTrials.gov Identifier: NCT01724450) phase III trial was the largest BB prevention study which randomized carvedilol *vs* placebo as 1:1 in 192 women with HER2-negative breast cancer receiving doxorubicin 240 mg/m^2 (60 mg/m^2 every 3 wk) with cyclophosphamide followed by paclitaxel[26]. Patients were given incremental dosing of carvedilol or placebo during chemotherapy. The carvedilol group did not meet the primary endpoint which was prevention of early systolic dysfunction within 6 mo of starting doxorubicin. LVEF reduction of at least 10% was noted in 14.5% of the carvedilol group *vs* 13.5% of the placebo group (P = 1.0). Nevertheless, the carvedilol group had lower troponin I levels over 24 wk (P = 0.003) and a lower incidence of LV diastolic dysfunction (P = 0.04). A meta-analysis of 633 patients from 8 randomized trials (including CECCY) comparing carvedilol *vs* placebo to prevent AIC showed significantly reduced rates of low LVEF favoring the carvedilol group (3.2% *vs* 5.8%; OR: 0.42; 95%CI: 0.18-0.99; P = 0.05)[27]. In addition, there were significantly smaller reductions in LVEF in carvedilol-treated patients compared to placebo group.

Prophylactic use of ACE-I to prevent AIC has also been under active investigation. Janbabai *et al*[28] randomized 69 cancer patients receiving enalapril or placebo during doxorubicin treatment of cumulative dose of 365 mg/m^2. The primary end point was change in LVEF measured by echocardiogram from baseline to 6 mo after randomization. There was no change in mean LVEF at 6 mo from baseline in the enalapril treated group, yet there was significant drop in mean LVEF at 6 mo from baseline in control group (46.31% ± 7.04% *vs* 59.61% ± 5.7%; P < 0.001). This study also showed that serum troponin I and creatinine kinase-MB levels were significantly higher 1 mo after the initiation of chemotherapy in the control group than in the enalapril group, suggesting a cardioprotective effect from enalapril. Cardinale *et al*[29]

randomized 114 cancer patients with elevated troponin levels after starting high-dose chemotherapy with either concurrent or prior anthracycline exposure to enalapril *vs* placebo. The primary endpoint was an absolute decrease of more than 10% in LVEF with a decline below 50%, which was prevented in enalapril treatment group when compared with placebo (0% *vs* 43%; $P < 0.001$).

The phase III International Cardio Oncology Society-ONE trial randomized 273 cancer patients taking anthracycline treatment (40% of them receiving median cumulative dose of 240 mg/m^2 doxorubicin) to receive enalapril from initiation of chemotherapy (the prevention group) or during chemotherapy with increased serum troponin level (the troponin-triggered group) (ClinicalTrials.gov Identifier: NCT01968200)[30]. The primary outcome was the incidence of troponin elevation above the threshold at any time during the trial for up to 1 year, and troponin level was measured before and after each anthracycline treatment. There was no difference in the incidence of troponin increase (23% in the prevention *vs* 26% in the troponin-triggered group; $P = 0.50$). Two patients in the prevention and one patient in the troponin-triggered group developed LV dysfunction. This study indicates in patients receiving low cumulative dose of anthracycline, a troponin-triggered strategy to use ACE-I for prevention of AIC seems to be a more convenient and sensible option.

In the OVERCOME phase III trial (ClinicalTrials.gov Identifier: NCT01110824), Bosch *et al*[31] randomized 90 patients with malignant hematologic disorders and normal LVEF in 1:1 ratio to receive either enalapril and carvedilol or nothing during anthracycline therapy. The primary efficacy endpoint was the absolute change from baseline in LVEF, measured by echocardiogram and cardiac MRI at 6 mo after randomization. LVEF did not change in the intervention arm with a median cumulative anthracycline dose of 290 mg/m^2 but significantly decreased in control group with a median cumulative dose of anthracycline of 240 mg/m^2, leading to a -3.1% absolute difference by echocardiography ($P = 0.035$). However, the interventional group did not show any statistically significant reduction in the incidence of heart failure or decreased LVEF > 10% (9.5% *vs* 19%, respectively, $P = 0.22$). The clinical relevance of combined treatment strategy with ACE-I and BB is currently explored in a phase III SAFE trial (ClinicalTrials.gov Identifier: NCT02236806) which uses 2 × 2 factorial design to randomize 480 breast cancer patients[32].

In the PRADA phase II trial (ClinicalTrials.gov Identifier: NCT01434134), Gulati *et al*[33] randomized 120 women with breast cancer receiving adjuvant chemotherapy with epirubicin-based regimen to one of four groups: Candesartan plus placebo, metoprolol plus placebo, candesartan plus metoprolol, and placebo plus placebo. The primary endpoint was change in LVEF measured by MRI after completion of adjuvant treatment. No effect of metoprolol on the overall decline in LVEF was observed. Candesartan group had a smaller mean decline in LVEF than the placebo group (0.8% *vs* 2.6%, $P = 0.03$), indicating prophylactic use of ARB prevents AIC. There are several ongoing large-scale phase II/III randomized clinical trials exploring novel pharmacological intervention in preventing AIC (Table 3). These approaches include hydroxymethylglutaryl-CoA reductase inhibitor (statins) and LCZ696 (neprilysin inhibitor plus angiotensin receptor blocker).

CONCLUSION

Anthracyclines have the potential to exert a direct toxic effect on cardiac myocytes, precipitating symptomatic heart failure. The case presented above demonstrates an example of acute heart failure in a well-compensated young adult who did not, at first glance, warrant greater than routine cardiac surveillance during her treatment course. Most cardiotoxicity after anthracycline-containing therapy occurs within the first year and is associated with the anthracycline dose and LVEF at the end of treatment. Early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function. When symptoms of heart failure are identified early, discontinuation of anthracycline followed by frequent monitoring of cardiac function can help to alleviate further decline. Yet, when a patient is asymptomatic, it is difficult to predict how often cardiac testing should be done.

While published ASCO recommendations regarding baseline and subsequent cardiac imaging are readily available, there are no clear current consensus for criteria by which to stratify asymptomatic patients who do not fall into the high-risk categories. In patients with cardiovascular risk factors, an increased frequency of cardiac imaging should be considered. As evidence mounts regarding the role of ethnicity or genetic polymorphisms in prognosticating the relative risk of

Table 3 Selected ongoing randomized adult clinical trials on the pharmacological prevention of anthracycline-induced cardiotoxicity

Trial No./phase/name	Patient (*n*) and selection	Randomization schema	Primary endpoint
NCT02236806/Phase III/Cardiotoxicity prevention in breast cancer patients treated with anthracyclines and/or trastuzumab (SAFE)	480 non-metastatic breast cancer receiving anthracycline-based regimens with or without trastuzumab	2 × 2 factorial design. Arm 1: Bisoprolol plus ramipril; Arm 2: Bisoprolol plus placebo; Arm 3: Ramipril plus placebo; and Arm 4: Placebo	Maximum change in left ventricular ejection fraction at months 6, 9, 12 and 24, compared to baseline
NCT03265574/Phase III/Can we prevent chemotherapy-related heart damage in patients with breast cancer? (PROACT)	170 breast cancer receiving epirubicin-based adjuvant chemotherapy	Open-label comparing enalapril versus standard care	Cardiac troponin T release during epirubicin treatment
NCT03760588/Phase II/Prevention of cardiac dysfunction during breast cancer therapy (PRADAII)	300 breast cancer receiving anthracycline-based adjuvant chemotherapy	Double-blinded comparing LCZ696 (neprilysin inhibitor plus angiotensin receptor blocker) versus placebo	Left ventricular ejection fraction at 18 mo
ISRCTN24439460/Phase II/Can heart muscle injury related to chemotherapy be prevented? (cardiac CARE)	168 breast cancer or non-Hodgkin's lymphoma with elevated troponin I level during anthracycline-based chemotherapy	Open-label comparing carvedilol plus candesartan versus standard care	Left ventricular ejection fraction at 6 mo
NCT02943590/Phase II/Statins to prevent the cardiotoxicity from anthracyclines (STOP-CA)	300 newly diagnosed non-Hodgkin's lymphoma receiving doxorubicin-based regimens	Double-blinded comparing atorvastatin versus placebo	Left ventricular ejection fraction at 12 mo
NCT01988571/Phase II/Preventing anthracycline cardiovascular toxicity with statins (PREVENT)	279 breast cancer receiving anthracycline-based adjuvant chemotherapy	Double-blinded comparing atorvastatin versus placebo	Left ventricular ejection fraction at 24 mo

chemotherapy side effects, these risk factors could potentially factor in towards an overall risk assessment and for cardiac monitoring frequency.

Furthermore, while there is evidence that cardioprotective agents such as ACE-I, ARB and BB may help to reduce the severity of LVEF depression following anthracycline exposure, it is not clear whether the observed modest reduction in risk translates to actual reduction in symptomatic heart failure and death. More studies may be needed to explore the utility of cardiac strain markers such as troponin and BNP in identifying early-onset cardiac dysfunction in asymptomatic patients.

Prevention of AIC and cardiovascular toxicities of other anti-cancer therapy requires multidisciplinary approaches such as modification of cardiovascular risk factors, active management of co-morbidities, and pharmacologic therapy in selected patients[34]. The emergence of cardio-oncology program provides opportunities for comprehensive management and in-depth investigation, and is supported by the 2019 American Heart Association Scientific Statement on Cardio-Oncology Rehabilitation to manage cardiovascular outcomes in cancer patients and survivors[35].

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The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

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EDITORIAL

New Year's greeting and overview of *World Journal of Cardiology* in 2021

Ya-Juan Ma, Ramdas G Pai

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Abstract

On behalf of the Editorial Office of *World Journal of Cardiology (WJC)*, we extend our sincere gratitude to our authors, readers, Editorial Board members, and peer reviewers, thanking each and every one for their contributions to *WJC* in 2020 and with wishes for a Happy New Year. It was the collective support of all authors, Editorial Board members, peer reviewers and staff of the Editorial Office that allowed the Baishideng Publishing Group Inc. to carry out successfully the complete peer review, editing and publishing processes for *WJC* in 2020. We have now analyzed the metric data of *WJC*'s manuscripts that were submitted and published in 2020, the peer review of manuscripts in 2020, the invited manuscripts for 2021 and the Editorial Board members' composition and activities. As a global academic journal in cardiology, the findings from such will facilitate greater productivity and more efficient collaborative efforts to raise the academic rank of *WJC* in 2021. We enthusiastically anticipate *WJC*'s contributions to promote further cardiology research sharing and exchange in 2021.

Key Words: *World Journal of Cardiology*; Baishideng; Editorial board members; Cardiology; New Year's message; Academic rank

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Core Tip: With the support of all authors, Editorial Board members, peer reviewers and staff of the Editorial Office, Baishideng Publishing Group Inc. successfully carried out the complete peer review, editing and publishing processes for *World Journal of Cardiology* (*WJC*) in 2020. We are sincerely grateful for their contributions to and

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support of the *WJC* in 2020 and appreciate their continuous endeavors that will promote our productivity and raise the academic rank of *WJC* in 2021.

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INTRODUCTION

The *World Journal of Cardiology* (*WJC*) launched on December 31, 2009 and remains a high-quality, online, open-access, single-blind peer-reviewed journal published by the Baishideng Publishing Group[1]. All articles published in *WJC* are high-quality, basic and clinical, influential research articles by established academic authors as well as new researchers. The paramount objective of *WJC* is to showcase and promote distinguished research in the field of cardiology in order to help advance development of this field.

To date, *WJC* has 123 Editorial Board members[2] hailing from countries across the globe. *WJC* has published 638 articles, which have been cited 1071 times. The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed and PubMed Central. It was through the continuous support, dedication and encouragement of all authors, subscribers and readers, along with an excellent team effort by our Editorial Board members and staff of the Editorial Office, that the *WJC* was able to advance so appreciably in 2020.

DEVELOPMENT OF *WJC* IN 2020

We received a total of 103 manuscripts in 2020, of which 26 (25.24%) were rejected, 11 (10.68%) were withdrawn, eight (7.77%) were under review and 58 (56.31%) were published online by the Production Department. The 58 published manuscripts included 28 (48.28%) invited manuscripts and 30 (51.72%) unsolicited manuscripts. The main columns represented by the published manuscripts were original articles and reviews (Figure 1). The authors of the published manuscripts were from 17 countries and regions, with the most being from the United States (Figure 2).

In 2020, *WJC* sent out 3145 invitations to peer reviewers and its Editorial Board members to conduct peer review of submitted manuscripts. These invitations yielded 487 acceptances (15.48%), 311 declines (9.89%) and 2347 non-responses (74.63%). Among those who accepted the invitation, 176 (36.24%) submitted the peer review report on time, 425 (63.86%) failed to submit the peer review report on time and four have not submitted the peer review report yet.

As of December 31, 2020, *WJC* had received a total of 163 proposals for titles of invited manuscripts for submission and review in 2021. These include 96 (58.90%) review articles, 47 (28.83%) original articles, eight (4.91%) editorials, and 12 (7.36%) 'other' types. Among them, 19 (11.66%) articles have already been submitted online, and 144 (88.34%) will be submitted in the future.

The Editorial Board members of *WJC*[2] represent 123 experts from 30 countries and regions, with the greatest number from Italy (21.50%) (Figure 3). Among them, 49 (39.84%) submitted their peer review reports on time, and 20 (33.3%) failed to submit their peer review reports on time.

As of January 14, 2021, the number of total visits to the *WJC* homepage was about 1219647, of which 21.7% of those visits were from the United States, 17.2% from China and 9.7% from United Kingdom. The number of total downloads of *WJC* articles was about 477708, of which 37% of those visits were from the United States, 19.9% from China, and 15% from Germany (Figure 4). According to data from the Web of Science[3], which *WJC* published 66 articles in 2018-2019, the yielded total cites in 2020 was 188 times.

As editors of *WJC* ourselves, we strive to work with the journal's Editorial Office staff to make the manuscript submission process as simple as possible and ensure an efficient communication with the authors to provide our support and answer their

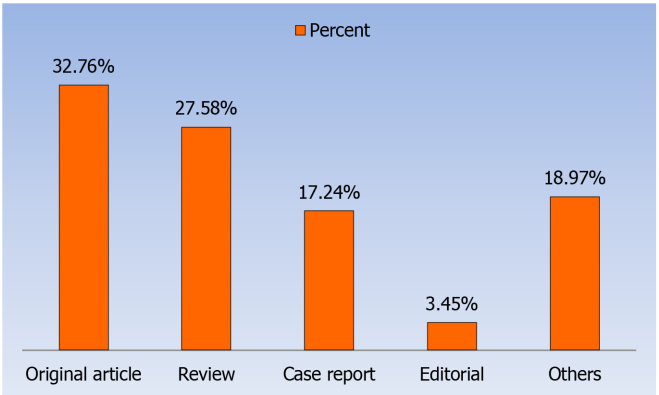


Figure 1 Column type distribution of manuscripts published in *World Journal of Cardiology* in 2020.

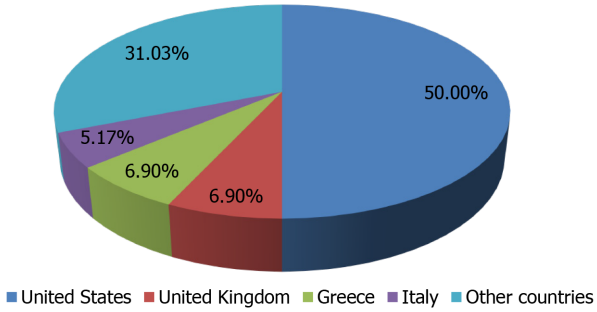


Figure 2 Distribution of authors' countries for the manuscripts published in *World Journal of Cardiology* in 2020.

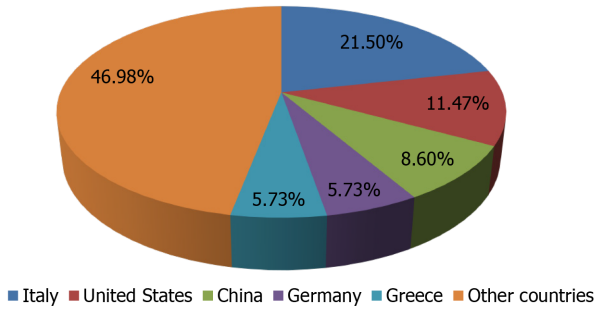


Figure 3 Distribution of Editorial Board members' countries for *World Journal of Cardiology*.

questions. In order to maximize readers' access to the latest research results, thereby promoting development of the field of cardiology, we have invited all Editorial Board members to conduct Article Quality Tracking-Peer-Review and published their comments after article publication. In order to advance the publishing efficiency and quality of *WJC*, Baishideng Publishing Group developed an automated manuscript editor system for manuscript revision and submission as well as an artificially intelligent program to generate a PDF version of the manuscript. Finally, to enable more peers to read, share and cite authors' published research results and to help enhance their global academic influence and reputations, thereby also promoting the overall development of the field of cardiology, we have begun the routine of sending published articles *via* email to many highly influential experts, in a topically-accurate manner.

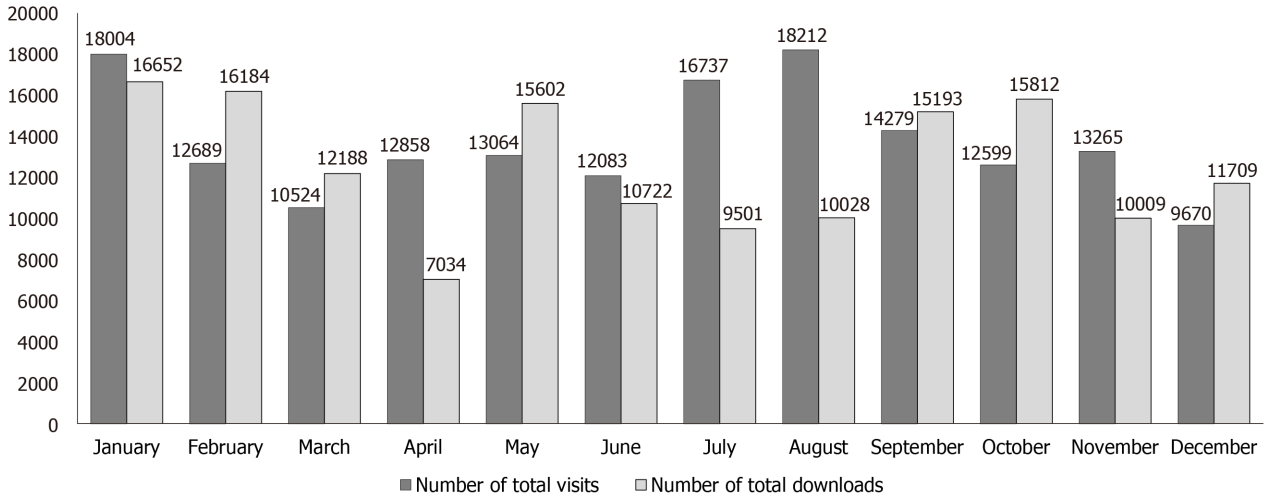


Figure 4 Number of total visits to the *World Journal of Cardiology (WJC)* homepage and number of total downloads to the *WJC* articles in 2020.

CONCLUSION

In 2020, with the great support of all our authors, readers, Editorial Board members, independent expert referees and staff of the editorial office, we successfully published 12 issues of *WJC*. In order to raise the academic rank of *WJC* in 2021, we will rely on the continuous support and submissions from our established and new authors and the dedicated efforts and expertise of our invited reviewers, many of whom also serve on our Editorial Board. We will invite more scientists in the field of cardiology to join the *WJC* Editorial Board, more active scientists to conduct peer review for *WJC* manuscripts and more scientists to contribute high-quality original and review manuscripts to *WJC*. By publishing more high-quality articles, the *WJC* will be able to make more substantive contributions to the development of basic medical and clinical research in the field of cardiology.

We remain open to any suggestions that could improve *WJC*'s operation and publication. If you have any questions or suggestions on *WJC*, please feel free to contact us at y.j.ma@wjgnet.com.

Once again, on behalf of the Editorial Office of *WJC*, we wish you and your families the best for the New Year.

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1 **Baishideng Publishing Group Inc.** *World Journal of Cardiology* home page. Available form: https://www.wjgnet.com/1949-8462/index.htm

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ACADEMIC ACTIVITY REPORT

Survey concerning internal medicine physicians and prolonged QT interval: Knowledge and treatment practices

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Abstract

Prolongation of the QT interval is associated with adverse cardiac events specifically Torsades de pointes (TdP). There are multiple mediations that have a known, possible, or conditional risk for prolonged QT interval, but general practitioners' knowledge of these medications is unknown. We conducted a survey to assess internal medicine (IM) providers' knowledge of risk factors and medications associated with prolonged QT as well as provider experience and comfort when treating patients with prolonged QT. A 17-question, anonymous survey was constructed in 2019 and distributed to IM providers and residents at a tertiary care center. Questions included demographic information, 6 Likert-scale questions gauging provider experience with prolonged QT, and 10 multiple choice clinical vignettes to assess clinical knowledge. Data was analyzed descriptively. Knowledge was assessed *via* clinical vignettes and compared by level of training. Forty-one responses were received out of a total of 87 possible respondents (47.1% response rate). About 70% of respondents see patients with acquired prolonged QT once monthly or more. 95% rarely see congenital prolonged QT. When presented with QTc drug issues, 73% of providers seldom or sometimes consulted pharmacy, but about half used online resources. The average correct score on the clinical vignettes was 5.59/10, with the highest scores seen in attending physicians in their first five years of practice (6.96/10). Our survey suggests that IM providers commonly encounter QT prolonging drugs. Educational efforts to improve knowledge of drug and patient risk factors for TdP may be needed.

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Key Words: QTc; Torsades de pointes; Pharmacotherapy; Survey; Long QT syndrome; Drug interactions

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Core Tip: Knowledge of drugs that prolong the QTc interval and patient risk factors varies significantly among internal medicine physicians and trainees.

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INTRODUCTION

In 1966 Dessertenne[1] first described the electrocardiogram (ECG) morphology of a ventricular tachycardia that had a peculiar undulating or twisting appearance which he termed Torsades de pointes (TdP). In the over 50 years since this paper was published drug-induced TdP, which may be fatal, has been described for numerous drugs. Indeed, in past years drug induced TdP has been a cause of boxed warnings by the FDA as well as the withdrawal of several drugs from the United States market[2]. One of the leading markers of drug induced TdP is the prolonging of the QT interval on the ECG. This measurement (reported in milliseconds) is corrected *via* formula to account for heart rate and is often used as a harbinger of increasing TdP risk[3-4]. With their training in pharmacology and its application to the bedside, pharmacists are often sought out for their opinion on the appropriateness of QTc prolonging medication and often seek to counsel prescribers on the risk of drug induced TdP, often by assessment of drug-drug interactions[5]. Despite this resource little is known of the background knowledge and attitudes of groups of physicians regarding QTc prolonging medications, especially in various stages of their training. To explore this we designed and administered a survey that aimed to determine the knowledge and attitudes of attending physicians and physician trainees.

METHODS

A 17-question, anonymous survey was jointly constructed by an internal medicine (IM) physician, a clinical cardiologist and clinical pharmacist. This survey was distributed in 2019 using Qualtrics (www.qualtrics.com, Qualtrics XM, Seattle, WA, United States). Questions included demographic information, 6 Likert-scale questions gauging provider exposure and comfort with their knowledge of prolonged QT, and 10 multiple choice clinical vignettes. The clinical vignettes covered knowledge of risk factors and medications that prolonged QT as well as treatment of congenital and acquired prolonged QT. This survey was distributed *via* an email invitation to all IM providers and residents as well as psychiatry providers and residents at a tertiary care center in the Midwest. Data was analyzed by evaluating trends and using means to determine provider comfort with prolonged QT identification and treatment. Knowledge was assessed by clinical vignettes and compared by level of training. After data analysis, psychiatry providers and residents were excluded from final data analysis due to low response rate. Descriptive statistics were used in this study. Our Institutional Review Board exempted this study.

RESULTS

After excluding 4 responses from psychiatric staff and residents, a total of 87 surveys were sent of which 41 responses were received [41 responses out of a total of 87 possible respondents (47.1% response rate)]. This included 18/52 IM providers and

23/35 IM residents. Table 1 lists the characteristics of our cohort, and Table 2 lists abbreviated responses to select survey questions. Only 2 respondents reported never having seen patients taking QT prolonging medications; while 17/41 (27%) providers saw such patients weekly or daily. However, 95% participants reported rarely seeing patients with congenital prolonged QT. When presented with patient care issues surrounding prolonged QT, 71% (29/41) of providers seldom or sometimes consulted pharmacy, 99% seldom or never consulted cardiology, and ~50% sometimes used online resources. Thirty-four percent (14/41) reported consulting online resources weekly or daily. We gave examples of types of online resources, but did not ask which types respondents used. The average number correct on the clinical vignettes was 5.59/10 (56%), with the highest scores seen in attending physicians in their first five years of practice [mean 6.96/10 (69%)]. There were no statistically significant differences between the correct responses on the clinical vignettes based on level of training. However, in general, attending physicians generally seemed more familiar with medications prolonging QT while residents were more familiar with patient risk factors prolonging QT.

DISCUSSION

Drug induced QT prolongation can be a harbinger of the TdP which can be lethal. As more drugs enter the market with the propensity to cause QTc prolongation, the chances for a serious cardiac adverse reaction in patients also increases. This behooves prescribers and pharmacists to be aware of the patient risk factors for TdP, including congenital prolonged QT syndrome, and the medications which prolong the QTc and increase this risk. To our knowledge this is one of the only reports of a dedicated assessment of this subject in general IM physicians and their trainees. A previous report from 2005 from the U.S. is similar to ours surveyed a variety of health care practitioners who attended Grand Rounds Conferences at 12 hospitals[6]. In this 20 question survey the median number of correct answers from respondents was 10 (50%) which is similar to our outcomes. This survey also included a problem having respondents manually measure a QTc and found that only 43% did so correctly. Although our survey did not repeat this measure we did find that roughly similar numbers in the knowledge assessment of QTc prolongation. Congenital Long QT syndrome is somewhat rare with a prevalence of 1/2500 live births[7]. It may be less surprising then that our respondents did not encounter it frequently. Somewhat more surprising was the relatively low level of pharmacist consultation indicated by our survey. Our health system is a large tertiary teaching hospital where pharmacy services are decentralized and well established. Perhaps the relatively high use of online resources may explain this finding. Certainly, we feel our findings suggest that an educational activity to discuss QT prolonging drugs, and patient risk factors for TdP may be a worthwhile effort given the low scores on our vignettes. Our study has some limitations, chief of which is the small sample size. However, we did receive a high number of overall responses. Also, we only surveyed IM physicians and trainees in our health-system. The application of this information to other geographic areas or other subspecialties of medicine is unknown. Finally although an academic clinical pharmacist and a staff cardiologist designed the vignettes it is possible that errors in designing or writing these problems led to respondents choosing the incorrect answer.

CONCLUSION

Our survey indicates that our IM physicians often encounter patients receiving QT prolonging medications. They only occasionally consult clinical pharmacists for this problem and use online resources at least half the time. The results of the vignettes suggest a knowledge gap concerning these issues that we plan to address with an interdisciplinary educational program. It would be worthwhile to repeat this study in a larger academic institution to obtain a larger sample size and consider sampling other specialties such as family medicine and psychiatry.

Table 1 Survey participant level of training

Training status	*n* (%)
PGY-1	12 (29.2)
PGY-2	6 (13.3)
PGY-3	6 (13.3)
Attending physician	17 (37.7)

Table 2 Abbreviated responses to select survey questions

Question	Never, *n* (%)	Seldom, *n* (%)	Sometimes, *n* (%)	Often, *n* (%)	Daily, *n* (%)
See patients with QTc prolonging drug	2 (4.4)	11 (29.2)	15 (33.3)	10 (22.2)	2 (4.4)
See patients with congenital long QT	20 (44.4)	19 (46.3)	1 (2.2%)	1 (2.2)	0
Consult pharmacy	11 (24.4)	16 (44.4)	13 (28.8)	1 (2.2)	0
Consult cardiology	20 (44.4)	21 (49.0)	0	0	0
Consult online reference	1 (2.2)	8 (17.7)	18 (43.9)	10 (22.2)	4 (8.8)

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ORIGINAL ARTICLE

Retrospective Cohort Study

Remote monitoring of implantable defibrillators is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area

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Abstract

BACKGROUND

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy with defibrillators (CRT-D) reduce mortality in certain cardiac patient populations. However, inappropriate shocks pose a problem, having both adverse physical and psychological effects on the patient. The advances in device technology now allow remote monitoring (RM) of devices to replace clinic follow up appointments. This allows real time data to be analysed and actioned and this may improve patient care.

AIM

To determine if RM in patients with an ICD is associated with fewer inappropriate shocks and reduced time to medical assessment.

METHODS

This was a single centre, retrospective observational study, involving 156 patients implanted with an ICD or CRT-D, followed up for 2 years post implant. Both appropriate and inappropriate shocks were recorded along with cause for inappropriate shocks and time to medical assessment.

RESULTS

RM was associated with fewer inappropriate shocks (13.6% clinic *vs* 3.9% RM; $P = 0.030$) and a reduced time to medical assessment (15.1 ± 6.8 *vs* 1.0 ± 0.0 d; $P < 0.001$).

CONCLUSION

RM in patients with an ICD is associated with improved patient outcomes.

Key Words: Implantable cardioverter defibrillator; Inappropriate shocks; Remote

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Core Tip: Advances in device technology now allow remote monitoring of implantable cardioverter defibrillators to replace clinic follow up appointments. This allows real time data to be analysed and actioned. This study shows that remote monitoring of such devices is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area. This represents better patient care and will reduce the morbidity caused by inappropriate shocks.

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INTRODUCTION

Implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy with defibrillation (CRT-D) are established treatments for a range of cardiac disorders and are proven to reduce mortality[1-4]. The continuing care for patients with ICDs and CRT-Ds involves regular follow up appointments to monitor the function of the device and the clinical status of the patient. A limitation of the conventional clinic follow up model is the lack of information between visits and immediately after therapy (*e.g.*, shocks). Remote monitoring (RM) using a telephonic transmission of pacemaker information from the patients home fills this gap with clinical trials having demonstrated the usefulness[5,6] including its safety[7], economic benefits[8] and improved clinical outcome[9].

The delivery of a shock can result in adverse effects for the patient, including impaired quality of life, psychiatric disturbances and is associated with increased all cause mortality[10], which increases with each subsequent shock. Shocks can be appropriate (*e.g.*, to treat potentially fatal rapid ventricular rhythms) or inappropriate (non-fatal tachyarrythmia or lead dysfunction). RM reduces inappropriate shocks[5,11,12] through the earlier detection of events preceding the delivery of inappropriate shocks. In addition, RM offers the ability to reduce the time from a clinical event (such as an appropriate or inappropriate shock) to a clinical decision being made [time to medical assessment (TMA)]. This is an especially pertinent issue in remote and rural areas where patients can live long distances from specialist care.

This study aimed to assess appropriate and inappropriate shocks in patients with and without RM and to measure differences in TMA in a real world, remote and rural population.

MATERIALS AND METHODS

Study design and population

This was a single site, retrospective observational study in a hospital serving a remote and rural population of 320000 spread over a geographical area of 32500 km^2 including several islands. Patients who were implanted with an ICD or CRT-D between January 1, 2010 and January 1, 2014 were included. All patients were followed up for 2 years post implant. There were no exclusion criteria. Device programming and the use of RM was decided on an individual basis at the discretion of the cardiac rhythm physiologists after discussion with the clinician and patient. All RM systems transmit a variety of parameters, (such as lead parameters, battery status, therapy delivery, arrhythmias, intracardiac electrograms (IEGM), heart rate and rhythm statistics and patient activity levels) from the patients' device *via* a mobile network link of landline, to the manufacturer's central repository. Clinicians responsible for the follow up of

patients receive automated email notifications if pre-specified criteria are met (*e.g.*, shock delivered). All transmitted data is stored on a dedicated, secure, password protected website. Follow up arrangements between groups were similar, and on a case by case basis at the discretion of the follow up clinician. All ad-hoc reviews prompted by events highlighted from home monitoring were also arranged at the discretion of the clinician.

Data collection

Baseline characteristics were collected from patient medical records. Device related data was retrieved from both hard and electronic copies of the patient records and from each of the companies' respective RM systems; Home Monitoring (Biotronik), CareLink (Medtronic) or Merlin (St Jude Medical).

TMA

TMA was calculated in days; beginning with event onset at the delivery of a shock and ending when a clinical decision was made. Clinical decision was defined as management of an event, medical intervention, physician decision, decision for follow up clinic, or hospitalisation.

Therapy analysis

An inappropriate shock was defined as the delivery of a shock not for true ventricular tachycardia or ventricular fibrillation. Shocks were classified on a shock by shock basis, rather than by episode. For example, 4 shocks all received for an episode of T wave over sensing would be counted as 4 shocks not 1. Analysis of the IEGM by cardiac physiologists was used to ascertain whether shocks were appropriate or inappropriate. Inappropriate shocks were classified in relation to their cause, for example, atrial fibrillation (AF) or flutter, supraventricular tachycardia (SVT), T wave over sensing, noise, or V lead displacement.

Data handling and statistical analysis

Patients were defined as "RM" if they had an ICD/RCT-D with RM function and "clinic" if they had a standard ICD/CRT-D with no RM function. Baseline characteristics from the "RM" *vs* "clinic" monitoring groups were compared using the Wilcoxon rank sum test for continuous variables, with the Chi squared test being used for categorical variables. Continuous variables were reported as mean with standard deviation. The Man Whitney *U*, chi squared test and the students *t* test were used to analyse the inappropriate shock and TMA as appropriate. All tests were performed at a $P = 0.05$ significance level. All data were processed and analysed using Microsoft Excel 2007 software and SPSS software version 18.0.

Ethics

This was a service evaluation using routinely collected data and therefore formal ethical approval was not required. Local Caldecott approval was obtained to access patients' records for this project.

RESULTS

Baseline characteristics

Of 156 patients were identified, with 45 in the clinic group and 111 in the RM group. Baseline characteristics are shown in Table 1. There was no significant difference between the two groups except for the manufacturer of the implanted device. A total of 16 patients were lost to follow up (10.3%) (Table 2).

Incidence of shocks

Table 2 shows the incidence of appropriate and inappropriate shocks for both groups. There was no significant difference between groups for the number of patients receiving appropriate shocks [3 (8.6%) clinic patients *vs* 14 (13.6%) RM patients, $P = 0.388$]. However, there was a significant difference for the number of patients receiving inappropriate shocks [4 (11.4%) clinic patients *vs* 4 (3.9%) RM patients, $P = 0.030$]. The maximum number of shocks received by 1 patient was 14, this patient was in the clinic follow up group and shocks were due to incorrectly identified SVT.

Table 1 Baseline characteristics

	Clinic, *n* (%)	RM, *n* (%)
n	45	111
Age at implant (year)	63.6 ± 13.0	64.2 ± 11.5
Male	30 (85.7)	85 (82.5)
NYHA functional class		
I	12 (34.3)	40 (38.8)
II	18 (51.4)	52 (50.5)
III	5(14.3)	11 (10.7)
Cardiac disease category		
Coronary artery disease	21 (60.0)	54 (52.4)
Non ischaemic dilated cardiomyopathy	4 (11.4)	15 (14.6)
Primary electrical disease	3 (8.6)	5 (4.9)
Hypertrophic cardiomyopathy	1 (2.9)	6 (5.8)
Valvular heart disease	1 (2.9)	2 (1.9)
Hypertensive	1 (2.9)	3 (2.9)
Other cardiomyopathy	1 (2.9)	5 (4.9)
Undetermined	2 (5.7)	10 (9.7)
None	1 (2.9)	1 (1.0)
ECG history of		
Sustained ventricular tachycardia	7 (20.0)	24 (23.3)
Ventricular fibrillation	6 (17.1)	19 (18.4)
Torsade de pointes	1 (2.9)	3 (2.9)
Indication for ICD		
Primary	20 (57.1)	57 (55.3)
Secondary	15 (42.9)	46 (44.7)
Implanted device		
Single chamber ICD	13 (37.1)	27 (26.2)
Dual chamber ICD	19 (54.3)	74 (71.8)
CRT-D	5 (14.3)	23 (22.3)
Type of implant		
Original	30 (85.7)	83 (80.6)
Replacement	5 (14.3)	20 (19.4)
Drug therapy		
Beta-blocker	25 (71.4)	69 (70.0)
Digoxin	2 (5.7)	12 (11.7)
Amiodarone	4 (11.4)	8 (7.8)
Manufacturer		
Biotronik	11 (31.4)	44 (42.7)
Boston scientific/guidant	8 (28.8)	0 (0)[1]
Medtronic	5 (14.3)	41 (39.8)
St Jude Medical	11 (31.4)	18 (17.5)

[1]Boston remote monitoring (latitude) was not available at the time of implant.
RM: Remote monitoring; NYHA: New York Heart Association; ECG: Electrocardiograph; ICD: Implantable cardioverter defibrillator; CRT-D: Cardiac resynchronisation therapy with defibrillators.

Table 2 Incidence of appropriate and inappropriate shocks and time to medical assessment

	Clinic, *n* (%)	RM, *n* (%)
n	45	111
Reason lost to follow up		
Out of area	3 (6.7)	4 (3.6)
Death	7(15.6)	4 (3.6)
Number of patients receiving shocks (appropriate)	3 (8.6)	14 (13.6)
1 shock	3 (8.6)	9 (8.7)
2-9 shocks	0	6 (5.8)
≥ 10	0	0
Number of patients receiving shocks (inappropriate)	4 (11.4)	4 (3.9)
1 shock	0	2 (1.9)
2-9 shocks	2 (5.7)	2 (1.9)
≥ 10	2 (5.7)	0
Causes inappropriate shocks (number of shocks)		
AF/flutter	18 (42.9)	2 (20.0)
SVT	14 (33.3)	1 (10.0)
T wave over sense	0	1 (10.0)
V lead displacement	0	6 (60.0)
Noise	10 (23.8)	0
TMA		
Appropriate shocks	11.7 ± 9.2	1.8 ± 0.6
Inappropriate shocks	15.1 ± 6.8	1.0 ± 0.0

TMA: Time to medical assessment; RM: Remote monitoring; AF: Atrial fibrillation; SVT: Supraventricular tachycardia.

Cause of inappropriate shocks

The most common cause of inappropriate shocks was AF/flutter in the clinic group and ventricular lead displacement in the RM group (Table 2).

TMA

TMA was significantly higher in clinic *vs* RM group for inappropriate shocks (15.1 ± 6.8 *vs* 1.0 ± 0.0 d; $P < 0.001$) and appropriate shocks (11.7 ± 9.2 *vs* 1.8 ± 0.6 d; $P < 0.001$). (Figure 1) Reasons for a delayed TMA included patients unaware of shocks, ability to travel and delayed transfers from community hospitals.

DISCUSSION

This study has shown that RM is associated with a reduced TMA and a reduced number of inappropriate shocks in a patient population living in a remote and rural area.

Prompt identification and intervention of inappropriate shocks is essential to prevent subsequent inappropriate shocks. Although patients are typically aware of receiving a shock there are occasions when patients are not. This study was able to demonstrate an association between RM and a reduced TMA following the delivery of

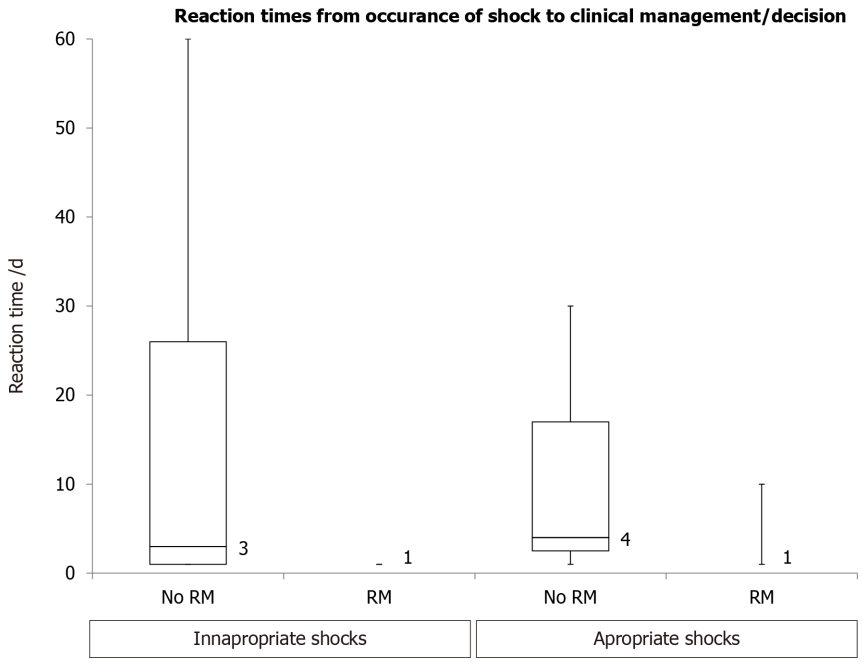


Figure 1 Box-whisker plot for time to medical assessment following a shock. RM: Remote monitoring.

a shock (appropriate or inappropriate) compared to clinic follow up. A quicker TMA following an inappropriate shock may reduce the likelihood of further inappropriate shocks due to medical or programming interventions. Although programming or prescribing changes are not necessarily required after an appropriate shock, RM is associated with a reduced TMA by allowing remote assessment of the device and care to be provided to the patient at local hospitals, with specialist device support provided remotely. The ability of RM to reduce TMA has been demonstrated in larger clinical trials[13,14] and the home guide registry[15]. However, it is worth noting that these trials included all device alerts when calculating TMA rather than just shock as is the case here. The ability of RM to reduce TMA and to deliver the same level of care to all patients regardless of geographical location is advantageous.

The reduced number of inappropriate shocks in the RM group is consistent with data from the ECOST and EVATEL trials[11,12]. ICD shocks are known to have both a physical and psychological effect on the patient, including acute pain, anxiety and depression[13], as well as having an adverse effect on the myocardial function, leading to an increased risk of death[16,17]. With these known detrimental effects of shocks it is well recognised that there is a need to reduce the occurrence of inappropriate shocks, in order to increase the quality of life for patients with ICDs and CRT-Ds.

Comparisons of service

The incidence of inappropriate shocks (all follow up methods) from major clinical trials were compared to the findings in this study. In contemporary trials with clinic follow up inappropriate ICD therapies have been reported in up to 25%-35% of cases[18-20], with more recent trials reporting inappropriate shock rate of 10%-11.5%[3,21], also with clinic follow up. Our study showed an inappropriate shock rate in clinic follow up patients of 11.4%, which is not dissimilar; suggesting that the service patients receive here is comparable to hospitals worldwide. There are fewer trials with inappropriate shock data for patients followed up with RM, but in a recently reported cohort a rate of 3.9% per annum was reported[22], which is identical to the rate in this current study.

Safety

The safety of RM compared to clinic follow up has been confirmed by several large clinical trials, such as TRUST[7] and ECOST[11], both of which have evaluated major adverse events to prove the non-inferiority of RM compared to clinic follow up. However, these trials only included those patients with Biotronik's Home Monitoring system. Although a similar trial by Al-Khatib *et al*[23] reported similar findings for Medtronic's Carelink system. Our study included patients with 3 manufacturers (Biotronik, Medtronic, St Jude Medical and Boston scientific/Guidant) with no obvious

differences between the four providers although numbers were small.

Limitations

This was a retrospective single centre study and therefore there is a risk that these results are not generalizable. However, all device follow up in our area is provided at this one site and all device patients were included. Our centre is the only cardiac unit in our region and therefore it is likely that our patient population is representative. A further potential limitation is the study design which was an observational cohort study and not randomised. Nevertheless, the groups although of differing size were similar with regard to demographics and the results are consistent with previous studies. The implant period covered 4 years, with RM perhaps becoming more available/widely adopted in those patients implanted later on in the study and improved experience and medical therapy may have skewed results. The number of inappropriate shocks in both groups is small and this is a statistical limitation of the study. It is also recognised that this study does not include data regarding anti-tachycardia pacing delivered to patients, whilst this would provide additional therapy and arrhythmia information it was out with the scope of this review.

Recommendations

The lower incidence of inappropriate shocks in patients with RM compared to published data is of interest. The geographical location of the study centre in a dispersed population has led to an increase use of RM, perhaps more than other centres and the informal response in terms of staff and patients has been positive.

CONCLUSION

RM was associated with fewer inappropriate shocks and reduced TMA post shock (for appropriate and inappropriate shock). Inappropriate shocks are known to have detrimental effects on a patient's quality of life and to increase mortality. For these reasons it is essential that reducing the incidence of inappropriate shocks is a high priority in the continuing care and follow up of patients. More widespread use of RM might lead to a decrease in inappropriate shocks.

ARTICLE HIGHLIGHTS

Research background

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy with defibrillators (CRT-D) reduce mortality in certain cardiac patient populations. However, inappropriate shocks pose a problem, having both adverse physical and psychological effects on the patient. The advances in device technology now allow remote monitoring (RM) of devices to replace clinic follow up appointments. This allows real time data to be analysed and actioned and this may improve patient care.

Research motivation

This is because inappropriate shocks and delayed assessment can lead to morbidity and reduced quality of life for patients.

Research objectives

The primary objective was to determine if RM in patients with an ICD is associated with fewer inappropriate shocks and reduced time to medical assessment.

Research methods

This was a single centre, retrospective observational study, involving 156 patients implanted with an ICD or CRT-D, followed up for 2 years post implant. Both appropriate and inappropriate shocks were recorded along with cause for inappropriate shocks and time to medical assessment.

Research results

RM was associated with fewer inappropriate shocks (13.6% clinic *vs* 3.9% RM; $P = 0.030$) and a reduced time to medical assessment (15.1 ± 6.8 *vs* 1.0 ± 0.0 d; $P < 0.001$).

Research conclusions

RM in patients with an ICD is associated with both improved patient outcomes.

Research perspectives

The role of RM in other areas should be investigated.

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ORIGINAL ARTICLE

Prospective Study

Elevated interleukin-6 levels are associated with impaired outcome in cardiac transthyretin amyloidosis

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Author contributions: Hein SJ was responsible for recruitment of the trial, data acquisition, conducting interleukin-6 measurements and drafted the manuscript; Knoll M was responsible for the statistical analyses of the data; Aus dem Siepen F was involved in recruitment for the trial and substantially revised the manuscript; Furkel J, Schönland S, Hegenbart U and Katus HA substantially revised the manuscript; Kristen AV and Konstandin MH were responsible for the funding, study design and substantially revised the manuscript.

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Abstract

BACKGROUND

Elevated interleukin (IL)-6-levels have been described in familial variant transthyretin amyloidosis (ATTRv) associated polyneuropathy and heart failure. However, IL-6 in cardiac ATTR amyloidosis (ATTR-CM) and its prognostic value have not been investigated yet.

AIM

We aim to study the correlation between IL-6 levels with clinical presentation (Gillmore-class) and outcome [heart transplantation or death (htx/death)], or the combined endpoint of cardiac decompensation or htx/death in ATTR-CM.

Institutional review board statement: The study was reviewed and approved by the ethical review committee Heidelberg (Approval No. S-485-2016).

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: Hegenbart U received honoraria of Pfizer, the other authors have nothing to declare.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 checklist, and the manuscript was prepared and revised according to the CONSORT 2010 checklist.

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METHODS

IL-6 levels of 106 ATTR-CM patients [54 wild-type ATTRwt, 52 ATTRv-CM], 15 asymptomatic carriers of ATTR mutations (aATTRv-CM) and 27 healthy donors were quantified using Luminex technology. Statistical analysis was performed using parametric survival regression models.

RESULTS

We found that IL-6 levels from wild-type ATTR patients were significantly elevated compared to healthy controls, while aATTRv-CM carriers and ATTRv-CM patients did not show a significant difference. IL-6 levels showed significantly higher values in increasing Gillmore classes. Univariate analyses revealed association of low IL-6 levels with cardiac decompensation and htx/death [odds ratio: 0.26 (0.09-0.72), P = 0.01] and htx/death [odds ratio: 0.15 (0.04-0.58), P = 0.006]. However, in the multivariate model, no significant improvement of risk prediction was seen for IL-6, while established prognostic factors were significantly associated with outcome.

CONCLUSION

Raised IL-6 levels correlate with clinical presentation and are associated with worse outcome in ATTR-CM but do not improve stratification in addition to established risk factors.

Key Words: Transthyretin amyloidosis; Inflammation; Heart failure; Interleukin-6; Outcome; Risk stratification

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Core Tip: This was a monocentric prospective trial with 106 patients suffering from transthyretin cardiomyopathy (ATTR-CM) seeking to evaluate the prognostic value of interleukin-6 in ATTR-CM. Interleukin-6 is associated with outcome in ATTR-CM but did not further ameliorate existing risk prediction models.

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INTRODUCTION

Systemic amyloidosis comprises a group of diseases leading to extracellular protein deposition in tissue resulting in organ dysfunction. Depending on the specific type of protein causing misfolding and amyloid formation, different organs are involved. In cardiac amyloidosis, protein deposition in myocardium is most frequently due to amyloid light chain or transthyretin (TTR) deposition[1]. In transthyretin cardiac amyloidosis (ATTR), two disease entities are found: Hereditary variant transthyretin amyloidosis (ATTRv) and wild-type transthyretin (ATTRwt) amyloidosis[2]. ATTRv results from a point mutation in the *TTR* gene. Until now, more than 100 different disease causing mutations are known. Depending on the mutation, patients present with leading neurological [familial transthyretin polyneuropathy (ATTRv-PN)] or cardiac symptoms (ATTRv-CM)[3]. Furthermore, thanks to increased awareness and also the establishment of new sensitive diagnostic methods, *e.g.*, 99mTc-labelled bone scintigraphy and cardiac MRI, the incidence of ATTR amyloidosis in general and particularly of ATTRwt, has increased over the last years[4]. In this disease entity, no mutation in the transthyretin gene is found. ATTRwt mainly affects elderly, predominantly male patients with cardiac symptoms leading. The clinical course of ATTR varies significantly within patients with rapid progression of symptoms, within a few months in some patients, and stable course for many years in others[2]. Therefore, early identification of patients at high risk for a more aggressive course of the disease

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is crucial for the preservation of quality of life, exercise capacity and ultimately survival and early initiation of amyloid specific therapies.

In the last years the role of systemic inflammation for progression of cardiovascular disease in general has been established, especially in coronary heart disease. Elevated interleukin (IL)-6 levels are described in patients suffering from heart failure with preserved ejection fraction (HFpEF), atrial fibrillation and elevated N-terminal pro-brain natriuretic peptide (NTproBNP)[5]. Furthermore, on a molecular level increased cardiac IL-6 and IL-6 receptor messenger ribonucleic acid (mRNA) levels in myocardial tissue have been associated with worsening of heart failure[6]. In animal models of pressure overload and heart failure inhibition of the IL-6 axis was protective[7]. In very recent studies, association of inflammation and disease progression could be documented for amyloidosis too. Immunohistochemical detection of lymphocytes, macrophages and cytotoxic cells in cardiac specimen of light-chain amyloidosis (AL) and ATTR amyloidosis patients was associated with impaired outcome[8]. Gene expression profiling of peripheral blood leukocytes was valuable for the diagnosis of symptomatic patients with ATTR amyloidosis[9]. Moreover, systemic inflammatory state quantified as cytokine panels in patients' blood plasma has been described in hereditary amyloid polyneuropathy[10,11]. In patients with ATTR-PN, data are inconsistent as IL-6 levels were found to be unchanged in ATTRv-PN patients and asymptomatic gene carriers compared to healthy controls[10]. In another study, increased IL-6 levels were seen in ATTRv-PN patients and asymptomatic mutation carriers as well[11].

Since nothing is known about IL-6 in patients with ATTR-CM to date, the aim of the present study was to quantify the levels of IL-6 in peripheral blood in this cohort and analyze the correlation with clinical presentation and prognosis.

MATERIALS AND METHODS

Study population

Between July 2016 and October 2018, 138 patients who consecutively presented in our tertiary referral center for amyloidosis at Heidelberg University Hospital were screened and asked to donate blood for this study. One patient declined study participation. Inclusion criteria were age > 18 and < 90 years, diagnosis of ATTRwt, ATTRv or asymptomatic carrier of a mutation causing ATTRv. Patients who suffered from AL amyloidosis (n = 7) were excluded due to other pathophysiologic disease mechanism. Patients who underwent liver transplantation (n = 1) or diagnosis remained unclear (n = 3) were excluded from study participation. Also, patients receiving TTR-lowering therapies (n = 5) were excluded due to reduction of disease driving protein. Patients who received TTR-stabilizer therapy, however, were eligible to participate in the study (n = 26), as dysfunctional protein is still present. These patients already received tafamidis 20 mg daily at study inclusion for grade 1 ATTR polyneuropathy during the whole follow-up period. Therefore, a total of n = 121 patients were included in the present study and subscribed written informed consent approved by the ethical review committee Heidelberg (S-485-2016), in accordance to the declaration of Helsinki. To attain a control group, healthy volunteers were asked to donate blood, when echocardiography, clinical presentation and biomarkers were normal [high-sensitive troponin T, C-reactive protein (CRP) and NTproBNP] (n = 27).

Blood samples were attained with regular venipuncture during the medical visit. Therefore, one additional lithium heparin monovette (4.9 mL, Sarstedt, Nümbrecht, Germany) was collected and plasma was prepared by standard centrifugation. Samples were aliquoted and stored at -80 °C, conditions well established to have no impact upon IL-6 stability[12,13]. After the inclusion of the last patient, IL-6 levels of all patients were measured simultaneously.

For subgroup analysis in Figure 1, patients were divided by positive cardiac TroponinT (cTnT) levels according to the estimated cutoff in our recent study[14]. For subcohort definition regarding natriuretic peptide levels [glomerular filtration rate (GFR) adjusted NTproBNP], NTproBNP levels were adjusted to renal function as described by Luchner *et al*[15].

Echocardiography was conducted using 2D imaging, M-Mode, Doppler and Strain analyses. Ejection fraction was calculated from 2D echocardiography imaging and diastolic dysfunction was graded in accordance to current guidelines from the American Society of Echocardiography[16]. Grade II and higher were considered as significant diastolic dysfunction.

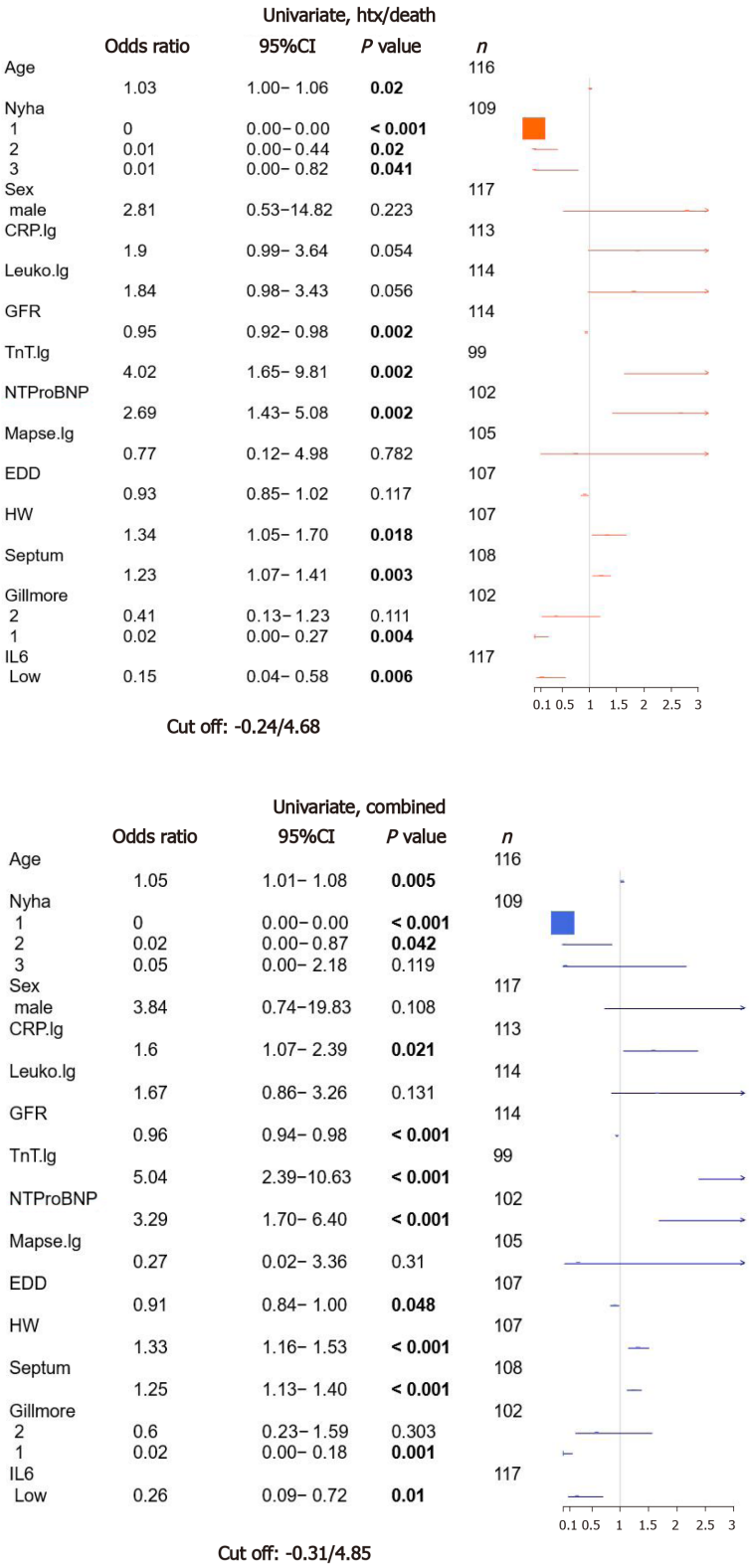


Figure 1 Univariate analysis for clinical/laboratory/risk score parameters and interleukin-6. Parametric survival regression, loglogistic distribution, wild-type *P* values. CRP: C-reactive protein; IL6: Interleukin-6; NTProBNP: N-terminal pro-brain natriuretic peptide; GFR: Glomerular filtration rate.

Follow-up

Endpoint follow-up was performed by interviewing patients directly during outpatient visits or *via* phone call after 12 mo. Additionally, patients' files of subsequent hospitalization due to cardiac decompensation were analyzed. Pre-specified endpoints were heart transplantation or death (htx/death) and a combination of htx/death or cardiac decompensation (major cardiac events, MACE).

Luminex assay

Plasma concentrations of IL-6 were quantified using the Luminex MAGPIX system (R&D systems, Minneapolis, MN, United States). IL-6 measurements were conducted in adherence to the manufacturer's instructions.

Statistical analysis

Statistical analyses were conducted using R, v3.6.3[17]. IL-6 concentrations were calculated from a standard curve attained by the standards provided by the Luminex kit. Values were fitted using a sigmoidal, three parameter, hill fit equation [$f = a*x^b/(c^b + x^b)$]. For further analysis, log transformed data were used. IL-6 values below the detection level were set to zero ($n = 1$). Measurements were transformed as described in[18] prior to log and z-transformation for subsequent analysis.

Time-to-event data were censored after 30 month. Median follow-up data were calculated with survreg using inverted event data. Confidence intervals were computed with the ciTools package[19]. Cutoff selection for prognostic stratification of patients (smallest P values, minimum group size of 10%) was performed with the dataAnalysisMisc package[20]. Cutoffs were calculated per endpoint.

Uni- and multivariate survival analyses were performed with parametric survival regression models assuming loglogistic distributed data.

Associations between diagnosis groups and patient characteristics were evaluated using analysis of variance or chi-squared tests for categorical and continuous variables, respectively. Significance level alpha was set to 5% (two-sided).

RESULTS

Study population

A total of 121 patients and 27 healthy controls participated in this study. In 50 patients, cardiac amyloidosis was confirmed by myocardial biopsy, 56 patients were diagnosed by specific myocardial storage in 99m-TC-DPD-bone scintigraphy and concomitant serological exclusion of AL amyloidosis. Furthermore, 15 asymptomatic gene carriers were diagnosed by familial history and genotyping. According to the examination results, patients were grouped into ATTRwt ($n = 54$), symptomatic ATTRv-CM ($n = 52$) and asymptomatic aATTRv-CM ($n = 15$).

The ATTRv-CM group consists of patients with mutations at Val30Met ($n = 18$), Val20Ile ($n = 11$), Ile107Val ($n = 5$), Leu58His ($n = 6$), Cys10Arg ($n = 4$), Val122Ile ($n = 3$), Ala45Thr ($n = 1$), Ile84Asn ($n = 1$), Ile107Phe ($n = 1$), Arg34Gly ($n = 1$), Thr126Arg ($n = 1$). Furthermore, the asymptomatic mutation carriers were Val20Ile ($n = 5$), Val30Met ($n = 6$), Val122Ile ($n = 1$), Cys10Arg ($n = 1$), Ile107Val ($n = 1$), Ile84Thr ($n = 1$). Table 1 presents clinical characteristics of study participants.

ATTRwt patients were significantly older and primarily male patients. Furthermore, treatment with diuretics, beta blockers and angiotensin converting enzyme inhibitors was more common in the ATTRwt group. In electrocardiogram (ECG), atrial fibrillation was more common in ATTRwt patients compared to both other patient groups, and ATTRwt patients presented higher prevalence of bundle branch blocks and were significantly more often equipped with pacemakers. Furthermore, diabetes was more often recorded in their medical history as co-existing diseases. Serologically, ATTRwt patients presented higher cTnT and NTproBNP levels as well as lower GFR compared to both other groups. This resulted in higher clinical risk classes when classification was specified according to Gillmore *et al*[4]. In echocardiography, ATTRwt patients presented more pronounced myocardial hypertrophy and lower ejection fraction than patients from the two other groups.

During the recruitment period of the study, Tafamidis was only approved for ATTRv patients with concomitant polyneuropathy; therefore, treatment with Tafamidis was significantly more frequent in the ATTRv group. IL-6 levels did not show significant differences in patients treated with Tafamidis (Supplementary Figure 1). New York Heart Association (NYHA) class was higher in ATTRwt. All other variables tested (body mass index, antihypertensive medication, times in the ECG and echocardiographic parameters) were not significantly different between groups.

IL-6 is elevated in ATTRwt patients and rising with Gillmore class in ATTR-CM patients

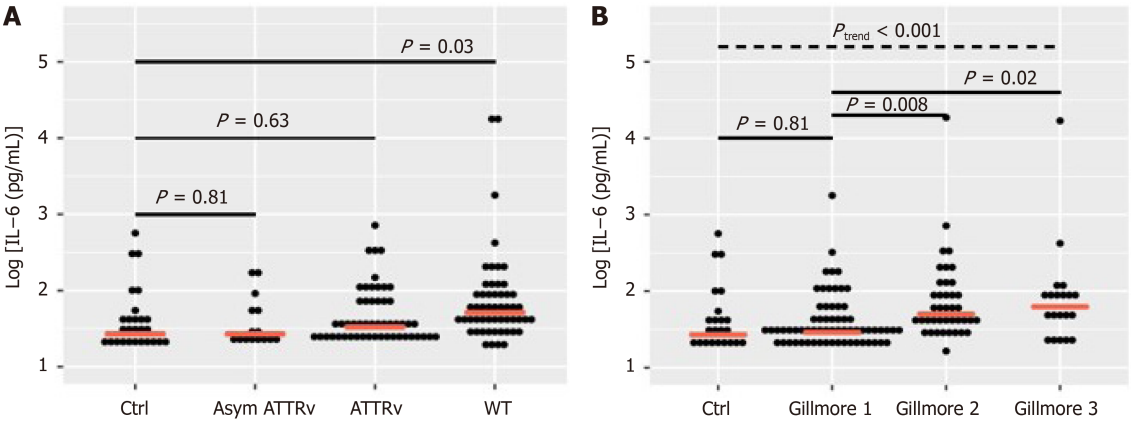
In healthy controls, median IL-6 level was 4.18 pg/mL (median absolute deviation (mad): 0.8) and in aATTRv-CM IL-6 was 4.18 (0.61) pg/mL as well (Figure 2A).

Table 1 Patient characteristics

Study population, *n* = 148	Asympt ATTRv, *n* = 15	ATTRv, *n* = 52	Ctrl, *n* = 27	ATTRwt, *n* = 54	*P* value
Age (yr)	46.9 ± 11.2	66.1 ± 8.1	53.3 ± 19.6	78.5 ± 6.8	< 0.001
Sex, *n* (%)					
Male	9 (60.0)	39 (75.0)	16 (59.3)	49 (90.7)	< 0.001
Female	6 (40.0)	13 (25.0)	11 (40.7)	5 (9.3)	
BMI	27.3 ± 5.6	26.1 ± 4.9	26.0 ± 5.5	25.5 ± 3.0	0.59
Medication, *n* (%)					
Tafamidis	0 (0)	25 (48.1)	0 (0)	1 (1.9)	< 0.001
Beta blocker	2 (13.3)	20 (38.5)	7 (25.9)	41 (75.9)	< 0.001
ACE inhibitors/AT1 antagonists	3 (25.0)	16 (30.8)	7 (25.9)	37 (68.5)	< 0.001
Diuretics	2 (13.3)	27 (51.9)	4 (14.8)	52 (96.3)	< 0.001
Other antihypertensive medication (amlodipin, doxacor, nitrendipin)	2 (13.3)	1 (1.9)	0 (0)	7 (13.0)	0.10
Functional impairment					
Karnofsky performance index, *n* (%)					< 0.001
≥ 80	15 (100)	39 (75.0)	27 (100)	45 (83.3)	
< 80	0 (0.0)	13 (25.0)	0 (0)	9 (16.7)	
NYHA class, *n* (%)					< 0.001
I	15 (100)	23 (44.2)	23 (85.2)	7 (12.9)	
II	0 (0.0)	15 (28.8)	3 (11.1)	16 (29.6)	
III/IV	0 (0.0)	14 (26.9)	1 (3.7)	31 (57.4)	
Risk classification, *n* (%)					
Gillmore					< 0.001
I	15 (100)	30 (57.7)		16 (29.6)	
II	0 (0.0)	14 (26.9)		26 (48.1)	
III	0 (0.0)	8 (15.4)		12 (22.2)	
Medical history, *n* (%)					
Pacemaker implantation	0 (0.0)	10 (19.2)	1 (3.7)	13(24.0)	0.03
Diabetes mellitus	0 (0.0)	3 (5.7)	0 (0)	9 (16.7)	0.02
Atrial fibrillation	1 (6.7)	16 (30.8)	3 (11.1)	35 (64.8)	< 0.001
ECG findings					
Number of bundle branch blocks	0.14 ± 0.36	0.70 ± 0.85	0.19 ± 0.49	1.1 ± 0.8	< 0.001
Sinus rhythm, *n* (%)	14 (93.3)	37 (71.2)	24 (88.9)	26 (48.1)	< 0.001
Pace maker rhythm, *n* (%)	0 (0.0)	4 (7.7)	0 (0)	7 (13.0)	0.11
Low voltage pattern, *n* (%)	2 (13.3)	9 (17.3)	0 (0)	8 (14.8)	0.18
Heart frequency (bpm)	68.8 ± 14.3	74.2 ± 14.5	69.4 ± 10.6	79.6 ± 13.9	0.006
PQ interval (ms)	142.1 ± 30.1	176.8 ± 39.2	158.3 ± 25.6	210.3 ± 41.9	< 0.001
QRS time (ms)	99.8 ± 16.6	112.7 ± 30.2	97.3 ± 11.4	128.0 ± 33.3	< 0.001
QTc duration (ms)	402.4 ± 15.9	432.8 ± 42.4	400.6 ± 12.5	445.7 ± 32.5	< 0.001
Echocardiography					
Posterior wall (mm)	9.5 ± 1.9	14.0 ± 0.5	10.0 ± 0.3	15.4 ± 3.2	< 0.001

IVS (mm)	10.9 ± 1.9	17.0 ± 0.7	11.0 ± 0.3	19.2 ± 3.9	< 0.001
Ejection fraction (%)	58.7 ± 2.2	52.5 ± 1.4	60.0 ± 1.9	44.3 ± 11.3	< 0.001
Diastolic dysfunction, *n* (%)	3 (20.0)	40 (76.9)	4 (14.8)	49 (90.7)	< 0.001
Global longitudinal strain	-14.6 ± 14.2	-12.0 ± 0.7		-9.8 ± 4.0	< 0.001
MAPSE (mm)	1.5 ± 0.3	1.1 ± 0.3	1.6 ± 0.09	0.9 ± 0.3	0.09
TAPSE (mm)	2.3 ± 0.4	1.8 ± 0.2	2.1 ± 0.1	1.5 ± 0.6	0.02
Pericardial effusion, *n* (%)	0 (0.0)	3 (5.8)	0 (0)	6 (11.1)	0.31
PA pressure (mmHg)	26.0 ± 4.1	31.0 ± 1.0	25.0 ± 1.3	35.8 ± 9.8	0.005
Biomarkers					
NtproBNP(ng/L)	173.6 ± 260.6	3457.3 ± 4321.9	258.8 ± 35.2	7219.4 ± 8213.5	< 0.001
hsTNT (pg/mL)	4.7 ± 2.4	59.0 ± 95.4	8.1 ± 7.6	63.6 ± 40.7	< 0.001
GFR (mL/min)	101.1 ± 14.6	75.9 ± 24.9	96.3 ± 22.1	55.8 ± 18.6	< 0.001

ACE: Angiotensin converting enzyme; AT1: Angiotensin type 1; ATTRv: Variant transthyretin amyloidosis; ATTRwt: Wild-type transthyretin amyloidosis; BMI: Body mass index; NtproBNP: N-terminal pro-brain natriuretic peptide; ECG: Electrocardiogram; GFR: Glomerular filtration rate; IVS: Intravenous sedation; MAPSE: Mitral annular plane systolic excursion; NYHA: New York Heart Association; TAPSE: Tricuspid annular plane systolic excursion; TNT: TroponinT.



Group	Median	Mad
Ctrl	4.18	0.79
Asym ATTRv	4.18	0.61
ATTRv	4.58	0.81
WT	5.52	1.59

Group	Median	Mad
Ctrl	4.18	0.80
Gillmore 1	4.31	0.61
Gillmore 2	5.47	1.55
Gillmore 3	6.05	2.03

Figure 2 Interleukin-6 values are depicted according to study group or Gillmore class. A: Study group; B: Gillmore class. Ctrl: Control group; asym ATTRv: Asymptomatic ATTRv; ATTRv: Symptomatic ATTRv amyloidosis; WT: Wild-type ATTR amyloidosis. Linear model *P* values for two-group comparisons and trend-test (Jonckheere-Terpstra). Median and median absolute deviation (mad) of non-log and non-z transformed data (pg/mL). Red dashed line: Median interleukin-6 value per group.

Symptomatic patients with hereditary ATTRv-CM showed slightly increased levels of IL-6 with 4.58 pg/mL (0.81) not reaching significance ($P = 0.63$). In contrast, ATTRwt patients showed significant increased median IL-6 levels compared to controls [5.52pg/mL (1.59), $P = 0.03$]. IL-6 levels showed an increase from control and Gillmore class 1 to Gillmore classes 2 and 3 (trend-test, $P < 0.001$). Median IL-6 levels were significantly increased in Gillmore 2 and 3 *vs* Gillmore 1 (Figure 2B).

IL-6 is associated with cardiovascular events in ATTR-CM

IL-6 levels were analyzed using parametric survival models to identify best separating cutoffs for the prognostic separation of patients for both evaluated endpoints. For death/htx endpoint, a cutoff of -0.24, corresponding to 4.68 pg/mL was identified (low: n = 78; high: n = 70).

For MACE, a cutoff of -0.31, corresponding to 4.85 pg/mL, was identified (low: n = 72; high: n = 76). For 117 of 148 patients (79%), follow-up after index event was available. Median follow-up was 13.5 [95% confidence interval (CI): 11.6-15.7] months for death/htx and 13.6 (95%CI: 11.7-15.9) months for MACE.

During follow-up period, 19 patients died, six were listed for high urgent heart transplantation, two died waiting for the organ and two patients were successfully transplanted. Fourteen patients were hospitalized due to cardiac decompensation requiring additional treatment with diuretics for recompensation. Twenty-four patients reached at least one of the prespecified combined endpoints. Patients with increased IL-6 levels had a higher risk for MACE (P = 0.01) or death/htx (P = 0.006) (Figure 3).

IL-6 allows improved risk prediction in NTproBNP positive patients and in cTnT negative patients

Two well established biomarkers for risk stratification in ATTR-CM are cTnT and NTproBNP levels[21-23]. Therefore, we repeated our risk assessment for patients in these two high-risk subgroups. In patients with low NTproBNP levels, no prespecified endpoint was observed during follow-up. In patients with elevated NTproBNP levels (above 450 ng/mL[24-26]), high IL-6 levels were significantly associated htx/death (P = 0.01) and a clear trend for increased incidence of MACE could be observed (P = 0.052). Dividing our cohort according to the established cutoff for cTnT of 50 ng/mL identified in the groups with cTnT negative group a prognostic separation for death/htx endpoint (P = 0.02) and a borderline significant prognostic separation for MACE (P = 0.049). In the cTnT negative group no significant prognostic separation was found (Figure 4).

IL-6 is no independent risk predictor in ATTR-CM

To estimate the value of IL-6 for the prespecified endpoints htx/death as well as MACE, we performed an univariate survival analysis for established risk parameters as age, NYHA classification, gender, GFR, echocardiographic parameters (mitral annular plane systolic excursion, end diastolic diameter, septum thickness, estimated heart weight) and Gillmore class and biomarkers (cTnT, NTproBNP). Furthermore inflammatory markers as CRP and leukocyte count were included as well as IL-6. As shown in Figure 1, age, NYHA class, GFR, cTnT, NTproBNP, heart weight, septum thickness, Gillmore class and IL-6 showed significant association with htx/death. The same characteristics were also significantly associated with MACE, but also CRP levels and EDD showed a significant correlation with MACE. The odds ratio (OR) for low IL-6 and htx/death was 0.15 (P = 0.006), and for MACE, OR of low *vs* high IL-6 was 0.26 (P = 0.01).

To test for independent risk prediction of IL-6, a multivariate analysis was calculated including IL-6 and all other parameters significant in the univariate model except for the combined feature Gillmore. However, in the multivariate model, IL-6 did not improve risk stratification, neither for htx/death [OR: 0.42; 95%CI (0.06-2.83); P = 0.37] nor MACE [OR: 1.11; 95%CI (0.23-5.29); P = 0.89] (Supplementary Figure 2).

DISCUSSION

In the present monocentric prospective study, elevated IL-6 levels were found in patients with ATTRwt amyloidosis but not aATTRv-CM carriers or ATTRv-CM patients. IL-6 concentrations correlated with severity of clinical presentation as quantified in the Gillmore classification. Furthermore, IL-6 levels were significantly associated with clinical outcome as death/htx or MACE in the univariate analysis. However, in the multivariate analysis IL-6 did not show a significant additional value over established risk predictors.

Elevated IL-6 levels have been described in amyloid A (AA) amyloidosis and ATTRv-PN. AA amyloidosis is a secondary amyloidosis in chronic inflammatory diseases (*e.g.*, rheumatoid arthritis)[27]. In these patients, application of the human monoclonal antibody tocilizumab directed against the IL-6 receptor induced rapid

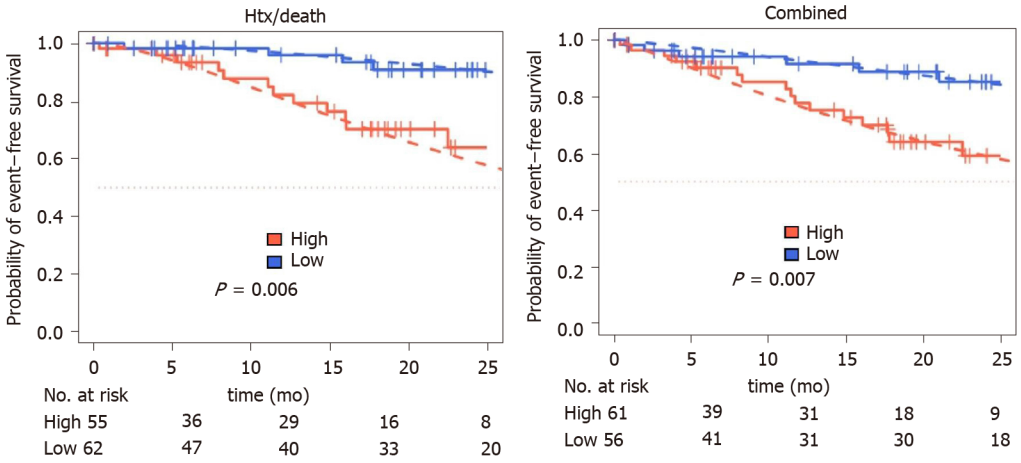


Figure 3 Kaplan-Meier curves for combined, decompensation and death or heart transplantation endpoints for dichotomized interleukin-6. Dashed: Parametric survival regression (log logistic distribution), wild-type *P* values.

clinical improvement without influencing the amyloid deposits[28,29]. Therefore, for AA-amyloidosis the IL-6 axis is known to be causally involved in the pathogenesis of the inflammatory disease. In contrast, for ATTRv-PN data are inconsistent: Increased IL-6 levels were found independent from clinical presentation: Asymptomatic mutation carriers as well as symptomatic ATTRv-PN patients show increased IL-6 levels[11]. On the other hand no differences for IL-6 were seen in the study by Azevedo *et al*[10] in the same cohort. These data suggest that mutated TTR might be able to evoke an inflammatory state but not sufficient to establish the disease. Therefore, other factors have to be present, which are not identified yet. In contrast, in our cardiac cohort ATTRwt patients show elevated IL-6 levels, however, aATTRv-CM carriers or ATTRv-CM patients did not. Therefore, in patients with preferentially cardiac manifestation of ATTR amyloidosis, IL-6 rather seems to be secondary to the manifestation of the disease as sign of heart failure but not preceding the organ affection and, therefore, not causing the manifestation in the first hand.

In the large BIOSTAT-CHF cohort (n = 2329 patients) IL-6 levels were elevated in patients with heart failure and HFpEF, atrial fibrillation or elevated NTproBNP levels[5]. These clinical findings are often present in ATTR-cardiomyopathy patients as well. During the last years new diagnostic methods and novel therapeutic approaches raised awareness for ATTR cardiomyopathy enabling differentiation between cardiac amyloidosis and HFpEF from other reasons. On a molecular basis, activation of the IL-6 axis is known to induce concentric hypertrophy and diastolic dysfunction in rats, which might contribute to the pathology in ATTR-CM[30]. In line with these data, a correlation of IL-6 levels with clinical severity and prognosis of ATTR-CM could be observed in the herein project; however, in the multivariate analysis including well established risk factors no additional value was seen in the IL-6 quantification. Therefore, IL-6 rather seems to be a factor associated with heart failure irrespective of the underlying disease.

CONCLUSION

Taken together, raised IL-6 levels correlate with clinical presentation and are associated with worse outcome in ATTR-CM, but do not improve stratification in addition to established risk factors. Since molecular animal studies suggest a contribution of IL-6 to the manifestation of heart failure and pathological remodeling[7,31], a study interfering with the IL-6 axis is needed to prove this concept in patients with heart failure in general and ATTR-CM amyloidosis specifically. Our data show an association to severity and prognosis of the disease; evidence for causality in the pathogenesis cannot be provided here. Since the multivariate analysis did not show a significant association, further research is needed to improve risk stratification.

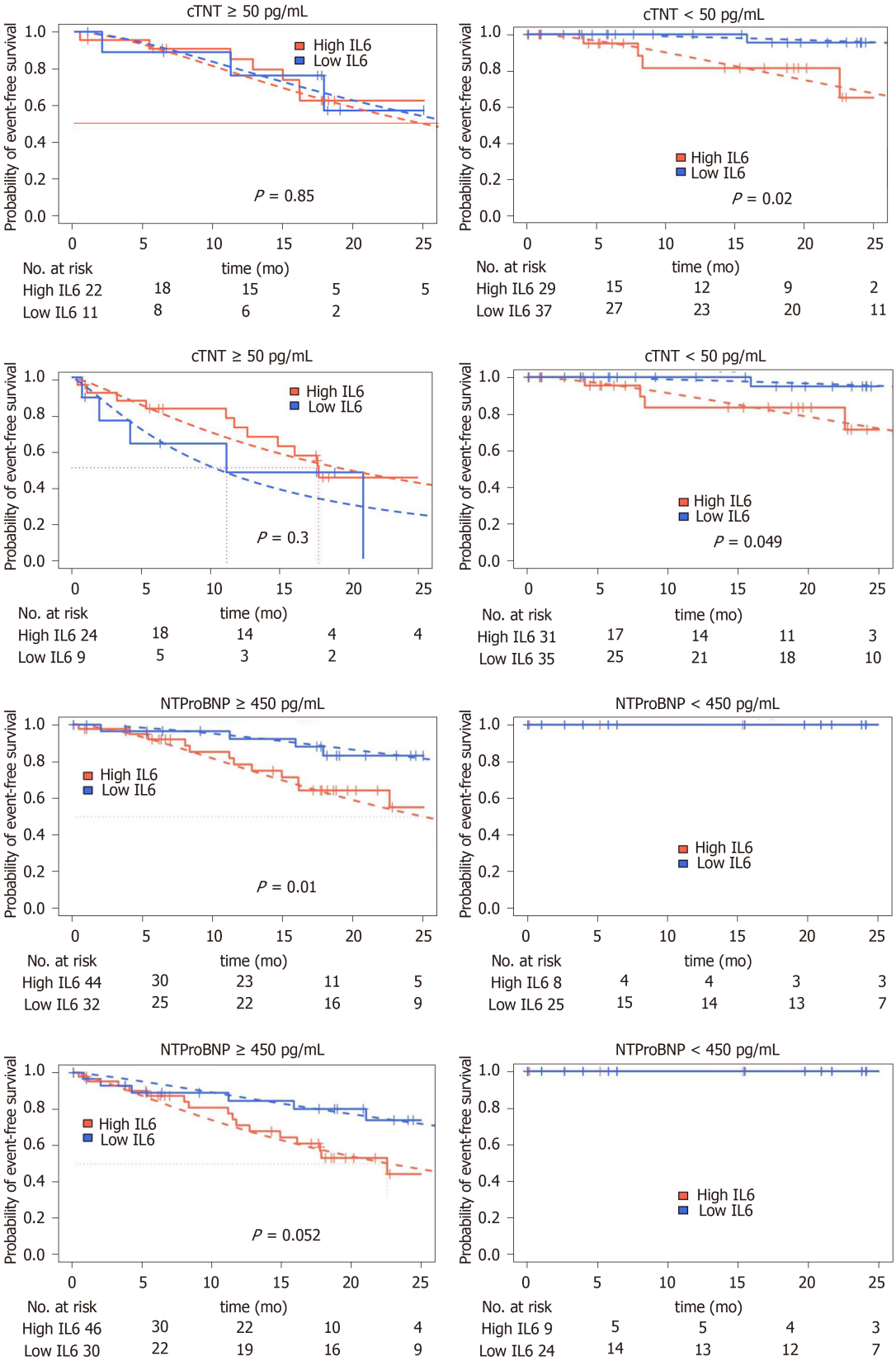


Figure 4 Kaplan-Meier curves for combined, decompensation and death or heart transplantation endpoints for dichotomized interleukin-6 in N-terminal pro-brain natriuretic peptide and TroponinT stratified patients. Dashed: Parametric survival regression (loglogistic distribution), likelihood ratio *P* values. cTNT: cardiac TroponinT; IL6: Interleukin-6; NTProBNP: N-terminal pro-brain natriuretic peptide.

ARTICLE HIGHLIGHTS

Research background

In transthyretin cardiac amyloidosis (ATTR), protein deposition leads to myocardial thickening and heart failure, which is defined as ATTR cardiomyopathy (ATTR-CM). Recently, evidence was raised that inflammation might be associated with disease progression in ATTR polyneuropathy and heart failure. But until now little is known about the inflammatory state in ATTR-CM. Therefore, we measured IL-6 levels in ATTR-CM and analyzed its predictive value for cardiac outcome.

Research motivation

In ATTR-CM stable disease over several years as well as rapidly progressive disease courses are described. This discrepancy might results from differences in immunological response to myocardial protein deposits in ATTR-CM.

Research objectives

The objective of the study was to investigate differences in IL-6 levels and evaluate its predictive value for cardiovascular outcome (death/heart transplantation, decompensation or a combined endpoint).

Research methods

In this monocentric prospective study, 106 ATTR-CM patients were included, and IL-6 levels were measured using Luminex technology. Follow-up period was 12 mo, and statistical analysis was performed using parametric survival regression models.

Research results

IL-6 is associated with outcome in ATTR-CM but does not improve risk stratification in addition to established risk prediction parameters. The study thereby provides evidence that IL-6 axis might be involved in the pathogenesis of ATTR-CM. To investigate this hypothesis further, additional studies are needed.

Research conclusions

The study showed that IL-6 is associated with outcome in ATTR-CM but does not add further risk stratification potential to established risk prediction models.

Research perspectives

Further studies are needed to investigate inflammatory response in ATTR-CM.

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OPINION REVIEW

Drug-induced gingival overgrowth in cardiovascular patients

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Abstract

Drug-induced gingival overgrowth (DIGO) is a pathological growth of gingival tissue, primarily associated with calcium channel blockers and immunosuppressants. Consequently, it is mainly seen in cardiovascular and transplanted patients. Nifedipine remains the main calcium channel blocker related to the development of this unpleasant side-effect. As for immunosuppress-ants, cyclosporin is the leading causative agent, whereas other drugs from this drug-group, including tacrolimus, have better safety profiles. Accumulated collagen with inflammatory infiltrates is the histological hallmark of this condition. Several factors are involved in the pathogenesis and can increase the risk, such as male gender, younger age, pre-existing periodontal inflammation, and concomitant use of other DIGO-inducing medications. Patients with DIGO may experience severe discomfort, trouble with speech and mastication, pain, and teeth loss, aside from cosmetic implications. Furthermore, these patients also have an increased risk for cardiovascular diseases. The interdisciplinary approach and cooperation with dental care experts are necessary for patient management. Treatment includes discontinuing the drug and switching to one with a better profile, improving oral hygiene, and surgical removal of enlarged tissue. Recognizing the potential of commonly used medications to cause DIGO and its effect on patients' health is necessary for early detection and adequate management of this complication.

Key Words: Drug-induced gingival overgrowth; Calcium channel blocker; Nifedipine;

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Core Tip: Drug-induced gingival overgrowth is a side-effect of the drugs such as calcium channel blockers and immunosuppressants, commonly used in cardiovascular and transplanted patients. The condition is multifactorial and mainly depends on the potential of the used drug to cause gingival changes and the state of oral hygiene. Patients who develop drug-induced gingival overgrowth may experience severe discomfort and pain in addition to troubles with mastication, speech, and maintaining oral hygiene. Since it significantly reduces the quality of life, preventive and curative measures should be implemented as part of a care plan for patients at risk.

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INTRODUCTION

Drug-induced gingival overgrowth (DIGO) is a pathological growth of the gingiva characterized by the accumulation of connective tissue that primarily affects the anterior regions of the maxilla and mandibula[1-3]. The first large DIGO case series was described in 1939, showing DIGO in 68 out of 119 patients treated by antiepileptic drug phenytoin[4].

Since then, various medications showed to be associated with this side-effect[5]. Although more than 20 different drugs are now known to cause DIGO, it most frequently results from calcium channel blockers (CCBs) and immunosuppressants[6,7]. Antiepic drugs (*e.g.*, phenytoin, valproic acid, phenobarbital, vigabatrin) are recognized as a prominent group of medications causing DIGO, although in recent years, cases of DIGO resulting from these drugs were less frequently reported[8].

Cardiovascular and transplanted patients are at particular risk due to the extensive use of CCBs alone or in combination with immunosuppressants[9,10]. Significant variability among patients medicated with the same drugs is observed[1], indicating the importance of additional risk factors involved in the pathogenesis. Genetic factors, male gender, bacterial plaque, and gingival inflammation are associated with increased DIGO risk[11]. Aside from the cosmetic effect, which is the most apparent feature, patients who develop DIGO experience difficulty maintaining oral hygiene, pronunciation, and mastication. Simultaneously, the extensive disease can cause pain and loss of the teeth. As a result, quality of life is reduced significantly[12,13]. Since this side-effect is not rare in a group of cardiovascular patients, oral health needs to be emphasized and included as part of a care plan for patients treated with the drugs mentioned above.

CLINICAL FEATURES AND PATHOGENESIS

DIGO usually starts as painless enlargement of interdental papillae and progresses towards facial and lingual margins, covering the teeth crowns. Fully developed, it forms generalized changes throughout the mouth, affecting the anterior gingiva the most[5], although it can also occur as a localized lesion[14]. A possible explanation for the predominance of lesions in anterior regions could be higher exposure of anterior gingiva to the irritation resulting from plaque[15]. DIGO initially appears as pink, lobulated, and thickened gingival tissue without concomitant inflammation, with no tendency to bleed[5,16]. In its course it becomes inflamed with red or bluish-red discolorations and frequent bleeding[5]. As it progresses, it spreads both vertically and horizontally and affects mastication and speech[14].

In advanced forms, enlarged gingiva may even interfere with the occlusion[5]. Patients with DIGO have problems maintaining oral hygiene, which leads to susceptibility to infections and periodontal disease and may result in the loss of the teeth[14]. A weakened immune system predisposes to more severe periodontal disease and puts patients on immunosuppressants at additional risk[17]. Furthermore, periodontitis may potentially carry a risk for cardiovascular diseases, including myocardial infarction, peripheral artery disease, stroke, and heart failure. In theory, possible mechanisms behind this association could be dissemination of oral pathogens into the bloodstream and invasion of cardiovascular organs and tissues to induce inflammatory response on a local and systemic level[18]. Additionally, periodontitis is associated with endothelial dysfunction, an important factor in atherosclerosis development[18,19]. Aside from the functional impairment and cardiovascular risk, gingival changes also represent a significant esthetic problem for the patients[14].

Etiopathology of DIGO is multifactorial and not fully understood[2,20]. Genetic factors (cytochrome P450, HLA, and MDR1 gene polymorphisms) influence the interindividual difference in gingival response to DIGO-inducing drugs and could have a role in identifying patients at risk[2,21,22]. The main histological finding in DIGO is the accumulation of collagen in the gingiva's extracellular matrix, along with the infiltration of inflammatory cells[1]. Most of the DIGO-inducing drugs act as inhibitors of calcium ion influx[23]. An inhibited influx of cations into fibroblasts causes a decrease in cation-dependent folic acid uptake. Folic acid is necessary for the proper function of matrix metalloproteinases, which activate collagenase. With no collagenase, there is no collagen breakdown, and it accumulates in connective tissue[1]. Furthermore, studies demonstrated a drug-induced increase in glycosaminoglycans[1] and collagen[24] production along with the proliferation of gingival fibroblasts[25]. These changes are mainly mediated by inflammatory cytokines that are a part of an inflammatory response to drugs[23]. Inflammatory infiltrates found in the gingiva mainly consist of plasma cells[26]. Periodontal status is a significant predictor of DIGO, as bacterial plaque induces inflammation. A significant correlation was found between bacterial plaque and a higher risk for DIGO in patients treated with CCBs or cyclosporin[1,15,27]. In gingival tissue of patients with CCBs-associated DIGO, higher expression of androgen receptors accompanied with higher levels of type I collagen were detected, implying androgens' role in its pathogenesis[28].

DIGO-INDUCING DRUGS

The first CCB-DIGO cases date from the early 80-ties, primarily associated with nifedipine[29] and later with the use of other CCBs such as verapamil, diltiazem, amlodipine, and felodipine[30]. Early studies demonstrated the highest prevalence in patients on nifedipine (6.3%), which remains to date the leading cause of DIGO in this drug group. Other CCBs, such as amlodipine (1.7%) and diltiazem (2.2%), have a lower potential to cause DIGO[31]. The various prevalence of DIGO among different CCBs may be a consequence of pharmacokinetic characteristics, as nifedipine is more lipophilic, so it passes through cell membranes more quickly and has a half-life which allows it to reach peak levels in the plasma needed for the initiation of gingival changes[31]. However, the prevalence of DIGO caused by CCBs varies in various studies, as for CCBs in general, it ranges between 10%-20%[32]. It amounts from 15% to 85%[33,34], for nifedipine, meaning that there are additional influencing factors. Male gender, drug dosage, smoking, periodontal status, previous myocardial infarction, and concomitant use of diuretics or antiepileptic drugs increase the risk of developing DIGO in CCBs users[12,31,35]. However, drug dosage depends mostly on pharmacokinetics and pharmacodynamics and is thought to be an unreliable predictor[36]. The majority of cases develop in the first six months of therapy, with the greatest occurrence in the first month, whereas the incidence decreases with long-term use[12]. On the other hand, the study of Hatahira *et al*[13] detected a median time to onset of 262 d, so long-term monitoring is still needed for patients who will develop the changes later. DIGO occurs less often using other antihypertensive drugs, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers[3,37]. Therefore, in patients at risk for developing DIGO or those who already did, switching to CCBs with better safety profiles or other antihypertensive drugs is a treatment option.

Cyclosporin and tacrolimus, from the group of calcineurin inhibitors, are the leading cause of DIGO among immunosuppressive drugs[38]. Cyclosporin was the primary immunosuppressive drug in heart-transplant patients since 1980[39]. Many

heart transplant recipients (8.3%-67%) develop gingival enlargement, most of whom are treated with cyclosporin[40]. The role of cyclosporin as an inducing drug in DIGO development is well known and recognized[41]. Gingival changes in patients treated with cyclosporine show symmetry between mandibula and maxilla and within the jaw, while incisors and canines are affected the most[15]. According to the research of Hatahira *et al*[13], 70% of gingival overgrowth is attributed to cyclosporin. On the other hand, tacrolimus is another immunosuppressant often used as an alternative to cyclosporin in primary or rescue therapy[27]. It is 100 times more potent and tends to cause some side-effects common to other immunosuppressants[27,42]. However, it less often causes gingival overgrowth, and changes are less severe than those caused by cyclosporin[27]. The prevalence of DIGO among tacrolimus treated patients is around 14%[27,43]. DIGO can be detected as soon as 1-3 mo after immunosuppressive therapy initiation, and the plateau phase is reached at 9-12 mo[44]. However, gingival changes resulting from tacrolimus use appear later compared to cyclosporin, as in various studies, no changes were observed before 90 d of treatment[38,45]. Interestingly, immunosuppressants differ from other DIGO-inducing drugs since high inflammation levels and low fibrosis mostly mediate the changes[46]. Some of the predisposing factors among cyclosporin users are male gender, gingivitis, bacterial plaque, and higher cyclosporine concentrations[15,22]. Furthermore, younger patients are more frequently affected by DIGO[15], and high rates have been reported among the group of pediatric heart-transplant patients treated with cyclosporin[39,47,48]. Younger age was also a risk factor for more severe changes in patients on tacrolimus[27]. Different therapeutic patterns and higher potential of fibroblasts to proliferate and produce collagen in a group of younger patients could be a possible explanation[15,49]. Additionally, a higher risk for DIGO in tacrolimus users was observed in patients with the worse periodontal state, those previously medicated with cyclosporin[27], and a with longer duration of tacrolimus therapy[50]. The occurrence and severity of changes also depend on the concomitant use of other medications. Simultaneous use of cyclosporin and CCBs doubles the risk for DIGO, compared to using cyclosporin alone (51.9% *vs* 25%)[22]. Furthermore, the use of CCBs in tacrolimus-treated patients results in higher severity of gingival changes[27]. These findings indicate the synergistic effect of CCBs and calcineurin inhibitors. On the contrary, azathioprine has a protective effect in patients on cyclosporin or tacrolimus and lowers the risk for DIGO[27,51]. Although tacrolimus provides a better safety profile regarding DIGO and could be a treatment option in patients with cyclosporin-induced gingival overgrowth, it is important to point out that in some cases, changes persist even after the switching of therapy, especially with concomitant use of CCBs[27].

TREATMENT OPTIONS

Management of DIGO can be conservative or surgical, with the aim to provide a satisfactory cosmetic outcome and minimize discomfort and pain[1]. Non-surgical methods are the treatment of choice, including proper oral hygiene and mechanical removal of dental plaque, together with the mandatory exclusion of the offending drug[14]. Periodontal treatment reduces inflammation and prevents the need for surgical treatment in cyclosporin-treated patients[52]. A rigorous oral hygiene regime has been recommended for patients with DIGO resulting from CCBs use[32]. Since a worse periodontal state has been associated with a higher risk for DIGO[15,27], preventive measures targeting oral health could be valuable. Reduction of drug dose or switching to that of a lower potential for side-effects should always be considered, if possible. In that case, complete improvement can be expected in 1-8 wk[53] (Figure 1).

Stopping the use of CCBs or switching to non-CCB antihypertensives provides satisfactory results, but it is not always possible, as some patients may have problems controlling their hypertension[54]. In an attempt to treat gingival overgrowth caused by cyclosporin, replacing this medication with tacrolimus or everolimus remains an option[55,56] (Figure 2).

Flutamide, an androgen receptor antagonist, inhibits gingival cells' response to nifedipine and could be used to prevent or treat nifedipine associated DIGO[28]. Non-surgical methods are often not sufficient if the drug cannot be withdrawn for other reasons[54]. Persistent DIGO requires surgical treatment, which could either involve gingivectomy or periodontal flap[57]. The use of carbon dioxide lasers is a solid choice that provides adequate postoperative hemostasis[23]. Recurrence of DIGO after surgical treatment was reported in about 40% of the patients still treated with the offending drug[58]. In conclusion, the prognosis of DIGO is good, as it can be successfully

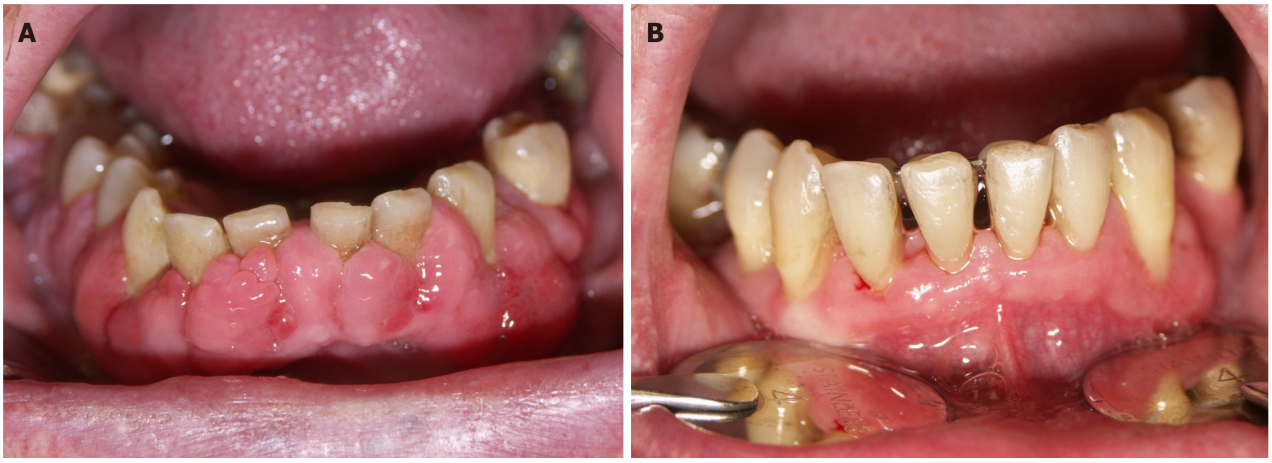


Figure 1 A complete response of a severe drug-induced gingival overgrowth case following seven weeks after amlodipine removal and six consecutive tooth scaling and cleaning treatments. A: Amlodipine induced gingival overgrowth successfully treated by vigorous weekly plaque control; B: Calculus removal during seven weeks following the drug withdrawal and substitution by angiotensin-converting enzyme inhibitor (courtesy of Prof. Vlaho Brailo).



Figure 2 An improvement in a heart transplant patient, whose medication included both cyclosporin and amlodipine, four weeks following professional teeth cleaning and switching to tacrolimus and alternative antihypertensive drug. A and B: Gingival overgrowth in a heart transplant patient receiving both cyclosporin and amlodipine; C and D: An improvement is observed following conservative periodontal treatment and four weeks of switching to tacrolimus and angiotensin-converting enzyme inhibitor.

managed and resolved with discontinuation of the inducing drugs[1].

CONCLUSION

Since CCBs and immunosuppressants are widely used medications in patients with hypertension or after heart transplantation[9,10], health professionals should be aware of gingival overgrowth as an unpleasant side-effect that can result from the use of these drugs[23,55]. Although it might not be life-threatening, it poses a significant problem for the patients, not only because of the cosmetic effect but also due to the impairment of speech, eating, and maintaining oral hygiene[12,13]. Furthermore, infections resulting from the lack of proper oral hygiene could enhance the risk for cardiovascular diseases[59]. Recognizing the importance of DIGO and its effect on the patients' health is crucial for providing better health outcomes and satisfactory quality of life. If possible, treatment of choice should be changing of a drug and conservative periodontal treatment, whereas surgical treatment is reasonable only in resistant cases. Since it is multifactorial and reoccurs if the drug must be continued, efforts need to be made to find each patient's optimal treatment. An interdisciplinary approach and cooperation of medical and dental professionals are necessary to reach this goal.

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EVIDENCE-BASED MEDICINE

Challenges in managing ST elevation myocardial infarction during the COVID-19 pandemic

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) may contribute to delayed presentations of acute myocardial infarction. Delayed presentation with late reperfusion is often associated with an increased risk of mechanical complications and adverse outcomes. Inherent delays are possible as every patient who is acutely sick is being considered a potential case or a career of COVID-19. Also, standardized personal protective equipment precautions are established for all members of the team, regardless of pending COVID-19 testing which might further add to delays.

AIM

To compare performance measures and clinical outcomes of all patients who presented to our facility with ST elevation myocardial infarction (STEMI) during the COVID-19 pandemic to same time cohort from 2019.

METHODS

All patients who presented to our facility with STEMI during the pandemic were compared to a matched cohort during the same time period in 2019. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to

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14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke. Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS
There was a significantly longer time interval from symptom onset to first medical contact (FMC) in the COVID-19 group ($P < 0.02$). Time to first electrocardiogram, door-to-balloon time, and FMC to balloon time were not significantly affected. The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive (> 50%) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

CONCLUSION
This single academic center study in the United States suggests that there is a delay in patients with STEMI seeking medical attention during the COVID-19 pandemic which could be translating into worse clinical outcomes.

Key Words: COVID-19; ST elevation myocardial infarction; First medical contact to balloon; Major adverse cardiac events; Cardiac arrest; Death

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has affected every aspect of healthcare and has created multiple challenges in treatment of time sensitive conditions like ST elevation myocardial infarction (STEMI). We aimed to assess the behavior of presentation and outcomes of all the STEMI admissions at our facility between March 16, 2020 and August 31, 2020. We found a significantly delay from symptom onset to first medical contact in the COVID-19 group which likely resulted in significantly higher in-hospital major adverse cardiac events (MACE) and MACE at 14 d in this cohort.

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INTRODUCTION

The pandemic caused by the coronavirus disease 2019 (COVID-19) has caused a complete global shutdown and greatly affected every aspect of life, especially in the healthcare field. This has created multiple challenges in treatment of time sensitive and potentially lethal conditions like acute ST elevation myocardial infarction (STEMI). The consensus from the American College of Cardiology for management of STEMI recommends maintaining the standard of care with primary percutaneous coronary intervention, as long as there is adequate supply of resources, personal protective equipment availability, and cardiac catheterization staff. In absence of these resources, fibrinolysis should be first line treatment. Patients who are felt to be high risk for COVID-19 are recommended to be evaluated with additional cardiac studies, COVID-19 testing, and may require respiratory support, all of which may delay door-to-balloon times[1].

Over 85% of the hospitals in the United States are considered community hospitals, yet the majority of studies are represented by university hospital systems[2]. In April 2020, Bowling Green, Kentucky was named one of the top ten COVID-19 hotspots in the United States[3]. Medical Center Health is a community hospital system in Bowling

Green, Kentucky with six hospitals covering ten counties in south central Kentucky, serving a population of more than 300000, and treating over 100 STEMI patients *per* year.

Given the limited observational studies guiding management of critical patients with STEMI during this pandemic, our study reports a United States community hospital's experience of management and outcomes of adult patients presenting with STEMI. One report from Hong Kong found large delays in patients seeking medical help and delays in evaluating patients with STEMI after hospital arrival but was limited by small sample size[4]. Extensive literature review revealed no such reports from United States hospitals as of yet.

MATERIALS AND METHODS

We compared performance measures and outcomes of all patients who presented to our facility with STEMI between March 16, 2020 (when Kentucky began incorporating emergency infection protocols, mandating stay-at-home orders, and halting all elective procedures) and August 31, 2020. This study period was compared to a matched cohort during the same time period in 2019. Every patient in the 2020 group was considered a possible COVID-19 carrier, although none of our patients tested positive for COVID-19. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to 14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke.

Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

A total of 52 patients from 2019 and 48 patients from 2020 were included. Baseline demographics and comorbidities are presented in Table 1. Age, gender, comorbidities, Killip score, and ejection fraction were well matched between the two groups. There was a significantly longer time interval from symptom onset to first medical contact (FMC) in the COVID-19 group ($P < 0.02$). Time to first electrocardiogram (ECG), door-to-balloon time, and FMC to balloon time were not significantly affected. The location of myocardial infarction and the state of culprit and non-culprit artery at the time of cardiac catheterization is detailed in Table 1. The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive (> 50%) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

DISCUSSION

Our study describes a United States acute care teaching hospital's experience in STEMI care utilizing emergency COVID-19 infection protocol. Contrary to reports out of major cities citing a decrease in STEMI patients, we noted a stable number of total STEMI cases compared with years prior[5]. The time interval from symptom onset to FMC was significantly longer in the COVID-19 group, which was likely due to the general fear of contracting COVID-19 in the healthcare setting. Triaging (time to first ECG) and performance measures (door-to-balloon time and FMC to balloon time) were not significantly different. We suspect that this was due to the long-standing efficient systems in place to triage and treat STEMI patients, as well as lower overall cardiac catheterization case volume allowing readily available personnel and staff for a faster throughput, despite the additional infection control protocol in triaging patients during this pandemic. MACE in-hospital and at 14 d was significantly higher in the COVID-19 group. In the 2019 group, in-hospital MACE was composed of 25% cardiac arrests (2 out of 8 patients), in contrast to the COVID-19 group, where in-hospital MACE was composed of 89% cardiac arrests (16 out of 18 patients). More cardiac arrests in the COVID-19 era could be due to late presentation to a medical facility,

Table 1 Characteristics and outcomes of patients presenting with ST elevation myocardial infarction during March-August 2019 (2019 Match Group) and March-August 2020 (coronavirus disease group)

	2019 Match		2020 COVID		*P* value
Patient characteristics					
Age (yr), mean ± SE	*n* = 52	60.23 + 1.77	*n* = 48	62.73 + 1.80	0.45
Females, *n* (%)	*n* = 52	43 (82.7)	*n* = 48	33 (68.8)	0.10
Comorbidities, mean ± SE	*n* = 47	2.67 ± 0.22	*n* = 44	2.74 ± 0.22	0.83
Hypertension, *n* (%)	*n* = 52	36 (69.2)	*n* = 48	35 (72.9)	
Hyperlipidemia, *n* (%)	*n* = 52	30 (57.7)	*n* = 48	28 (58.3)	
Diabetes, *n* (%)	*n* = 52	14 (26.9)	*n* = 48	18 (37.5)	
Coronary artery disease, *n* (%)	*n* = 52	21 (40.4)	*n* = 48	15 (31.3)	
Obesity, *n* (%)	*n* = 52	15 (28.8)	*n* = 48	19 (39.6)	
Smoking, *n* (%)	*n* = 47	20 (42.6)	*n* = 44	19 (43.2)	
Killip score (mean ± SE), *n* (%)	*n* = 52	1.10 ± 0.08	*n* = 48	1.27 ± 0.13	0.25
0		1 (1.9)		1 (2.1)	
1		49 (94.2)		42 (87.5)	
2		0 (0.0)		0 (0.00)	
3		0 (0.0)		1 (2.1)	
4		2 (3.9)		4 (8.3)	
Initial troponin level (ng/mL), mean ± SE	*n* = 43	2.22 ± 0.98	*n* = 45	2.38 ± 1.52	0.88
Peak troponin level (ng/mL), mean ± SE	*n* = 47	47.75 ± 7.07	*n* = 42	74.31 ± 14.25	0.20
Ejection fraction < 40, relative risk				1.99	
n (%)	*n* = 52	5 (9.6)	*n* = 47	9 (19.1)	0.17
Location and vessel involvement					
Location	*n* = 51		*n* = 48		
Anterior/anteroseptal, *n* (%)		11 (21.6)		16 (33.3)	
Anterolateral, *n* (%)		2 (3.9)		3 (6.2)	
Inferior/inferoposterior, *n* (%)		33 (64.7)		20 (41.7)	
Lateral, *n* (%)		5 (9.8)		9 (18.7)	
Culprit vessel, *n* (%)	*n* = 51		*n* = 48		0.28
LM		0		0	
RCA		31 (60.8)		22 (45.8)	
LAD		13 (25.5)		19 (39.6)	
LCx		7 (13.7)		7 (14.6)	
Non-culprit vessel stenosis ≥ 50%, *n* (%)	*n* = 32		*n* = 32		
RCA		7 (33.3)	*n* = 26	16 (61.5)	0.05
LAD		18 (47.4)	*n* = 29	17 (58.6)	0.36
LCx		16 (36.4)	*n* = 41	18 (43.9)	0.48
Patient outcomes					
Symptom onset to FMC (min), mean ± SE	*n* = 41	189.71 ± 70.18	*n* = 44	530.00 ± 143.53	0.02
Time to EKG (min), mean ± SE	*n* = 38	7.66 ± 2.31	*n* = 35	8.26 ± 2.54	0.81
Door to balloon (min), mean ± SE	*n* = 50	56.78 ± 5.65	*n* = 46	53.67 ± 3.43	0.73
FMC to balloon (min), mean ± SE	*n* = 50	89.14 ± 5.55	*n* = 42	90.02 ± 6.49	0.99

Hospital LOS (days), mean ± SE	*n* = 52	4.40 ± 0.88	*n* = 47	4.57 ± 0.50	0.87
Cardiogenic shock, relative risk				1.81	
n (%)	*n* = 52	3 (5.8)	*n* = 48	5 (10.4)	0.23
In-hospital MACE (death, MI, cardiac arrest, stroke), relative risk				2.49	
n (%)	*n* = 52	8 (15.4)	*n* = 47	18 (38.3)	0.01
MACE < 14 d from admission, relative risk				3.03	
n (%)	*n* = 52	8 (15.4)	*n* = 45	21 (46.7)	< 0.001

SE: Standard error; LM: Left main; RCA: Right coronary artery; LAD: Left anterior descending; LCx: Left circumflex; FMC: First medical contact; EKG: Electrocardiogram; MACE: Major adverse cardiac events; LOS: Length of stay; COVID: Coronavirus disease.

which was reflected by the significantly higher symptom onset to FMC time in the COVID-19 group.

Although we noticed significantly delayed presentation of patients with STEMI and higher MACE during the COVID-19 pandemic, we found that STEMI clinical performance and quality measures were maintained at the system level despite following extra infection protocol measures.

Our study has inherent limitations of a retrospective study and moreover the small sample size limits generalization of our results. While we could expect the time from symptom onset to FMC to hold, we should be cautious in assuming that the degree of delay and clinical outcomes can be generalized to healthcare facilities globally.

CONCLUSION

This study provides insight into quality control and performance metrics of an acute medical condition like STEMI during the unprecedented pandemic that has largely affected every aspect of healthcare. At our academic institute, we found that there is a delay in STEMI patients seeking medical attention during the COVID-19 pandemic which could be translating into worse clinical outcomes. Our study allows for an early experience of how this pandemic could affect treatment of acute medical conditions like STEMI.

ARTICLE HIGHLIGHTS

Research background

Treatment of time sensitive medical conditions like ST elevation myocardial infarction (STEMI) could have been adversely affected during the coronavirus disease 2019 (COVID-19) pandemic. This could be due to fear of contracting COVID-19 in the hospital setting, along with healthcare challenges such as lack of personal protective equipment and shifting policies on rapid COVID-19 testing in these acutely sick patients. All of these factors could prolong symptom onset to first medical contact (FMC) and FMC to balloon times. Prolonged time to coronary reperfusion has been shown to be related to increased mechanical complications and worse outcomes.

Research motivation

Currently no data from an academic United States institute exist on STEMI performance measures such as time to electrocardiogram, FMC to balloon, etc. during the current pandemic. There is also lack of STEMI outcomes data during the pandemic which could have been adversely affected.

Research objectives

We evaluated STEMI performance benchmarks and clinical outcomes of all patients who presented to our facility during the COVID-19 pandemic. These were compared to the same time cohort from 2019. Knowing, whether these standards are preserved currently during the pandemic is critical as it allows us to further investigate the mechanistic aspect of it and offer solution.

Research methods

All patients who presented to our facility with STEMI during the pandemic were compared to a matched cohort from 2019. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to 14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke. Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

Research results

Symptom onset to FMC time interval was significantly longer in the COVID-19 group ($P < 0.02$) when compared to 2019 cohort. Time to first electrocardiogram, door-to-balloon time, and FMC to balloon time were not significantly affected. The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive (> 50%) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

Research conclusions

This single academic center study conducted in the United States during the current pandemic reports longer time interval from symptom onset to first medical contact in patients presenting with STEMI. This is likely resulting in worse MACE outcomes when compared to the pre-COVID era as reflected from this report.

Research perspectives

Although a 'randomized control study' to assess the potential adverse impact on STEMI outcomes during the pandemic is not practical, our study provides observations from a teaching center during the 'natural experiment' conditions created by the current pandemic. Our findings suggest a need for data from bigger studies to confirm our study's pattern and outcomes.

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META-ANALYSIS

Dabigatran, rivaroxaban, and apixaban are superior to warfarin in Asian patients with non-valvular atrial fibrillation: An updated meta-analysis

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Abstract

BACKGROUND

Most of the randomized clinical trials that led to the wide use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation (AF) originated from western countries.

AIM

To systematically review and quantitatively synthesize the real-world data regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared to warfarin for stroke prevention in Asian patients with non-valvular AF.

METHODS

Medline, Cochrane, and ClinicalTrial.gov databases were reviewed. A random-effect model meta-analysis was used and I-square was utilized to assess the heterogeneity. The primary outcome was ischemic stroke. The secondary outcomes were all-cause mortality, major bleeding, intracranial hemorrhage, and

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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gastrointestinal bleeding.

RESULTS

Twelve studies from East Asia or Southeast Asia and 441450 patients were included. Dabigatran, rivaroxaban, and apixaban were associated with a significant reduction in the incidence of ischemic stroke [hazard ratio (HR) = 0.78, 95% confidence interval (CI): 0.65-0.94; HR = 0.79, 95%CI: 0.74-0.85, HR = 0.70, 95%CI: 0.62-0.78; respectively], all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83; HR = 0.66, 95%CI: 0.52-0.84; HR = 0.66, 95%CI: 0.49-0.90; respectively), and major bleeding (HR = 0.61, 95%CI: 0.54-0.69; HR = 0.70, 95%CI: 0.54-0.90; HR = 0.58, 95%CI: 0.43-0.78; respectively) compared to warfarin.

CONCLUSION

Dabigatran, rivaroxaban, and apixaban appear to be superior to warfarin in both efficacy and safety in Asians with non-valvular AF.

Key Words: Novel oral anticoagulant; Direct oral anticoagulant; Atrial fibrillation; Asian population; Dabigatran; Rivaroxaban; Apixaban; Warfarin

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Core Tip: Dabigatran, rivaroxaban, apixaban have better efficacy (reduction in ischemic stroke and all-cause mortality) and are safer (reduction in major bleeding) than warfarin. Dabigatran is associated with a lower rate of intracranial hemorrhage than warfarin, while rivaroxaban and apixaban appear to have a trend towards reduced intracranial hemorrhage, without statistical significance. Dabigatran, rivaroxaban, and apixaban are associated with a lower rate of gastrointestinal bleeding.

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INTRODUCTION

Stroke is the second leading cause of death and a major cause of disability globally[1,2]. It was estimated that more than 5.5 million people died secondary to stroke in 2016[3]. One third of all ischemic strokes are attributed to atrial fibrillation (AF), which leads to cardioembolism of large cerebral arteries[4]. As a consequence, AF-related strokes are more likely to be fatal or debilitating[4]. AF is the most common sustained cardiac arrhythmia with an estimated global prevalence of 2.8% and an estimated life time risk of about 25%[5]. The presence of AF is associated with a fivefold increase in stroke risk[6]. AF and stroke are independently associated with dementia onset in this population[7]. Therefore, anticoagulation therapy has been the mainstay of primary and secondary stroke prevention in patients with diagnosed AF for decades[8,9]. Warfarin was the standard of care until 2009, when dabigatran, a non-vitamin K oral anticoagulant (NOAC) was found to be non-inferior to warfarin with regards to stroke prevention in patients with AF[10]. Since then, three other NOACs have been approved, namely rivaroxaban, apixaban, and edoxaban, all of which have shown substantial clinical benefits in randomized clinical trials[10-13]. The relative ease of prescribing and adhering to NOAC therapy has resulted in a more widespread use of NOACs as opposed to warfarin[14]. However, most of the randomized clinical trials, which led to this substantial change in clinical practice, originated from western countries with underrepresentation of Asian population; yet a number of real-world studies have assessed the use of NOACs in Asians with AF. With this study we aimed to systematically review and quantitatively analyze the existing observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared

to warfarin for stroke prevention in Asians with non-valvular AF.

MATERIALS AND METHODS

The study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15]. The study protocol was submitted for registration at the International Prospective Register for Systematic Reviews.

Literature search and study eligibility

Medline, Cochrane Library, and ClinicalTial.gov were systematically searched from their inception to April 27, 2020. Two independent investigators (Li WJ and Archontakis-Barakakis P) independently searched for eligible studies. In cases where there was a disagreement regarding the eligibility of a study, a third investigator (Kokkinidis DG) was involved in order consensus to be reached.

The search algorithm was ("novel oral anticoagulants" OR "direct oral anticoagulants" OR "non-vitamin K antagonist oral anticoagulants" OR NOAC OR DOAC OR dabigatran OR rivaroxaban OR apixaban OR warfarin OR coumadin OR "vitamin K antagonist") AND (atrial fibrillation OR AF OR AFIB) AND (real-world OR "real world" OR observational OR cohort OR post-approval). The reference list of pertinent reviews and observational studies was also manually searched for further potentially eligible studies. Duplicate publications were removed at the end of the literature search.

The pre-specified inclusion criteria were: (1) Retrospective or prospective observational studies; (2) Studies where the majority or all study participants were of Asian race; (3) Studies comparing warfarin to one of the NOACs; and (4) Studies examining at least one of the following outcomes: Thromboembolic stroke, intracranial hemorrhage, any bleeding, major bleeding, gastrointestinal bleeding. We excluded randomized control trials and studies that presented comparisons between different NOACs. Studies on valvular AF (*i.e.*, diagnosis of mitral stenosis or mitral valve replacement or repair) were also excluded.

Data extraction and outcomes

Data extraction was performed based on a pre-defined data extraction form by two independent investigators (Li WJ and Kokkinidis DG) blinded to each other. Disagreements were resolved following discussion and final decision was reached by consensus and as needed with the addition of a third reviewer (Archontakis-Barakakis P). The primary outcome was ischemic stroke (as defined by the individual studies) occurring during study follow up period. The secondary outcomes were all-cause mortality, major bleeding (as defined by the included studies), intracranial hemorrhage, and gastrointestinal bleeding.

Risk of bias assessment

Two independent reviewers (Palaiodimos L and Tzelves L) assessed the risk of bias of the included studies with the Risk of Bias in Non-Randomized Studies - of Interventions tool[16]. Studies were assessed as having low, moderate, serious or critical risk of bias for the following domains: Confounding measurement and account, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and results reporting.

Statistical analysis

When potentially duplicated populations were encountered, studies were not analyzed together under the same comparison and outcome. The larger one of the two studies was the one that was prioritized. Hazard ratios (HRs) with the corresponding 95% confidence interval (CI) were used for evaluation of outcomes. A random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed with the Higgins I-square (I^2) statistic. $I^2 > 75\%$ indicated significant heterogeneity. Forest plots were used to graphically display the effect size in each study and the pooled estimates. Funnel plots and the Egger's test were used for assessment of publication bias. A P value < 0.05 was considered significant. R 3.4 version (RStudio software, RStudio, Inc.) was used as statistical software.

RESULTS

Our literature search has yielded 127 potentially relevant records after duplicates were removed. After excluding studies for multiple reasons (Figure 1), twelve studies were included in our analysis. All of the studies were conducted in countries or regions located in East Asia or Southeast Asia with the majority of their study participants being Asians. Most of the studies were products of large databases/registries (9 out of 12). In ClinicalTrials.gov database, we only found DARING-AF trial (comparison of efficacy and safety among dabigatran, rivaroxaban, and apixaban in non-valvular AF) which attempted to evaluate the efficacy and safety of NOACs in Asian patients but no results were posted. The baseline study characteristics are presented in Table 1. The patient characteristics are presented in Table 2. The risk of bias assessment is presented in Figure 2.

Dabigatran vs warfarin

Dabigatran was associated with a significant reduction in the incidence of ischemic stroke (HR = 0.78, 95%CI: 0.65-0.94, Figure 3), all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83, Figure 3), major bleeding (HR = 0.61, 95%CI: 0.54-0.69, Figure 3), intracranial hemorrhage (HR = 0.51, 95%CI: 0.42-0.62, Figure 3), and gastrointestinal bleeding (HR = 0.65, 95%CI: 0.46-0.94, Figure 3), compared to warfarin.

Rivaroxaban vs warfarin

Rivaroxaban was associated with a statistically significant lower rate of ischemic stroke (HR = 0.79, 95%CI: 0.74-0.85, Figure 4), all-cause mortality (HR = 0.66, 95%CI: 0.52-0.84, Figure 4), major bleeding (HR = 0.70, 95%CI: 0.54-0.90, Figure 4), and gastrointestinal bleeding (HR = 0.79, 95%CI: 0.69-0.90, Figure 4), compared with the warfarin group. Although there was a tendency towards reduction in the rate of intracranial hemorrhage (HR = 0.76, 95%CI: 0.52-1.11, Figure 4) in rivaroxaban group, the result was not statistically significant.

Apixaban vs warfarin

Apixaban was associated with a lower rate of ischemic stroke (HR = 0.70, 95%CI: 0.62-0.78, Figure 5), all-cause mortality (HR = 0.66, 95%CI: 0.49-0.90, Figure 5), major bleeding (HR = 0.58, 95%CI: 0.43-0.78, Figure 5), and gastrointestinal bleeding (HR = 0.39, 95%CI: 0.17-0.89, Figure 5). However, there was no difference in the intracranial hemorrhage, although a clear trend was noticed (HR = 0.64, 95%CI: 0.40-1.02, Figure 5) towards apixaban superiority.

DISCUSSION

This study was a systematic review and meta-analysis of observational studies comparing the efficacy and safety of NOACs to warfarin in Asians with non-valvular AF. To the best of our knowledge, this is the first real-world data meta-analysis on this topic that is focused on Asian patient population. Our findings can be summarized as following: (1) Dabigatran, rivaroxaban, and apixaban were associated with significantly lower incidence of ischemic stroke and all-cause mortality compared to warfarin; (2) NOACs were associated with significantly fewer major bleeding events and gastrointestinal bleeding events compared to warfarin; and (3) Dabigatran was associated with significantly fewer intracranial bleeding events compared to warfarin; no significant difference in intracranial bleeding between the other two studied NOACs and warfarin was found, but a trend favoring rivaroxaban and apixaban was noted.

Dabigatran is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin and has been used for stroke and systemic embolism prevention in non-valvular AF since 2010[8]. The landmark trial that led to the approval and wide use of dabigatran, the randomized evaluation of long-term anticoagulation therapy (RE-LY) study, demonstrated that patients in the dabigatran arm (dose 150 mg twice daily) had significantly lower risk for stroke or systemic embolism [relative risk (RR) = 0.66, 95%CI: 0.53-0.82] and intracranial bleeding (RR = 0.40, 95%CI: 0.27-0.60) compared to warfarin arm in the two-year follow-up[10]; these findings are consistent with the results of our meta-analysis. The RE-LY trial did not show a significant difference between dabigatran and warfarin in terms of all-cause mortality and major bleeding but revealed higher gastrointestinal bleeding event rates in the dabigatran arm[10]. Real-world studies, which mainly included non-Asians, have confirmed that dabigatran has

Table 1 Baseline characteristics of included studies

Ref.	Design	Setting/data source	Country/region	Study period	Major eligibility criteria	Major exclusion criteria	OAC comparison groups	Outcomes of interest
Chan *et al*[25], 2016	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2013	NVAF patients, age ≥ 30 years old	PE or DVT, joint replacement or valvular surgery within 6 mo before AF was diagnosed, ESRD, switcher from dabigatran to warfarin	Dabigatran *vs* warfarin	Ischemic stroke, intracranial hemorrhage, major GI bleeding, all-cause mortality
Yap *et al*[26], 2016	Single-center, retrospective cohort study	Malaysia's National Heart Institute	Malaysia	January, 2009 to December, 2013	NVAF patients	Not mentioned	Dabigatran *vs* warfarin	Ischemic CVA, major bleeding
Cha *et al*[27], 2017	Database, retrospective cohort study	Korean National Health Insurance Service database	Korea	January, 2014 to December, 2015	NVAF patients with CHA2DS2-VASc score ≥ 2 taking anticoagulants for primary prevention of stroke/systemic embolism	Thromboembolic event/TIA or ICH, patients received joint replacement, medications change between warfarin and NOACs	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, or all-cause mortality
Kohsaka *et al*[28], 2017	Database, retrospective cohort study	275 acute care hospitals across Japan	Japan	March 1, 2011 to March 31, 2016	NVAF patients 18 yr or older without use of any OAC within 180 d before the index date	Valvular AF, post-operative AF, mechanical-valvular AF, rheumatic AF	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Major bleeding
Chan *et al*[29], 2018	Database, retrospective cohort study	National HealthInsurance Research Database	Taiwan	June 1, 2012 to December 31, 2016	NVAF patients ≥ 30 years old	More than 1 NOAC use during treatment course, diagnosis of valvular AF, VTE or joint replacement therapy, ESRD requiring renal replacement therapy within 6 mo before the index date	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	All-cause mortality, intracranial hemorrhage, GI bleeding, major bleeding
Huang *et al*[30], 2018	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2015	NVAF patients ≥ 20 years old, at least 1 inpatient or 2 separate outpatient diagnoses of AF	Prosthetic heart valve or MV disease during the study period, pregnant, cancer, or chronic dialysis within 12 months prior to index date	Rivaroxaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding
Okumura *et al*[31], 2018	Multi-center, prospective cohort study	63 institutions in the Tokyo area	Japan	September 1, 2013 to December 31, 2015	NVAF patients, age ≥ 20 years old, treatment with any anticoagulant drug for stroke prophylaxis	Not mentioned	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Intracranial hemorrhage, major bleeding, all-cause mortality
Koretsune *et al*[32], 2018	Database, retrospective cohort study	Hospital Information systems and administration database by Medical Data Vision	Japan	March 14, 2011 to June 30, 2016	NVAF patients, age ≥ 18, new user of either dabigatran or warfarin	Dialysis, kidney transplant, atrial flutter, valvular AF, mechanical valve replacement, rheumatic AF or MV prolapse/regurgitation or stenosis; or DVT or PE < 6 months before the AF diagnosis	Dabigatran *vs* warfarin	Major bleeding, intracranial hemorrhage, GI bleeding
Chan *et al*[33], 2019	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2017	NVAF patients	More than one NOAC use, ESRD, DVT, PE, joint replacement therapy up to 6 mo prior to the index date.	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, major bleeding, major GI bleeding

Jeong *et al*[34], 2019	Single-center, retrospective cohort study	Chonnam National University Hospital	Korea	January, 2014 to December, 2016	NVAF patients, CHA2DS2-VASc > 2	Valvular AF, or any OAC class change	Rivaroxaban *vs* warfarin	Ischemic stroke, major bleeding, GI bleeding, intracranial bleeding, all-cause mortality
Lee *et al*[35], 2019	Database, retrospective cohort study	Korean Health Insurance Review Database	Korea	January, 2015 to December, 2017	NVAF patients naïve to OAC treatment	Not mentioned	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding, major bleeding
Cho *et al*[36], 2019	Database, retrospective cohort study	Korean National Health Insurance Service	Korea	July 1, 2015 to December 31, 2016	NVAF patients with new prescription of anticoagulants, age ≥ 18	Less than 30 d of anticoagulants use, two or more types of anticoagulants user, CHA2DS2-VASc score < 2, prior PE or DVT, underwent joint replacement surgery, dialysis patients	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	All-cause mortality, major bleeding

NVAF: Nonvalvular atrial fibrillation; OAC: Oral anticoagulant; DVT: Deep venous thrombosis; PE: Pulmonary embolism; MV: Mitral valve; ESRD: End stage renal disease; GI: Gastrointestinal.

an overall better efficacy and safety profile compared to warfarin, however superiority of dabigatran in each of the individual outcomes was not consistent across studies[17-19]. In contrast, our findings demonstrated that dabigatran was associated with 32% lower all-cause mortality, 39% lower risk for major bleeding, and 35% lower risk for gastrointestinal bleeding compared to warfarin. This meta-analysis focused on Asian population reveals consistent superiority of dabigatran compared to warfarin for all important outcomes.

Rivaroxaban acts by inhibiting activated factor Xa (FXa), a key molecule in the coagulation cascade[8]. Rivaroxaban once daily oral direct FXa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in AF (ROCKET AF) trial was published in 2011 paving the way for approval of rivaroxaban for stroke prevention in patients with non-valvular AF[11]. The rivaroxaban group was associated with significantly fewer stroke events compared to warfarin group (HR = 0.79, 95%CI: 0.66-0.96) which is in agreement with the findings of our meta-analysis but failed to demonstrate significant result in intention-to-treat population. No difference in major bleeding events between rivaroxaban and warfarin groups was demonstrated in ROCKET-AF (HR = 1.04, 95%CI: 0.90-1.20)[11]. However, an increased risk of decrease in hemoglobin more than or equal to 2 g/dL in rivaroxaban group was seen. This is different from our study that found that Asian patients on rivaroxaban had 30% lower risk for major bleeding events occurrence compared to patients receiving warfarin. The findings from a large real-world study from Canada and the United States revealed no significant difference for stroke and bleeding outcomes between the rivaroxaban and warfarin groups[20]. A propensity score matching analysis from Denmark demonstrated that patients on rivaroxaban had lower stroke rates but similar bleeding rates to patients on warfarin[21]. Observational data from Coleman *et al*[22] showed that rivaroxaban reduced stroke rates in patients with non-valvular AF compared to warfarin without any significant difference in bleeding rates. While

Table 2 Patient characteristics of included studies

Ref.	Patient Number (Api)	Patient Number (Riv)	Patient Number (Dab)	Patient Number (War)	Age (Api)	Age (Riv)	Age (Dab)	Age (War)	HAS-BLED (Api)	HAS-BLED (Riv)	HAS-BLED (Dab)	HAS-BLED (War)	CHA2DS2-VASc (Api)	CHA2DS2-VASc (Riv)	CHA2DS2-VASc (Dab)	CHA2DS2-VASc (War)
Chan *et al*[25], 2016	N/A	N/A	9940	9913	N/A	N/A	75 ± 10	76 ± 10	N/A	N/A	2.57 ± 1.01	2.58 ± 1.06	N/A	N/A	4.13 ± 1.59	4.16 ± 1.75
Yap *et al*[26], 2016	N/A	N/A	500	500	N/A	N/A	65.3 ± 11.3	66.8 ± 11.3	N/A	N/A	1.57 ± 0.96	1.67 ± 0.94	N/A	N/A	2.69 ± 1.54	3.40 ± 1.54
Cha *et al*[27], 2017	2189	5681	3741	23222	70.3 ± 10.0	70.5 ± 9.9	69.3 ± 10.0	68.82 ± 11.1	N/A	N/A	N/A	N/A	3.57 ± 1.29	3.60 ± 1.32	3.51 ± 1.28	3.57 ± 1.31
Kohsaka *et al*[28], 2017	5977	5090	6726	6726 (War-Dab matched); 5090 (War-Riv matched); 5977 (War-Api matched)	77.4 ± 10.0	75.8 ± 10.0	73.1 ± 9.9	73.3 ± 10.5 (War-Dab matched); 76.2 ± 10.5 (War-Riv matched); 77.7 ± 10.0 (War-Api matched)	N/A	N/A	N/A	N/A	3.5 ± 1.6	3.3 ± 1.6	3.0 ± 1.6	3.0 ± 1.6 (War-Dab matched); 3.4 ± 1.6 (War-Riv matched); 3.5 ± 1.5 (War-Api matched)
Chan *et al*[29], 2018	5843	27777	20079	19375	76 ± 10	76 ± 10	76 ± 10	76 ± 10	2.96 ± 1.12	2.96 ± 0.51	2.96 ± 0.59	2.97 ± 0.61	3.89 ± 1.56	3.89 ± 0.71	3.88 ± 0.82	3.89 ± 0.88
Huang *et al*[30], 2018	N/A	9637	N/A	9637	N/A	75.2 ± 10.24	N/A	74.98 ± 10.6	N/A	2.21 ± 1.46	N/A	2.33 ± 1.49	N/A	4.02 ± 1.92	N/A	4.11 ± 2
Okumura *et al*[31], 2018	428	761	456	1561	73.2 ± 10.1	71.5 ± 9.1	70.9 ± 9.5	72.2 ± 9.3	1.42 ± 0.81	1.32 ± 0.77	1.07 ± 0.71	1.61 ± 0.88	3.12 ± 1.47	2.87 ± 1.45	2.83 ± 1.46	3.08 ± 1.51
Koretsune *et al*[32], 2018	N/A	N/A	4606	4606	N/A	N/A	74 ± 10	73 ± 11	N/A	N/A	2.1 ± 1.0	2.1 ± 1.1	N/A	N/A	3.3 ± 1.7	3.3 ± 1.7
Chan *et al*[33], 2019	9952	33022	22371	19761	76 ± 10.5	75.3 ± 10.6	74.2 ± 10.4	70.6 ± 13.4	2.9 ± 1.1	2.9 ± 1.1	2.8 ± 1.1	2.6 ± 1.3	3.9 ± 1.6	3.8 ± 1.6	3.7 ± 1.5	3.2 ± 1.8
Jeong *et al*[34], 2019	N/A	804	N/A	804	N/A	71.4 ± 10.5	N/A	70.4 ± 10.2	N/A	N/A	N/A	N/A	N/A	3.3 ± 1.8	N/A	3.4 ± 1.8
Lee *et al*[35], 2019	22177	35965	17745	25420	72.7 ± 10.2	72.0 ± 9.9	70.8 ± 9.9	67.3 ± 12.6	2.75 ± 1.04	2.77 ± 1.02	2.67 ± 1.01	2.58 ± 1.14	3.76 ± 1.41	3.63 ± 1.40	3.55 ± 1.37	3.18 ± 1.61
Cho *et al*[36], 2019	12502	21000	12593	10409	74.3 ± 8.9	73.8 ± 8.8	72.9 ± 8.9	70.8 ± 11	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 1.0	3.7 ± 1.2	3.6 ± 1.2	3.5 ± 1.2	3.5 ± 1.2

HAS-BLED: Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; War: Warfarin; Dab: Dabigatran; Riv: Rivaroxaban; Api: Apixaban; N/A: Not applicable.

another study from the United States showed higher risk of gastrointestinal bleeding in the rivaroxaban group[23], our study yielded favorable result pointing toward reduction of gastrointestinal bleeding of rivaroxaban in Asian patients. In summary,

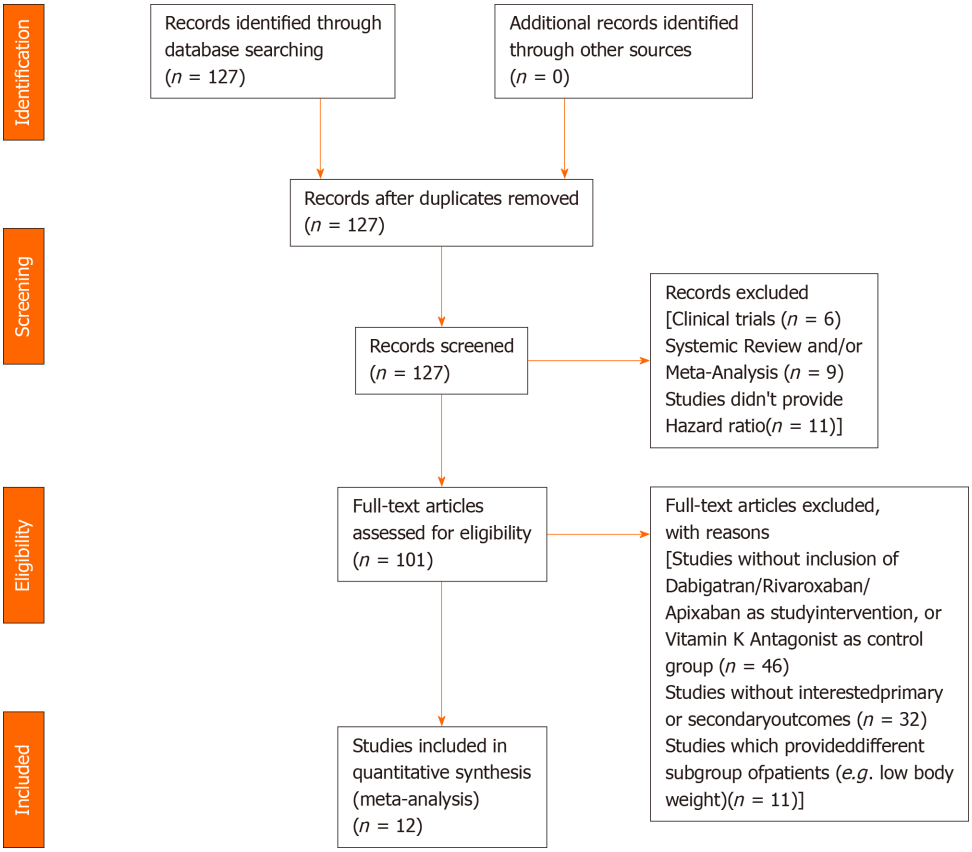


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

our meta-analysis showed that Asian patients with non-valvular AF on rivaroxaban had less stroke and bleeding rates compared to those on warfarin.

Apixaban is another FXa inhibitor approved for stroke prevention in patients with non-valvular AF[8]. The publication of the results of the apixaban for reduction in stroke and other thromboembolic events in AF (ARISTOTLE) trial was the milestone after which apixaban became one of the most widely prescribed oral anticoagulants[12]. In ARISTOTLE trial, patients with non-valvular AF were randomized in the apixaban and warfarin groups. The apixaban group had significantly lower stroke and major bleeding events rates, and lower mortality compared to warfarin group. Large real-world studies mainly in non-Asians confirmed the randomized trial data[18,24]. With this meta-analysis, we demonstrate that apixaban is more efficacious and safer than warfarin in our Asian population, as well.

The main strengths of our study are its strict methodology, robust analysis, and the relatively large number of included studies and overall patient sample. Our study has a number of limitations, mainly associated with the observational nature of the included studies. The patient populations of the individual studies were heterogeneous despite the fact that the vast majority was of Asian race. We were unable to adjust for baseline comorbidities because we did not have access to patient level data. For some of the outcomes, the number of eligible studies was limited which decreases the certainty in our findings.

CONCLUSION

In conclusion, the present systematic review and meta-analysis revealed that dabigatran, rivaroxaban, and apixaban, appear to be superior to warfarin in terms of efficacy (stroke prevention, all-cause mortality) and safety outcomes (bleeding events) in Asians with non-valvular AF.

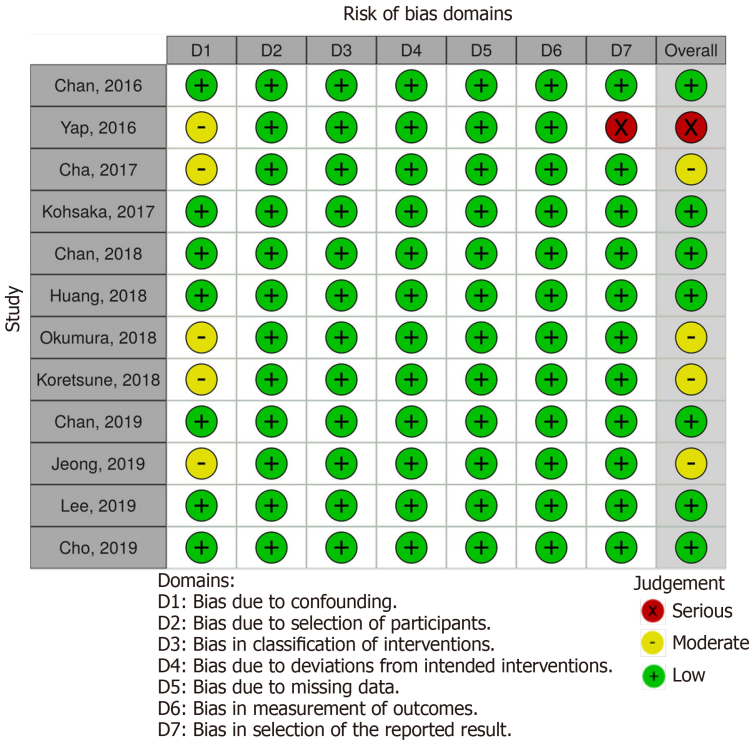


Figure 2 Risk of bias assessment of included studies using risk of bias in non-randomized studies-of interventions tool.

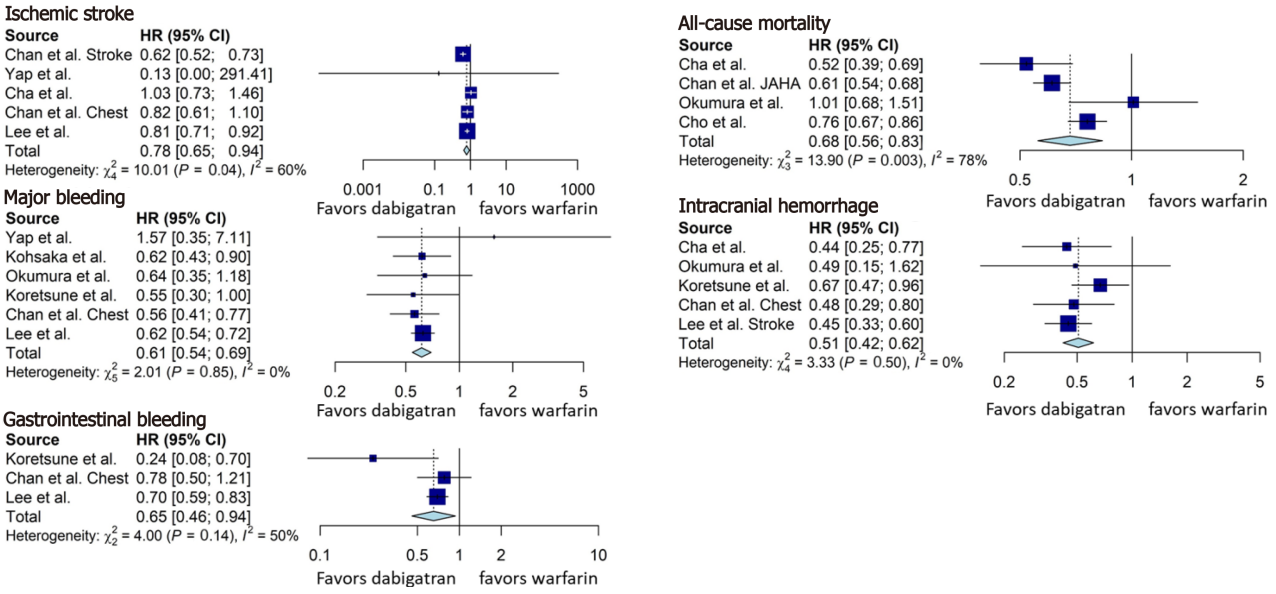


Figure 3 Forest plots comparing dabigatran with warfarin regarding hazard ratios of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

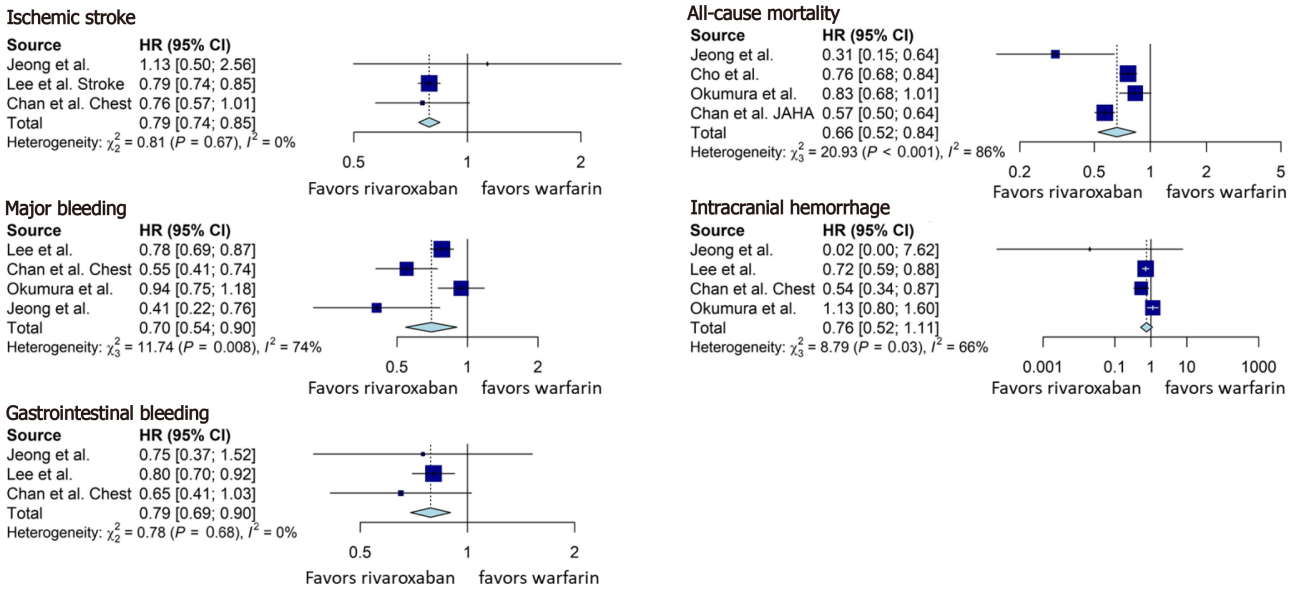


Figure 4 Forest plots comparing rivaroxaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

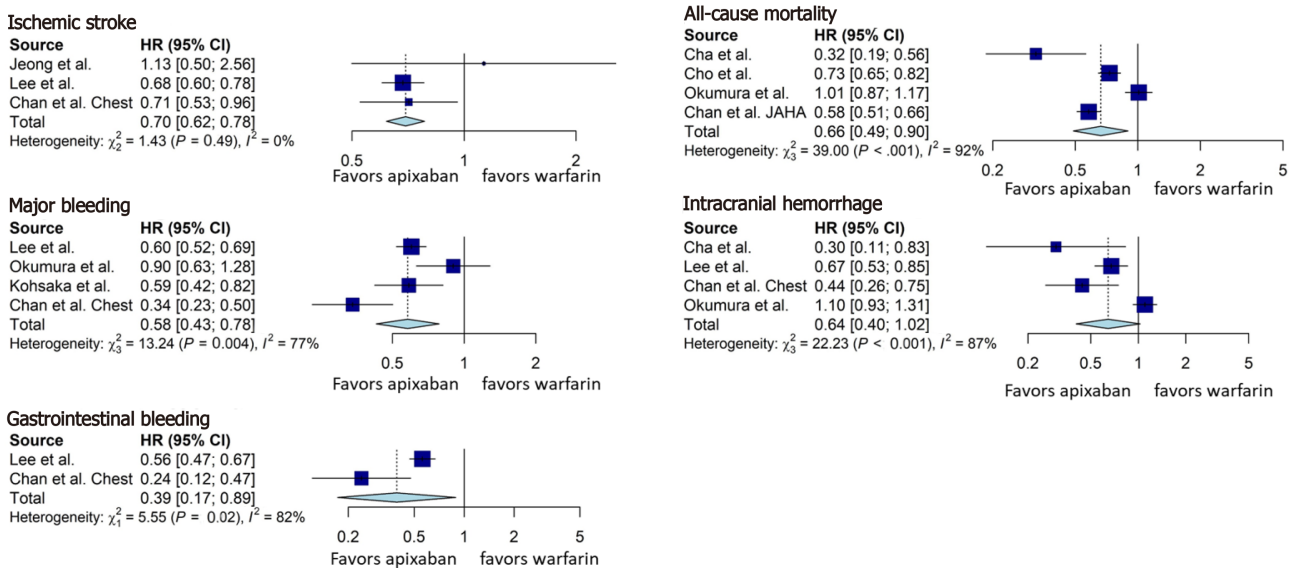


Figure 5 Forest plots comparing apixaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Stroke is the second leading cause of mortality and disability worldwide with one-third of all ischemic stroke cases attributed to atrial fibrillation (AF).

Research motivation

Warfarin was the standard of care of stroke prevention in patients with nonvalvular AF but novel oral anticoagulants including dabigatran, rivaroxaban, and apixaban have demonstrated better efficacy and safety than warfarin in randomized clinical trials but they originated from Western countries where the Asian population was underrepresented.

Research objectives

We aimed to systematically review and quantitatively analyze the existing real-world observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban when they are compared with warfarin for stroke prevention in Asian patients with non-valvular AF.

Research methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Medline, Cochrane, and ClinicalTrial.gov databases were systematically searched. A random-effect model meta-analysis was used and I^2 was utilized to assess heterogeneity. Risk of bias assessment was performed for every study included.

Research results

Twelve studies were qualified for our study. Dabigatran, rivaroxaban, and apixaban were all associated with significantly reduced incidence of ischemic stroke, all-cause mortality, major bleeding, and gastrointestinal bleeding. Dabigatran was also found associated with a lower risk of intracranial hemorrhage.

Research conclusions

Dabigatran, rivaroxaban, and apixaban have better efficacy and safety profile than warfarin for stroke prevention in Asian patients with non-valvular AF.

Research perspectives

Future research which conducts a head-to-head comparison between different novel oral anticoagulants is necessary to determine the best option for Asian patients with non-valvular AF.

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META-ANALYSIS

Intracoronary brachytherapy for the treatment of recurrent drug-eluting stent in-stent restenosis: A systematic review and meta-analysis

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Abstract

BACKGROUND

We performed a meta-analysis on observational studies since randomized control trials are not available. We studied intracoronary brachytherapy (ICBT) and recurrent drug eluting stent in-stent restenosis (DES-ISR) to evaluate the procedural success, target lesion revascularization (TLR), incidence of myocardial infarction (MI) and all-cause mortality at 2 years follow-up.

AIM

To perform meta-analysis for patients undergoing ICBT for recurrent DES-ISR.

METHODS

We performed a systematic search of the PubMed/MEDLINE, Cochrane and DARE databases to identify relevant articles. Studies were excluded if intra-

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coronary brachytherapy was used as a treatment modality for initial ISR and studies with bare metal stents. We used a random-effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics.

RESULTS

A total of 6 observational studies were included in the final analysis. Procedural angiographic success following intra-coronary brachytherapy was 99.8%. Incidence of MI at 1-year was 2% and 4.1% at 2-years, respectively. The incidence of TLR 14.1% at 1-year and 22.7% at 2-years, respectively. All-cause mortality at 1- and 2-year follow-up was 3% and 7.5%, respectively.

CONCLUSION

Given the observational nature of the studies included in the analysis, heterogeneity was significantly higher for outcomes. While there are no randomized controlled trials or definitive guidelines available for recurrent ISR associated with DES, this analysis suggests that brachytherapy might be the alternative approach for recurrent DES-ISR. Randomized controlled trials are required to confirm results from this study.

Key Words: Intracoronary brachytherapy; In-stent restenosis; Meta-analysis; Drug eluting stent; Systematic review; Brachytherapy

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Core Tip: Information is not readily available for the management of recurrent drug-eluting in-stent restenosis. There have been recent advances in the management of in-stent restenosis. While the use of a drug-eluting stent is still associated with in-stent restenosis, the use of intracoronary brachytherapy (ICBT) has resurged as one of the modalities in the management of such a complex problem. This analysis focuses on myocardial infarction and target lesion revascularization after the use of ICBT with a follow-up out to 2 years. Future studies with longer follow up are required to see if these benefits last longer.

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INTRODUCTION

As percutaneous coronary intervention has evolved, drug eluting stents (DES) have become the mainstay of therapy given their lower rates of in-stent restenosis (ISR) and other complications in comparison to bare metal stents (BMS). ISR occurs due to vascular remodeling and neointimal hyperplasia which can lead to the reoccurrence of anginal symptoms[1]. Various clinical factors, including stent type, other comorbidities and patient characteristics, contribute to the development of ISR. This makes it difficult to ascertain the exact incidence of ISR, however, with the advent of second-generation DES, ISR rates have decreased to approximately 8%[2]. Patients with ISR will often undergo revascularization with repeat stenting per guideline, however, the recommendations are less clear for 2 or more previously implanted stents[3,4]. There have been several modalities used for such lesion without clear benefits which includes but not limited to the use of laser atherectomy, intracoronary brachytherapy (ICBT), and drug coated balloons. The intracoronary irradiation may limit intravascular smooth muscle proliferation by promoting novel cell cycle regulation and eventually reduces the rate of ISR[5]. There have been promising results with the use of ICBT for recurrent DES-ISR[6-8]. Given the inherent limitations and logistic issues

associated with the use of ICBT, the use has been very limited to a few centres in the United States. We performed a meta-analysis on observational studies studying ICBT in the absence of randomized controlled trials and recurrent DES-ISR to evaluate the procedural success, target lesion revascularization (TLR), incidence of myocardial infarction (MI) and all-cause mortality at 1- and 2-years follow-up.

MATERIALS AND METHODS

Literature search

We performed a systematic search of the PubMed/MEDLINE, Cochrane and DARE databases to identify relevant articles. The literature search was performed from the inception of the database to January 2019. Since studies included in the present meta-analysis were approved my institutional ethical committee, no additional ethical clearance was required for the present meta-analysis. The reporting of the present systematic review and meta-analysis was in accordance with the PRISMA guidelines[9].

Study selection

Each of the three databases were searched using the search terms "Intra-coronary Brachytherapy", "ICBT" OR "Intra-vascular Brachytherapy" "Intravascular Brachytherapy", "Drug eluting stent", "Drug-eluting stent", DES, "In-stent restenosis", ISR, to identify citations without language restrictions (Supplementary Table 1). Studies were not excluded based on sample size. The identified studies were imported into Mendeley reference manager and checked for duplicates. The reference list of the relevant articles searched were reviewed to identify additional articles.

The inclusion criteria were (1) observational studies of ICBT; and (2) for recurrent ISR of DES reporting either one of the following event rates: Procedural success; TLR, MI and all-cause mortality at 1 and/or 2 years follow up. Studies were excluded if intra-coronary brachytherapy was used as a treatment modality for initial ISR and studies with BMS (Supplementary eMethod1).

Data extraction

The screening of searched citations was performed at two levels. At the first level, two reviewers independently screened the title and abstracts of citations searched. At the second level, full text of citations identified by first level of screening was reviewed by two independent reviewers and included if the studies met the inclusion criteria. Any disparity during the review process was rectified by mutual consensus. Data extraction from included studies was performed by two reviewers independently. The following information was extracted from each included study, author's name, year, number of patients, mean age, percentage male, procedural angiographic success rates, TLR, MI and all-cause mortality rates at 1- and 2-year follow-up that were reported.

Statistical analysis

We used random effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics. Estimates with $I^2 > 50\%$ was considered statistically heterogeneous. To allow for inclusion in the meta-analysis, a correction of 0.5 was added to the events of studies reporting event rate of 0%. All statistical analysis was carried out using R statistical software version 3.6.2.

RESULTS

Summary of included studies

The database search identified a total of 26 citations. After applying the inclusion criteria, 6 studies were included in the final analysis[6,7,10-12]. The PRISMA flow chart for inclusion of studies is provided in Figure 1. All studies included in the present study analysed intra-coronary brachytherapy as treatment strategy in patients with recurrent ISR. The baseline characteristics of included studies are provided in Table 1. The mean age of the patients ranges from 65-67 years in all studies. All studies included patients with ≥ 2 stents. However, information regarding previous stent DES or BMS was not clear in any of the manuscript. Males were significantly higher in all studies. All studies utilized Strontium/yttrium-90 beta radiation system at the depth of 2 mm in almost all studies. Mean radiation dose was 18-23 gray in all studies. All the studies performed brachytherapy on DES as the most recent layer of the stent. Although

Table 1 Baseline characteristics of included studies

	Ref.	Year	Number of patients (*n*)	Mean age (years)	Percentage male (%)	DM (%)	Hypertension (%)	Type of brachytherapy	Mean/median radiation dose
1	Negi *et al*[6]	2016	186	65	62	47	95	Strontium/yttrium-90 beta radiation	23-25 Gray
2	Ohri *et al*[8]	2016	134	65	75	59	99	Strontium/yttrium-90 beta radiation	18.4 or 23 Gray
3	Mangione *et al*[7]	2017	101	66	67	53	98	Strontium/yttrium-90 beta radiation	18-23 Gray
4	Varghese *et al*[12]	2018	197	65	75	60	99	Strontium/yttrium-90 beta radiation	22 Gray
5	Megaly *et al*[10]	2021	116	66	69	-	-	Strontium/yttrium-90 beta radiation	22.6 Gray
6	Meraj *et al*[11]	2021	290	67	66	58	97	Strontium/yttrium-90 beta radiation	23 Gray

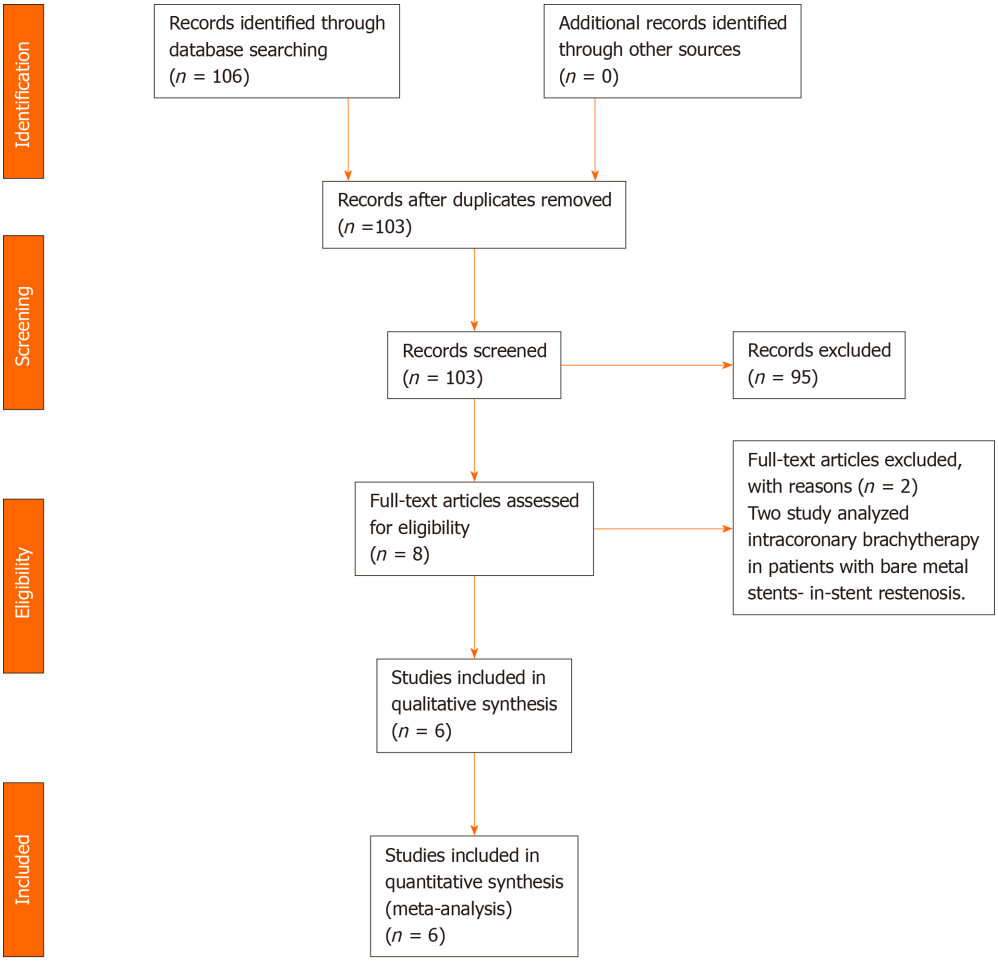


Figure 1 PRISMA flow chart for the selection of studies included in the meta-analysis.

studies did not mention which stent was utilized prior to this brachytherapy procedure, all studies included patients after calendar year 2011, and hence, we can safely assume that all studies utilized second generation DES stent after the procedure.

Results of analysis of outcomes

Procedural angiographic success following intra-coronary brachytherapy was 99.8% (95%CI: 99.5%-100.1%) (Figure 2A). TLR at 1-year follow-up was 14.1% (95%CI: 9.2%-19%) (Figure 2B) and at 2-year follow-up was 22.7% (95%CI: 15.4%-30%) (Figure 3A) following intra-coronary brachytherapy. MI at 1- and 2-year follow-up were 2%

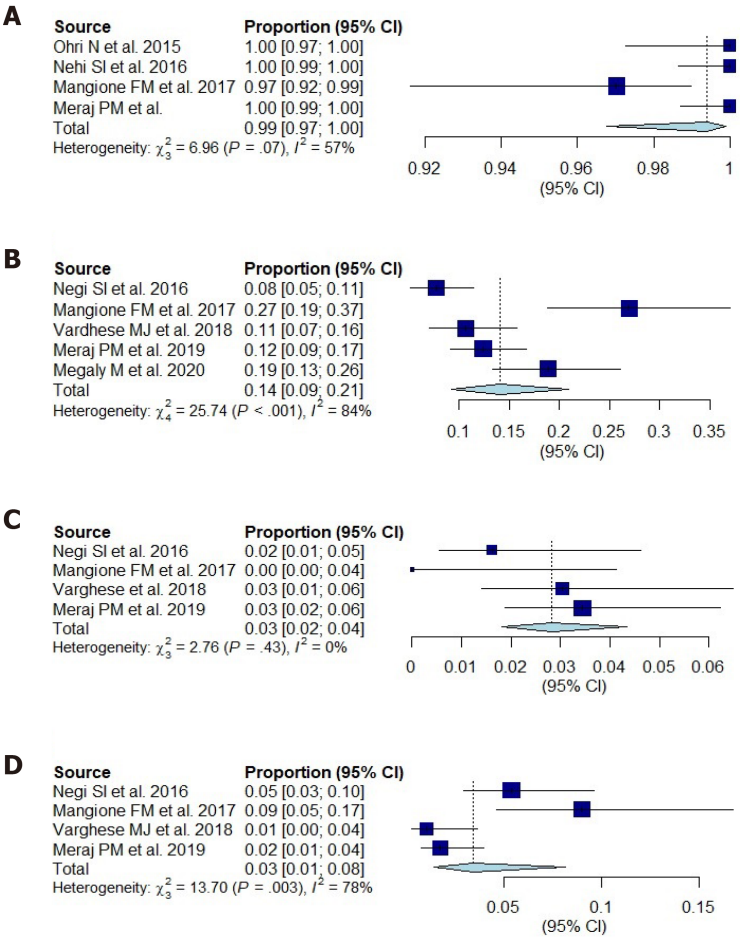


Figure 2 Forest plot for the clinical outcomes at 1 year. A: Demonstrated procedural success at 1 year; B: Demonstrates target lesion revascularization at 1 year; C: Demonstrates myocardial infarction at 1 year; D: Demonstrates all-cause mortality at 1 year.

(95%CI: 0.6%-3.3%) and 4.1% (95%CI: 2.5%-5.8%) (Figures 2C and 3B), respectively. All-cause mortality rates were 3% (95%CI: 0.8%-5.3%) and 7.5% (95%CI: 0.8%-14.3%) (Figures 2D and 3C), at 1- and 2-year follow-up, respectively.

DISCUSSION

In the absence of randomized controlled trials, we analysed observational studies demonstrating the favourable outcomes of brachytherapy following DES-ISR. The findings demonstrate high rates of procedural success, with TLR (14.1%) at 1-year and (22.7%) at 2-years, respectively. Incidence of MI at 1-year was 2% and 4.1% at 2-years, respectively. All-cause mortality at 1- and 2-year follow-up was 3% and 7.5%, respectively.

Brachytherapy targets adventitial fibromyoblasts that is the main source for neoproliferation of the tissue and causes apoptosis. Since there is overall suppression of neointimal growth by DES, DES-ISR tends to be focal, predominantly occurring at the stent edge[13]. ICBT inhibits neointimal formation within the stent by delivering radioactive strontium-90 beta-radiation *via* a hydraulic mechanism. This may not be as effective at the stent edge which may account for the minority of patients requiring revascularization at the 1- and 2-year follow-up[14]. Between the 1- and 2-year marks, there has been a remarkable increase in TLR, 14.1% *vs* 22.7%, leading to increases in MI and all-cause mortality at the two-year mark. This suggests that radiation may delay but does not eliminate the development of restenosis, leading to higher occurrences of MI and all-cause mortality at the two-year mark.

Management of resistant DES-ISR remains challenging and the best therapeutic option is still unclear. Some experts suggested that combined use of excimer laser coronary atherectomy may improve further clinical outcomes, however, the data is limited. Another option would be to use drug coated balloons; however, more data is

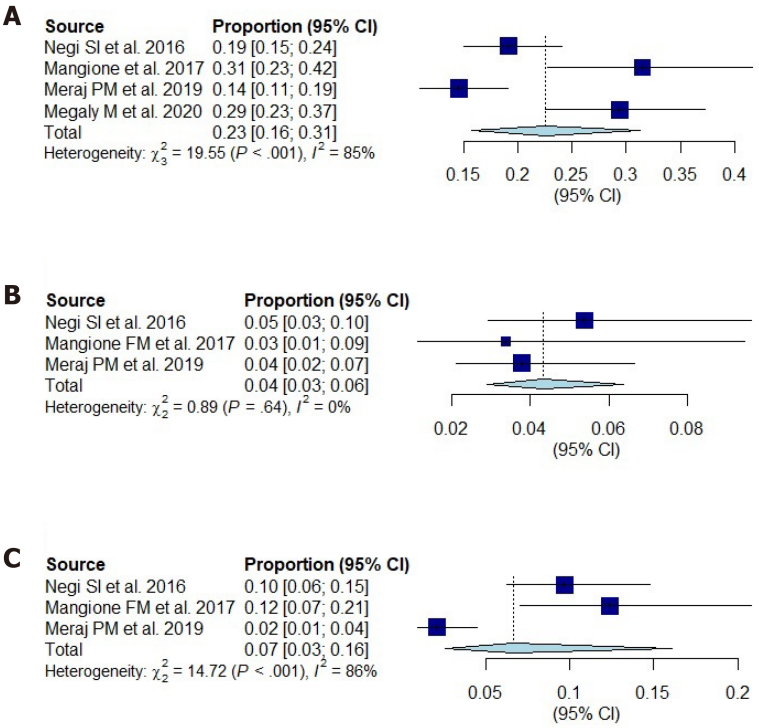


Figure 3 Forest plot for the clinical outcomes at 2 year. A: Demonstrates target lesion revascularization at 2 years; B: Demonstrates myocardial infarction at 2 years; C: Demonstrates all-cause mortality at 2 years.

needed to determine use of this technology. The use of rotational and orbital atherectomy is also on the rise. As technology is growing, use of third generation DES stent would be helpful in reducing ISR rates itself. Intravascular imaging is another growing field which might help determine pathophysiology in the development of DES-ISR. Since stent under-expansion is thought to be the main reason for DES-ISR, this can probably be prevented with the use of intravascular ultrasonography.

There are some limitations to our analysis. Three of the six studies included data for all the seven endpoints we analysed. This may have led to a smaller data pool. Additionally, we did not analyse the vessel diameter of the targeted lesion as this information was not readily available. Though, it should be a matter that, it should be investigated further given that ICBT has the greatest benefit in small vessel diameters[15]. It has been previously established that patients with diabetes are more prone to develop ISR, yet it would be interesting to note the long-term procedural success in patients with co-morbid conditions following ICBT after DES-ISR[16]. The number of stent varied in different studies. With each additional layer of stent, chances of ISR and other outcomes may increase. Finally, we do not have enough randomized control trials and we have to rely on observational studies to guide management in such patients. Overall, our analysis shows that ICBT is a feasible treatment option for the treatment of DES-ISR, is associated with high rates of procedural success and favourable efficacy at the one and two-year marks.

CONCLUSION

Currently, United States Food and Drug Administration has approved intracoronary radiation as an adjunctive treatment for ISR. While there are no definitive guidelines or recommendations for the management of recurrent ISR associated with DES, this analysis on brachytherapy with DES-ISR demonstrated that ICBT could be an effective alternate modality for such complex lesions. However, heterogeneity was significantly higher given the observational nature of the studies included in the analysis which must be kept in mind. Analysis shows that the initial intra-coronary brachytherapy procedure is highly successful. Brachytherapy is a practical treatment option for difficult to treat DES-ISR in patients with limited life expectancy or multiple comorbid states who may not be able to tolerate alternative treatment options, though, further analysis is needed on the long-term effects following ICBT in medically complex

patients.

ARTICLE HIGHLIGHTS

Research background

There is no established strategy for the management of in-stent restenosis which is common even when using drug eluting stents. There is a resurgence of the use of intracoronary brachytherapy (ICBT) for the treatment of drug eluting stent in-stent restenosis (DES-ISR).

Research motivation

The use of ICBT was common in the late 1990s era. Even with the use of second and third generation drug-eluting stents, in-stent restenosis have remined a significant problem. There have been multiple strategies used to manage this complex problem. Along with other strategies, ICBT has re-emerged as a potential solution.

Research objectives

The main objective was to perform a meta-analysis for patients undergoing ICBT for recurrent DES-ISR and analyze clinically important outcomes.

Research methods

We have reviewed PubMed/MEDLINE, Cochrane and DARE databases to identify studies that used ICBT for the management of in-stent restenosis. We used a random-effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics.

Research results

We included 6 observational studies in this meta-analysis. Procedural angiographic success following intra-coronary brachytherapy was 99.8%. The incidence of myocardial infarction and all-cause mortality was within acceptable range at 2 years. Incidence of target lesion revascularization (14.1%) at 1-year and (22.7%) at 2-years, respectively.

Research conclusions

Brachytherapy should be one of the preferred approach for recurrent DES-ISR.

Research perspectives

There is an unmet need for randomized control trial comparing brachytherapy *vs* another drug eluting stent with a longer follow-up.

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CASE REPORT

Pregnancy associated spontaneous coronary artery dissection: A case report and review of literature

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Author contributions: Prudhvi K, Jonnadula J, Rokkam VRP, Kutti Sridharan G, all four authors equally contributed to this manuscript; all four authors have analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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Abstract

BACKGROUND

Pregnancy-associated spontaneous coronary artery dissection (PSCAD) is an important cause of chest pain and acute myocardial infarction in pregnant and postpartum women. Pregnancy is considered an isolated risk factor for spontaneous coronary artery dissection. The etiology, pathogenesis, and incidence of PSCAD are not known.

CASE SUMMARY

We present a case of a 33-year-old postpartum female who presented with sudden onset chest pain and was diagnosed with spontaneous coronary artery dissection and needed urgent catheterization revealing left anterior descending coronary artery dissection. She underwent emergent coronary artery bypass graft surgery with good post-operative recovery.

CONCLUSION

Most patients with PSCAD can be managed conservatively with medical management and have good outcomes. Patients with high-risk presentations benefit from the invasive approach. Coronary artery bypass graft may be required in select few patients based on angiography findings. Due to the risk of recurrent spontaneous coronary artery dissection, subsequent pregnancies are discouraged.

Key Words: Pregnancy; Spontaneous artery dissection; Acute coronary syndrome; Coronary artery bypass surgery; Percutaneous coronary intervention; Pregnancy; Dissection; Myocardial Infraction; Case report

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Core Tip: Chest pain during pregnancy and peripartum period need a comprehensive workup. Pregnancy is an isolated risk factor for spontaneous coronary artery dissection. Patients with pregnancy-associated spontaneous coronary artery dissection often have an elevated rate of high-risk presentations and may require invasive treatment or coronary artery bypass graft in few cases. Multidisciplinary care coordinated by a team of experts including interventional cardiologists, high-risk obstetricians, internists, cardiothoracic surgeons and Critical care specialists is essential in managing these patients in the peripartum period. Early diagnosis and timely intervention are lifesaving in cases involving Pregnancy associated spontaneous coronary artery dissection.

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INTRODUCTION

Chest pain is the second most common chief complaint for emergency room visits[1]. Common causes of chest pain presenting to the emergency department are gastrointestinal causes, musculoskeletal causes, acute coronary syndrome, pericarditis and pulmonary embolism[2,3]. Spontaneous coronary artery dissection (SCAD) leading to coronary ischemia is an uncommon cause of chest pain predominantly seen in women. SCAD is defined as an epicardial coronary artery dissection that is not associated with trauma, atherosclerosis or due to iatrogenic causes. Many cases of SCAD in women happen during the peripartum period, and this can be life-threatening events in young females[4,5].

Pregnancy-associated spontaneous coronary artery dissection (PSCAD) is an important cause of chest pain and acute myocardial infarction in pregnant and postpartum women. It remains rare in incidence overall, with a handful of case reports and few small case series reported in the literature. Pregnancy and puerperium are considered major risk factors for SCAD because of hormonal changes. The etiology of PSCAD is not clearly understood. Patients with PSCAD often have high-risk presentations and have a complicated course. Failure to diagnose and treat PSCAD timely may lead to worse outcomes.

Here, we report a case of a 33-year-old postpartum female who had a complicated course following SCAD requiring coronary artery bypass graft (CABG) and had an uneventful recovery. To further improve understanding of PSCAD, we conducted an extensive literature search of Medline database for articles published until October 2020 using the following search terms "Myocardial infarction", "Pregnancy", "Spontaneous Coronary artery dissection" and "postpartum" in various combinations. We have reviewed the etiology, clinical presentation, diagnosis and treatment strategy of PSCAD in this literature review.

CASE PRESENTATION

Chief complaints

Sudden onset chest pain.

History of present illness

A previously healthy 33-year-old Hispanic female with no significant medical history presented to the emergency room with sudden onset of chest pain while she was cooking dinner. The pain originated in the neck area on the left side and mid-back region, radiated to the anterior chest, was 10/10 intensity, pressure-like, lasted for 15 min, and resolved with aspirin. Chest pain was associated with nausea, vomiting, diaphoresis, shortness of breath, and lightheadedness. A month ago, she delivered her

third child by normal vaginal delivery at 37 wk of gestation. The review of systems was otherwise unremarkable.

History of past illness

The patient had no prior history of coronary artery disease, aortic dissection, or pulmonary embolism.

Personal and family history

She had no significant social history including smoking, alcohol or recreational substance use. She denied use of any over the counter medicines and denied use of any hormonal contraceptives before. Her only medications included prenatal vitamins and iron supplements. There was no history of sudden cardiac death or early myocardial infarction in the family.

Physical examination

Her physical examination was unremarkable. Blood pressure was 104/56 mmHg and heart rate was 82 beats per minute. Equal intensity pulses were palpable in both arms. There were no cardiac murmurs, jugular venous distension, crackles on auscultatory lung areas, and pedal edema.

Laboratory examinations

Laboratory markers showed low hemoglobin of 11.6 g/dL (normal 12-15.5 g/dL) , white blood cell count of 6 × 10^9 cells/L, creatinine of 0.6 mg/dL, ESR of 16 mm/h (normal range, 0-20 mm/h) and CRP of 2.7 mg/L (normal range, 0-10 mg/L). Serial Troponins (Troponin T) were abnormal and trended up from 0.01 ng/mL and peaked at 15.5 ng/mL.

Imaging examinations

Her initial electrocardiogram (EKG) was normal. Subsequent EKGs showed dynamic T wave inversions. Chest radiography did not reveal mediastinal widening or any fractures and dislocations. Transthoracic echocardiogram revealed 48% LVEF, moderate-sized apical wall motion abnormality with akinesia of the anteroseptal segments.

MULTIDISCIPLINARY EXPERT CONSULTATION

A multidisciplinary team including cardiology, cardiothoracic surgery, critical care medicine was consulted, and they recommended starting heparin drip, high intensity statin therapy, and giving loading doses of aspirin and clopidogrel.

FINAL DIAGNOSIS

She underwent Left heart catheterization, which revealed spontaneous circumferential dissection extending from Ostia to mid-left anterior descending (LAD) with distal 90% stenosis (Figures 1 and 2). Diagnosis was made on the basis of symptoms of chest pain, elevated troponins, EKG findings of T-wave inversions, echocardiogram findings of wall motion abnormalities with low ejection fraction 48% and more importantly angiographic findings of dissection.

TREATMENT

An intra-aortic balloon pump was placed, IV nitroglycerine and metoprolol were started. Conservative management was not an option for her owing to ongoing ischemia. Percutaneous coronary intervention (PCI) was considered extremely high risk for her due to extensive involvement of left anterior descending and CABG was favored. The patient underwent a CABG (free left internal mammary artery to left anterior descending and saphenous vein graft to diagonal 1 and 2) and was transferred to the cardiac intensive care unit with an intra-aortic balloon pump and dopamine infusion.

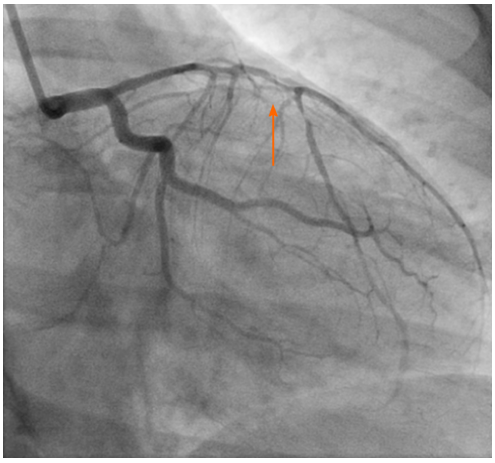


Figure 1 Right anterior oblique caudal view: Dissection extending from Ostium to mid LAD beyond the 2nd diagonal (arrow) with 90% stenosis (indicated by arrow).



Figure 2 Right anterior oblique cranial view.

OUTCOME AND FOLLOW-UP

She had an uneventful post-operative recovery and was discharged home on Aspirin, Atorvastatin and Metoprolol with close clinic follow-up. Autoimmune workup including antinuclear antibody, anti-DS antibody, ANCA antibodies, anticardiolipin antibody, and diluted Russell Viper venom test was negative. Post-discharge clinic follow up in one and 3 mo were uneventful, and she was advised to continue medical management.

DISCUSSION

Pregnancy predisposes to an increased risk of myocardial infarction by three-fold compared to non-pregnant females in the reproductive age group[4]. PSCAD comprises about 40% of pregnancy-associated myocardial infarction[5]. PSCAD occurs in approximately 1.8 per 100000 pregnancies[6].

Etiology and pathogenesis

Given the rarity of this condition, the etiology of PSCAD is largely unknown. Black race, hyperlipidemia, hypertension and migraine have been associated with the development of PSCAD[6]. A meta-analysis of Genome wise studies has identified a common genetic locus PHACTR1-EDN1 implicated in the development of both fibromuscular dysplasia (FMD) and SCAD in affected patients[7]. In a PSCAD cohort, Fibromuscular dysplasia was noted in greater than 40% of cases who underwent

imaging, revealing there may be a strong connection between FMD and PSCAD[8,9]. Autopsy studies have suggested that SCAD may be an initial manifestation of FMD[10,11]. Besides, several conditions that have been associated with SCAD including advanced maternal age, intense exercise, oral contraceptives, immunosuppressive therapy, menopause, sleep deprivation, cocaine abuse, connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome, polyarteritis nodosa and systemic lupus erythematosus may be related to PSCAD[12-14]. PSCAD patients also have higher rates of prior infertility treatments.

Pregnancy and puerperium are considered major risk factors for SCAD because of hormonal changes[15]. Changes in the levels of sex hormones leading to alterations in intima and media layers of arterial walls were proposed as a cause of PSCAD. Impaired collagen synthesis, myocyte proliferation and altered texture of mucopolysaccharides may weaken the layers of the coronary arterial wall. During pregnancy, a hyperdynamic circulatory state with increased shear stress on the labile coronary artery leads to coronary artery dissection[16,17]. PSCAD is more commonly observed in the left anterior descending coronary artery and Left main artery[15].

Clinical features and diagnosis

Clinical features are related to myocardial ischemia. Myocardial hypoperfusion is due to true luminal narrowing by false lumen compression caused by intramural hematoma. Clinical features depend on the anatomy of coronary involvement and the severity of involvement. The clinical spectrum varies from nonspecific chest pain, anginal equivalent, typical chest pain suggestive of unstable angina, cardiogenic shock leading to hemodynamic instability and sudden cardiac death.

Elevated cardiac biomarkers including troponins due to myocyte injury from ischemia may be seen. EKG may reflect changes corresponding to the involvement and extent of coronary territory and the severity of ischemia. Emergent coronary catheterization is essential for establishing a definitive diagnosis. Computed tomographic angiography coronary angiography may be useful in postpartum patients for diagnosing dissection and also during follow-up evaluation for resolution[18]. Unlike SCAD, where mid and distal coronary artery occlusions are common, PSCAD patients are more likely to have proximal vessel (mainly left main and left anterior descending) or multivessel involvement[19]. They present with worse LVEF compared with other SCAD patients. EKG could be normal but may also show a nonspecific ischemic pattern, T wave inversions, ST-segment depression, or ST-segment elevation.

Treatment and prognosis

The management strategy employed in PSCAD is similar to the management of SCAD with special attention to the stage of pregnancy and emphasis on fetal and maternal well-being. Both conservative treatment with medical therapy alone and percutaneous coronary intervention have been used in the management of PSCAD. There are no evidence-based guideline recommendations from professional societies yet as SCAD/PSCAD is rare. There have been no randomized controlled trials to guide management and so there is no established strategy to guide treatment. Emergent coronary angiography is the key in reviewing coronary arteries' anatomy and diagnosing SCAD and also to identify the severity and extent of the coronary artery dissection[5]. Intravascular ultrasound and optical coherence tomography may help in differentiating true lumen *vs* false lumen. Conservative management strategy may be followed in stable PSCAD patients as in one case series of 750 patients, about 85% were managed conservatively and had good long-term outcomes[20]. PCI may be considered in patients in patients with proximal occlusions, cardiogenic shock, unstable rhythm and those who fail conservative treatment strategy[15]. However, PCI in SCAD patients has higher rates of complications such as propagation of hematoma (noted in one-third of cases) and iatrogenic dissection[21,22]. Difficulty in identifying true lumen limits the success rate with stenting in establishing the coronary flow. Coronary arteries may be more friable due to hormonal changes in pregnancy and PCI may further worsen dissection in PSCAD patients[6].

CABG is reserved for patients with multivessel involvement or involvement of the left main coronary artery with ongoing ischemia/infarction[5,23-25]. Thrombolytics should be avoided due to the risk of reexpansion of hematoma, causing expanding dissection leading to compression of the true lumen with worsening ischemia. Besides, thrombolytics fall in risk category C for use in pregnancy[26,27]. Caution advised with medical management as certain drugs are contraindicated or not well studied during pregnancy. Antiplatelet agents such as aspirin, beta-blockers such as labetalol are safe during pregnancy. Available human data suggests the benefits of Clopidogrel use

outweigh risks during pregnancy and risk of fetal harm is not expected[28,29]. Angiotensin converting enzyme inhibitors should be avoided during pregnancy.

Previously considered a universally fatal condition, survival outcomes of PSCAD have improved in the past decades due to advances in the management of acute myocardial infarction. Maternal mortality rates are still high and variable in PSCAD patients, with one recent study reporting in-hospital mortality rates of 4.5%[30,31]. In another recent series of 750 patients containing 34 peripartum patients, PSCAD was associated with a higher rate of major adverse events (20.6%) such as Stroke/TIA, all-cause mortality, re-infection, Cardiogenic shock, congestive heart failure and cardiac arrest[20]. Patients with PSCAD were found to have an elevated rate of high-risk presentations and also known to have low ejection fraction compared to females with acute myocardial infarction in the same age group. Recurrence after SCAD has been noted, although less common. There is a paucity of information on the risk of recurrent SCAD in patients with prior PSCAD. Due to the high risk of mortality and morbidity associated with PSCAD, pre-conceptional counseling is recommended for subsequent pregnancies. Coronary tortuosity, migraine headaches, fibromuscular dysplasia, hypertension are associated with recurrent PSCAD. Careful evaluation, low threshold for coronary angiography referral and early intervention may help reduce the rate of missed diagnosis in high-risk women during the peripartum period. Multidisciplinary care coordinated by a team of experts including interventional cardiologists, high-risk obstetricians, internists, cardiothoracic surgeons and critical care specialists is essential in managing these patients in the peripartum period[32]. Targeted cardiac rehabilitation programs are preferred over strenuous high-intensity exercise programs in postpartum women[33].

CONCLUSION

Strong suspicion and emergent catheterization should be considered when pregnant and postpartum women present with chest pain, electrocardiogram changes and elevated biomarkers. Emergent coronary catheterization is essential for establishing a definitive diagnosis. Although no standard guidelines exist, conservative therapy with medical management has been increasingly adopted in pregnancy-associated spontaneous coronary artery dissection with good outcomes. Selected cases with high-risk presentations like ours have definitive benefit from PCI and coronary artery bypass graft. Hence, PCI should be reserved only for high-risk patients and coronary artery bypass graft in extremely high-risk or PCI failure cases.

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CASE REPORT

Device closure of fistula from left lower pulmonary artery to left atrium using a vascular plug: A case report

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Author contributions: Barik R planned, performed the device closure and wrote the manuscript; Mahapatra R was the cardiothoracic surgeon who suggested device closure and supported editing of the manuscript; Mahanta D and Singh J supported the intervention as a fellow in training; Acharya D assisted in the planning of the case management and helped during the procedure.

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Abstract

BACKGROUND

Pulmonary artery-to-left atrial fistula is a variant of pulmonary arteriovenous fistula and is a developmental anomaly. Delayed presentation, cyanosis and effort intolerance are some of the important features. The diagnosis is confirmed by computed tomography or pulmonary artery angiography. Catheter-based closure is preferred to surgery.

CASE SUMMARY

Left pulmonary artery-to-left atrial fistula is rare. A 40-year-old male presented with effort intolerance, central cyanosis, and recurrent seizures. He had a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in the course. Catheter-based closure was performed using a vascular plug.

CONCLUSION

Left pulmonary artery-to-left atrial fistula is relatively uncommon compared to right pulmonary artery-to-left atrial fistula. Percutaneous closure by either a transeptal technique or guide wire insertion into the pulmonary vein through the pulmonary artery is preferred. The need for an arteriovenous loop depends on the tortuosity of the course of the fistula and the size of the device to be implanted because a larger device needs a larger sheath, necessitating firm guide wire support to facilitate negotiation of the stiff combination of the delivery sheath and dilator.

Key Words: Pulmonary artery; Left atrium; Fistula; Hemangioma; Catheter-based; Vascular plug; Case report

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Core Tip: Pulmonary artery-to-left atrial fistula is a variant of pulmonary arterio-venous fistula and is a developmental anomaly. Left pulmonary artery-to-left atrial fistula is rare. We report the case of a 40-year-old male who presented with effort intolerance, central cyanosis, and recurrent seizures. He had a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in the course. Catheter-based closure was performed using a vascular plug.

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INTRODUCTION

Left pulmonary artery-to-left atrial fistula is relatively rare compared to right pulmonary artery-to-left atrial fistula, as previously reported[1]. The first case of pulmonary artery-to-left atrial fistula was reported in 1989 as an unusual cause of cyanosis in a newborn[2]. A significant right-to-left shunt is clinically marked by effort intolerance, cyanosis, and polycythemia, as well as sometimes bleeding issues related to associated hemangioma[3,4]. Pulmonary artery-to-left atrial fistula is a variant of pulmonary arteriovenous malformation. There is significant clinical suspicion of this condition when there is cyanosis without any obvious murmur in the precordium. Echocardiography shows a significant increase in pulmonary venous return to the left atrium, which is an additional clue and can be confirmed by cardiac catheterization or contrast-enhanced computed tomography. This case reports the relevant issues we encountered during the percutaneous device closure of a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in its course in an adult.

CASE PRESENTATION

Chief complaints

A 40-year-old male weighing 47 kg presented with effort intolerance, cyanosis, and clubbing.

History of present illness

The patient had a history of recurrent seizures and was on levetiracetam.

Personal and family history

The patient was a school teacher in profession and had no other significant comorbidities and no family history of congenital malformation.

Physical examination

The patient had central cyanosis and pandigital clubbing, and his room air oxygen saturation was 87%. There was no murmur on auscultation.

Laboratory examinations

The results of routine blood tests were normal. A genetic study could not be performed to exclude Osler-Weber-Rendu syndrome, which is also known as hereditary hemorrhagic telangiectasia[4,5].

Imaging examinations

Chest X-ray examination showed a dilated and enlarged left perihilar region. There were multiple small hemangiomas in several organs, including the brain. Echo-

cardiography showed increased pulmonary venous return to the left atrium. Enhanced computed tomography of the pulmonary artery showed a left pulmonary artery-to-left atrial fistula with a highly tortuous course associated with an aneurysmal sac on its course from the pulmonary artery to the left atrium (Figure 1A, Video 1 and 2). The narrowest diameter of the fistula was 1 cm just proximal to the aneurysmal sac in its course. A significant branch of the pulmonary artery was supplying the posterior segment of the left lower lobe.

MULTIDISCIPLINARY EXPERT CONSULTATION

The cardiothoracic surgeon suggested device closure as the first option if possible.

FINAL DIAGNOSIS

The final diagnosis was a large left lower pulmonary artery-to-left atrial fistula associated with an aneurysmal sac.

TREATMENT

Because the patient had multiple hemangiomas and recurrent seizures related to cerebral hemangioma based on the magnetic resonance angiography findings of the brain, the cardiac team suggested that a catheter-based intervention would be preferred over surgery. Device closure was planned after informed consent was obtained. Under local anesthesia and after infective endocarditis prophylaxis, the patient was taken for percutaneous vascular plugging of the fistula. Right ventricular saturation was 78%, and left ventricular saturation was 92% in room air. The pulmonary artery systolic pressure was 37 mmHg. The angiograms of the frontal and lateral projections showed a significantly tortuous course of the left lower pulmonary artery-to-left atrial fistula with an aneurysmal sac of 6 cm in diameter in its course (Figure 1B). The landing zone diameter was 16 cm, and the landing zone length was 2 cm after the origin of the left lower lobe segmental pulmonary artery branch (Figure 2A). A Terumo wire 0.35 cm × 260 cm in size (Terumo, Tokyo, Japan) was passed across the fistula from the left pulmonary artery through the sac far into the upper right pulmonary vein (Figure 2B). The insertion of a compatible 8-Fr sheath with its dilator was up to the sac was attempted but was not possible because of the tortuous course. The dilator was exchanged with a 5-Fr multipurpose diagnostic catheter, and the sheath was placed just proximal to the neck of the fistula. A 20-mm Amplatzer vascular plug (St. Jude Medical, Minnesota, United States) was deployed without any residual shunting (Figure 3, Video 3 and 4). The arterial oxygen saturation immediately increased to 98%. The patient was discharged on aspirin on day three after the procedure. Oral anticoagulation was avoided in this case because of bleeding issues related to multiple hemangiomas.

OUTCOME AND FOLLOW-UP

At the 2-mo follow-up, contrast-enhanced computed tomography showed the position of the vascular plug *in situ*; there was no residual shunting, and the patient's room air saturation was 98%.

DISCUSSION

Incomplete degeneration of the partition between the arterial and venous plexus of the splanchnic pulmonary vascular bed leads to the formation of thin-walled sacs, resulting in the formation of pulmonary arteriovenous fistulas, which may sometimes be absorbed into the left atrium, causing the pulmonary artery to form a left atrial fistula. The potential right-to-left shunt and aneurysmal dilatation of the pathway can cause thromboembolism and death due to rupture of the sac. The incidence of this kind of fistula is higher in males. Routine frontal chest X-ray examination may show

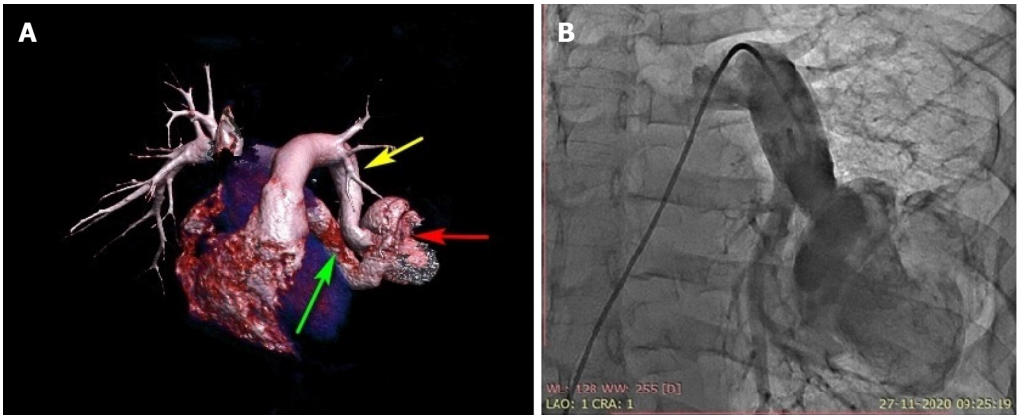


Figure 1 Three-dimensional computed tomography volume rendering and pulmonary artery angiogram. A: Contrast-enhanced computed tomography with three-dimensional reconstruction showing the left lower pulmonary artery-to-left atrial fistula with a highly tortuous course associated with an aneurysmal sac. Yellow arrow: left lower segmental artery; red arrow: aneurysmal sac; green arrow: last part of fistula connecting the left atrium; B: Anterior-posterior projection of pulmonary artery angiography using a 6-Fr pigtail catheter showing a highly tortuous large left pulmonary artery-to-left atrial fistula associated with a 6-cm aneurysmal sac. The right ventricular oxygen saturation was 79%, and the left ventricular saturation was 92% in room air without anesthesia.

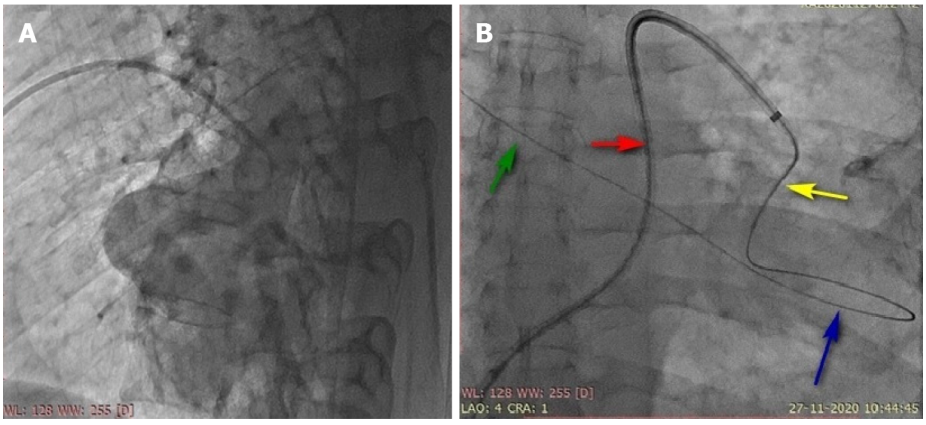


Figure 2 Lateral pulmonary angiography and the course of the guidewire. A: Lateral pulmonary artery angiography using a 6-Fr pigtail catheter showing a large left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac; B: A Terumo wire (0.35 cm × 260 cm) and 5-Fr multipurpose catheter helped to negotiate the highly tortuous course of the fistula to reach beyond the targeted landing zone and the site of guide wire placement in the upper right pulmonary vein *via* the aneurysmal sac for adequate support. Red arrow: 8-Fr sheath; yellow arrow: 5-Fr multipurpose catheter through the delivery sheath; blue arrow: guidewire in the aneurysmal sac; green arrow: upper right pulmonary vein.

perihilar vascular enlargement. Agitated saline contrast echocardiography could provide additional information when pulmonary artery-to-left atrial fistula is suspected. A close differential diagnosis of pulmonary arteriovenous fistula must always be kept in mind[6]. Although invasive pulmonary angiography is diagnostic, it should be reserved for intervention because computed tomography angiography with three-dimensional reconstruction provides most of the information needed to decide whether a fistula can be percutaneously plugged by a device or requires surgical closure[7]. Various plugging devices, such as vascular plugs, duct occluders and septal defect occluders, can be used depending upon the tortuosity of the course, availability of the landing zone and available delivery sheath and age of the patient. The plug can be deployed with or without an arteriovenous loop depending on the tortuosity of the course and size of the fistula[8] with or without general anesthesia depending upon the age of the patient.

The proximal part of the left lower lobe pulmonary artery was tortuous before its division into anterior and posterior segmental branches. The sac was located along the course of the anterior segmental artery. We faced five major challenges to the catheter-based intervention in this case. (1) Negotiation of the 8-Fr sheath with its stiff default dilator was not possible; we overcame this difficulty by using a 5-Fr multipurpose catheter and substituting the dilator; (2) Although device implantation could have been performed using a transseptal approach with or without a loop, we could manage the antegrade approach from the pulmonary artery because of the good

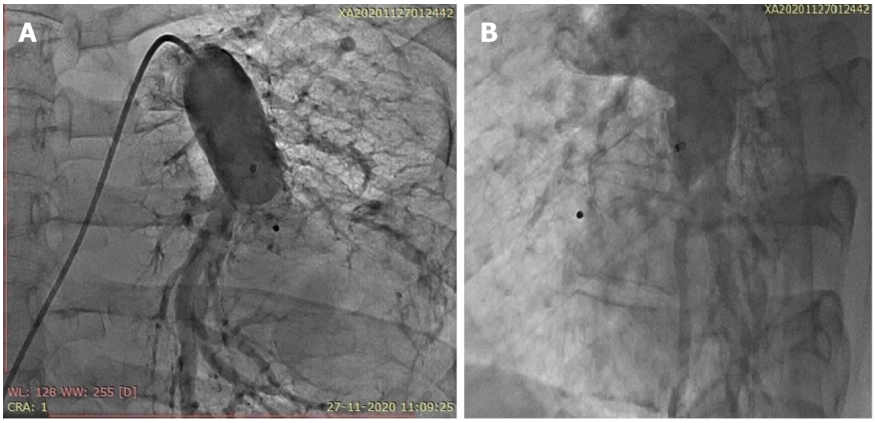


Figure 3 Pulmonary artery angiography after device deployment. Pulmonary artery angiography in the frontal projection and in the lateral projection showing perfect device positioning, no residual shunting and uncompromised blood flow in the left lower segmental artery. A: Frontal projection; B: Lateral projection.

support provided by the guidewire in the upper right pulmonary vein; (3) The proximal end of the landing zone in this case was quite close to the ostium of a large posterior segmental left pulmonary artery branch, but the procedure was completed well because of the proper device selection, which is evident in the provided video clips (Video 3 and 4); (4) The possibility of device embolization in this case was avoided by proper identification of the landing zone and its diameter and the selection of a well-fitting device; and (5) Although there was a fair indication for oral anticoagulation to prevent atheroembolism from the aneurysmal sac after device implantation, we only administered aspirin to avoid bleeding issues related to multiple hemangiomas. Percutaneous closure is preferred to open heart surgery whenever the anatomy allows, as in this case.

CONCLUSION

Left pulmonary artery-to-left atrial fistula is relatively uncommon compared to right pulmonary artery-to-left atrial fistula. Percutaneous closure by either a transeptal technique or guide wire insertion in the pulmonary vein through the pulmonary artery is preferred. The need for an arteriovenous loop depends upon the tortuosity of the course of the fistula and this size of the device to be implanted because a larger device needs a larger sheath, necessitating firm guide wire support to facilitate negotiation of the stiff combination of the delivery sheath and dilator.

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MINIREVIEWS

Transcatheter pulmonic valve implantation: Techniques, current roles, and future implications

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Abstract

Right ventricular outflow tract (RVOT) obstruction is present in a variety of congenital heart disease states including tetralogy of Fallot, pulmonary atresia/stenosis and other conotruncal abnormalities *etc.* After surgical repair, these patients develop RVOT residual abnormalities of pulmonic stenosis and/or insufficiency of their native outflow tract or right ventricle to pulmonary artery conduit. There are also sequelae of other surgeries like the Ross operation for aortic valve disease that lead to right ventricle to pulmonary artery conduit dysfunction. Surgical pulmonic valve replacement (SPVR) has been the mainstay for these patients and is considered standard of care. Transcatheter pulmonic valve implantation (TPVI) was first reported in 2000 and has made strides as a comparable alternative to SPVR, being approved in the United States in 2010. We provide a comprehensive review in this space–indications for TPVI, detailed procedural facets and up-to-date review of the literature regarding outcomes of TPVI. TPVI has been shown to have favorable medium-term outcomes free of re-interventions especially after the adoption of the practice of pre-stenting the RVOT. Procedural mortality and complications are uncommon. With more experience, recognition of risk of dreaded outcomes like coronary compression has improved. Also, conduit rupture is increasingly being managed with transcatheter tools. Questions over endocarditis risk still prevail in the TPVI population. Head-to-head comparisons to SPVR are still limited but available data suggests equivalence. We also discuss newer valve technologies that have limited data currently and may have more applicability for treatment of native dysfunctional RVOT substrates.

Key Words: Pulmonary valve; Congenital heart defects; Heart valve prosthesis implant; Pulmonary valve insufficiency; Pulmonary atresia; Pulmonary valve stenosis

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Core Tip: As patients with congenital heart defects continue to survive well into adult life, right ventricular function preservation and management of the right ventricular outflow tract has become increasingly important and sophisticated. As an alternative to surgical pulmonary valve replacement (PVR), the advent of transcatheter pulmonic valve therapy has offered a less invasive approach for many patients. Improved techniques and technologies have rapidly expanded its use in increasingly complex anatomy. In this review we summarize the indications for PVR, transcatheter pulmonic valve implantation techniques, clinical outcomes and also future directions of this treatment.

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INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease occurring in approximately 3 *per* 10000 live births[1]. This defect is comprised of the following four components: Ventricular septal defect (VSD), aortic override, right ventricular hypertrophy, and right ventricular outflow tract (OT) obstruction in the form of infundibular stenosis/pulmonary valve stenosis/pulmonary artery stenosis. Correction of this heart defect involves patch closure of the VSD and relief of the right ventricular outflow tract (RVOT) obstruction. The end result uniformly leaves the patient with residual OT dysfunction with some form of pulmonic stenosis (PS)[2] and/or pulmonary valve insufficiency (PI) leading to deleterious effects over the long-term[3,4]. The chronic effects of pressure and volume loading on the right ventricular (RV) ultimately lead to symptomatic ventricular dysfunction and arrhythmia[2,3].

While TOF is the stereotypic diagnosis for the management of residual RVOT disease, other congenital heart defects are managed similarly. Conotruncal defects such as truncus arteriosus, d-transposition of the great arteries with a VSD and pulmonary stenosis, double outlet right ventricle can be repaired with a VSD closure to the aortic valve and placement of a RV to pulmonary artery conduit. Another common example is the Ross operation for aortic valve stenosis which leaves the patient with a reconstructed RV to pulmonary artery connection. These surgically reconstructed outflows all universally fail over time leading to the same long-term deleterious effect on the RV.

Until recently, surgical pulmonic valve replacement (SPVR) was utilized universally for pulmonary valve replacement (PVR) and relief of RVOT dysfunction. In 2000, Bonhoeffer *et al*[5] implanted the first transcatheter valve into a human[5]. This led to the development of Melody Transcatheter Pulmonary Valve (Medtronic Inc, Minneapolis, MN), receiving Humanitarian Device Exemption (HDE) Food and Drug approval (FDA) for commercial use in dysfunctional RV to pulmonary conduits in the United States in 2010. Subsequent studies allowed for approval of the Sapien XT valve (Edwards Lifesciences LLC, Irvine, California) as transcatheter PVR in failed RV to pulmonary conduits[6].

In the following review we will review the indications for transcatheter pulmonic valve implantation (TPVI), discuss procedural considerations, techniques, outcomes as well as future considerations.

INDICATIONS FOR INTERVENTION

The indications for PVR, especially *via* transcatheter means are gradually evolving. Most clinical societies agree with need for PVR in symptomatic patients in the TOF spectrum with moderate to severe PS or PI (Table 1). However, the question of asymptomatic PI persists. The deleterious effects of progressive RV dilation with

Table 1 Comparison of American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for pulmonic valve placement

Indication	Recommendation		Level of evidence	
	ACC/AHA 2018	ESC 2010	ACC/AHA 2018	ESC 2010
Symptomatic with moderate/severe PR	I	I	B	C
Asymptomatic with moderate/severe PR and RV dilation	IIa	IIa	B	C
Asymptomatic with moderate/severe PR and ventricular arrhythmias	IIb	IIa	C	C

ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; PR: Pulmonary regurgitation; RV: Right ventricle

respect to increased mortality are well known, however it has not been convincingly proven that SPVR improves mortality or the incidence of ventricular arrhythmias[7]. There have been multiple studies to investigate what threshold of RV dilation should be used to pursue PVR in an asymptomatic patient which allows a reasonable chance of reversal of structural abnormalities[8]. However, surgical PVR for asymptomatic patients with lesser degrees of RV dilation has also been shown to increase chances of heart failure, atrial arrhythmias or ventricular tachycardia[9]. Thus, the need to balance the deleterious effects of progressive RV dilation with those of repeated operations and cardiopulmonary bypass need to be weighed together. With the increase in use of TPVI, the latter can be circumvented and with solutions for native RVOT also on horizon, it is likely that more asymptomatic patients may benefit from the procedure. Currently, generally accepted indications for TPVI in asymptomatic patients are the following[3]: (1) RV indexed end diastolic volume > 160 mL/m^2 or RV indexed end systolic volume > 80 mL/m^2; (2) RV end diastolic volume > 2 times of left ventricular end diastolic volume; (3) Significant RV dysfunction (RV ejection fraction < 45%); (4) Progressive tricuspid regurgitation in the setting of a dilated RV; and (5) Ventricular arrhythmias with a dilated RV.

PROCEDURE

Generally multidisciplinary discussion with different cardiology subspecialties (almost always with adult congenital specialists), congenital cardiac surgery and cardiac anesthesia is recommended to determine best strategy for each individual patient. Multi-modality imaging review and good understanding of prior operations is essential. It is of vital importance to understand the nominal size of RV to pulmonary artery conduits and bioprosthetic pulmonary valves as well as any known coronary artery anomalies.

General anesthesia is usually preferred[10]. Biplane fluoroscopy is most often employed to understand the RVOT and pulmonary artery anatomy in two views and requires patient positioning with the arms elevated in a non-stretched position to avoid brachial plexus injury[11]. Most patients have had multiple catheterizations/surgeries and may have unique vascular access considerations. While femoral venous access is often the first choice, the jugular (ideally right) can offer advantages for valve delivery as well for flexing of Edwards Sapien delivery systems[12].

Baseline data

A baseline right and left heart catheterization hemodynamic assessment is performed as well as RVOT, pulmonary artery, and aorta/coronary angiography. From this data, a plan for conduit rehabilitation and final balloon sizing is developed as well as ascertaining risk for conduit rupture and coronary artery compression. It also identifies other pulmonary artery stenosis that might need to be intervened upon during the procedure. After baseline data is obtained a stiff wire [Lunderquist Extra Stiff Guidewire (Cook Medical, Bloomington, IN), Amplatz Superstiff Guidewire (Boston Scientific, Boston, MA)] is positioned into the distal lower lobe of right or left pulmonary artery.

Conduit preparation-balloon/stent

Many dysfunctional RVOTs involve significant conduit stenosis. This requires conduit rehabilitation and stenting to achieve acceptable post procedure RV pressure. Serial balloon dilation with high pressure balloon angioplasty is often necessary. This places the conduit at risk for rupture necessitating covered stent angioplasty with a Cheatham-platinum covered stent (Numed, Hopkinton, New York, United States) (Figure 1)[13]. Once assured that an adequate final diameter can be achieved, bare metal stent angioplasty with large bore hand mounted stainless-steel stents [Palmaz XL (Cordis, Milpitas, CA, United States), InstraStent Max LD (EV3, Plymouth, MN, United States)] are implanted. Because of stent fracture risk of the Melody valve, multiple stents might be necessary to avoid recoil and limit metal fatigue[14]. Ideally, for an adult, the final diameter of the conduit should be at least 20-22 mm, otherwise, a residual RVOT gradient will persist.

Coronary artery and aorta testing

Prior to initial stenting of the conduit, assessment for risk of coronary artery obstruction is necessary. A variety of coronary artery anomalies can be at risk including a left anterior descending from the right coronary artery, ostial stenosis, abnormal location secondary to reimplantation. Coronary artery testing is performed with either aortic root angiography and/or selective coronary angiography. This is performed with the Anteroposterior tube angled caudal to perform and "down the barrel" assessment (Figure 2). If the coronary artery flow is compromised during balloon testing, this is considered a contraindication to proceeding with stent or PVI. While less commonly a problem, aortic root distortion causing aortic valve insufficiency has also been demonstrated[15].

Valve implant

Once the conduit is adequately prepared-the Melody valve is hand crimped onto the balloon Ensemble system (Medtronic, Minneapolis, MN, United States) (Figure 3). Balloons range from 18-22 mm and there are descriptions of maintained valve competency even when mounted on a 24 mm balloon[16]. The outer diameter of the valve is approximately 2 mm larger than the balloon diameter. The Edwards XT valve is crimped onto the Novaflex delivery system using the proprietary process (Figure 4).

After delivery system preparation, the delivery system is advanced into the appropriate position. Numerous techniques can be used to aid in delivery system advancement such as balloon assisted or a buddy wire methods[17]. Secondary to the stiffness of the delivery system, Edwards Sapien XT valve is more difficult to pass into the OT. Use of the Sapien S3 and the smaller delivery system is more amenable to traversing the RVOT. Use of the Edwards XT or Sapien S3 through a long (65 cm) large bore Gore sheath (Flagstaff, AZ) into position has mitigated some of the difficulty[18]. While the valve implant is typically stable, rapid pacing at 140-160 beats per minute can be performed to aid in valve positioning. Following valve implant, post implant hemodynamic data are obtained, and an angiogram is performed to evaluate for perivalvar leak and valve competence. Some have advocated for intracardiac echocardiogram imaging post implant to evaluate the implant and have a reference for the future[19]. Typically for hemostasis post procedure a figure of 8 stitch is sufficient[20].

Special considerations–valve in valve

Valve in bioprosthetic valve implantation tends to be a less complex procedure. The risk of coronary compression is less as the valve cannot be over-expanded at low pressure, and generally there is no need to pre-stent unless there is significant conduit stenosis separate from the valve. The type and size of bioprosthetic valve is of utmost importance as the inner diameter dictates the size of transcatheter valve. Many descriptions of valve fracture exist, expanding the valve to the size or just larger of the outer diameter with a high pressure True balloon (Atlas, Atlas Gold, or True Balloon, Bard Peripheral Vascular, Inc, Tempe, AZ) (Figure 5)[21]. This avoids future development of valve patient size mismatch. In the pulmonary system, fracture can be safely performed prior to valve implantation. One must be mindful of the coronary artery anatomy when considering valve fracture.

Special consideration–native OT

The OT after transannular patch repair for TOF can be quite complex. Many times, it lacks a tubular landing zone and can have a funnel shape from the RV out to the pulmonary arteries. However, some native OTs have anatomy suitable for currently available valve to be used off-label. Balloon sizing with a large diameter (> 35 mm)

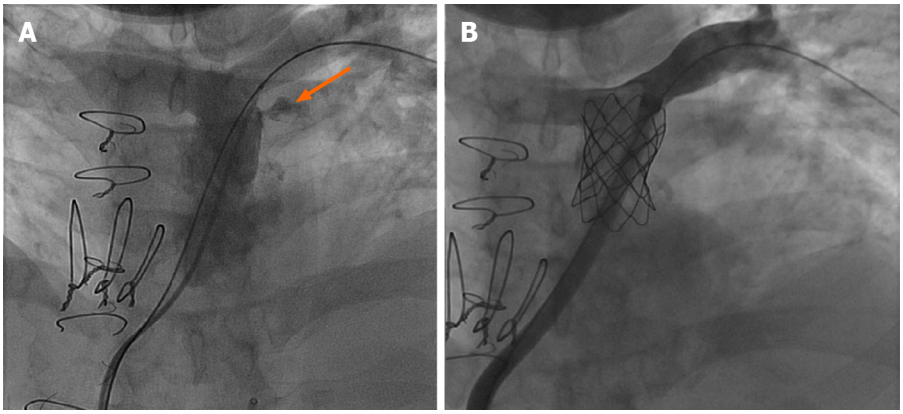


Figure 1 Covered Cheatham Platinum stent placement after conduit disruption. 23 years old patient with truncus arteriosus status post repair with a 20 mm homograft. A: With high pressure dilation at 22 mm, disruption of wall of conduit is noted (orange arrow) but contained; B: Covered Cheatham Platinum stent placed with resolution of the extravasation.

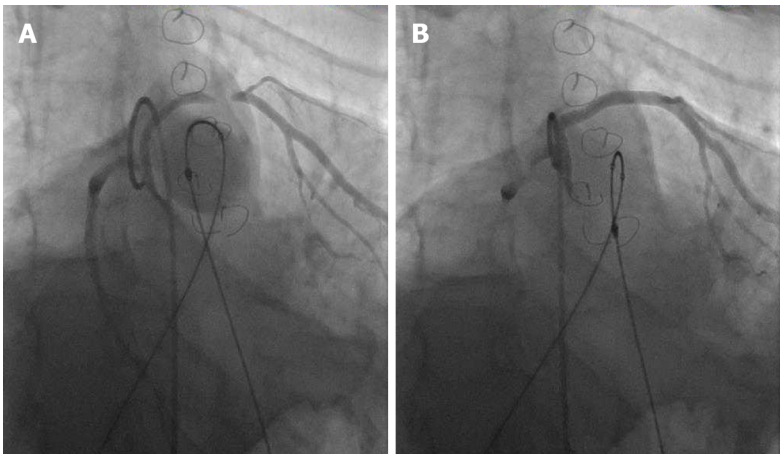


Figure 2 Tetralogy of Fallot full repair with 20 mm homograft. 28-year-old with tetralogy of Fallot status post repair with 20 mm homograft. A: Left anterior descending (LAD) arise from the right coronary coursing around the homograft. With inflation of a 22 mm balloon, the mid LAD is compressed; B: The coronary flow returns back to baseline upon balloon deflation.

compliant balloon can identify a suitable landing zone for a balloon expandable stent. In appropriate anatomic arrangements, this is reported with good short- and long-term success (Figure 6)[22]. Valve implant into one or both of the proximal branch pulmonary arteries has also been shown to be effective in reducing the degree of PI[23].

The Medtronic Harmony Valve (Minneapolis, MN, United States) (Figure 7) is a self-expanding valve that can be used in native OT after three-dimensional sizing data has been obtained. Similarly, the Alterra pre-stent (Edwards Lifesciences LLC, Irvine, California) (Figure 8) allows for creation of a landing zone to allow for implantation of a 29 Sapien S3 valve. Both are currently under investigation at the time of writing this review[24,25].

AVAILABLE AND UPCOMING VALVE SYSTEMS

The Melody valve (Medtronic Inc, Minneapolis, MN, United States) traces its origins to the implantation of an 18 mm bovine jugular vein mounted on a platinum stent in a 12 year old patient with conduit failure by Bonhoeffer *et at*[5]. In its current iteration, the Melody valve is a bovine jugular vein sutured inside of a Platinum Iridium stent, available in two sizes – 20 and 22 mm. The two sizes use 16 and 18 mm vein segments intended to be expanded up to 20 and 22 mm respectively. The valve is delivered *via* the Medtronic Ensemble delivery system which utilizes a "balloon-in-balloon" (NuMED Inc, Hopkinton, NY, United States). The delivery system is 22F and is available in 18, 20, and 22 mm sizes.

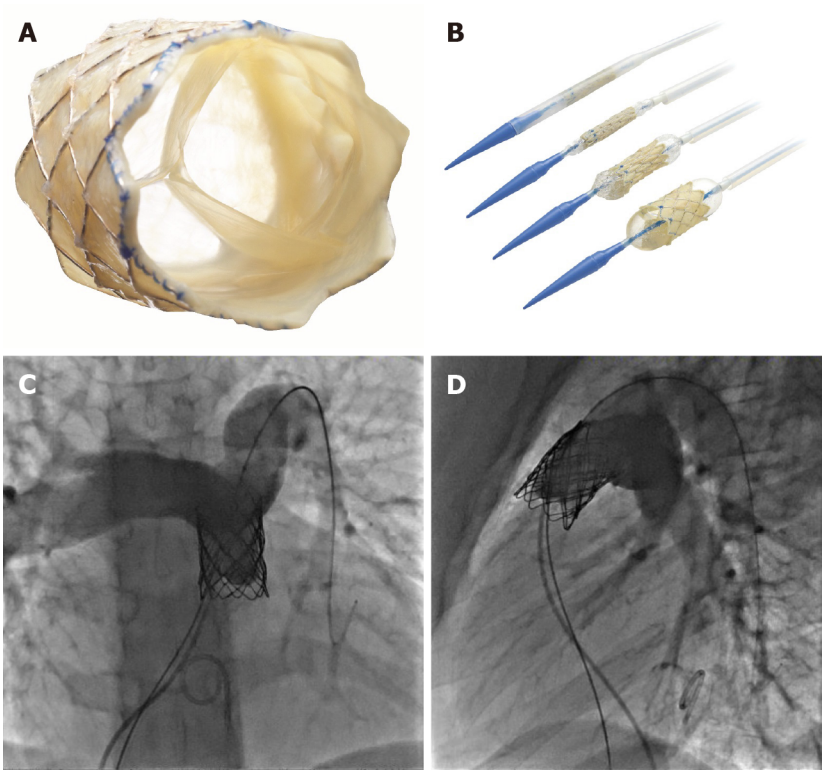


Figure 3 Melody transcatheter pulmonic valve. A: En-face view of Melody transcatheter pulmonic valve; B: Melody valve Ensemble with loaded valve demonstrating the two-stage balloon-in-balloon inflation (Reproduced with permission from Medtronic, Inc, Minneapolis, MN, United States); C: Angiogram after placement of a stainless steel pre-stent; D: 20 mm Melody valve in Antero-posterior and lateral projections.

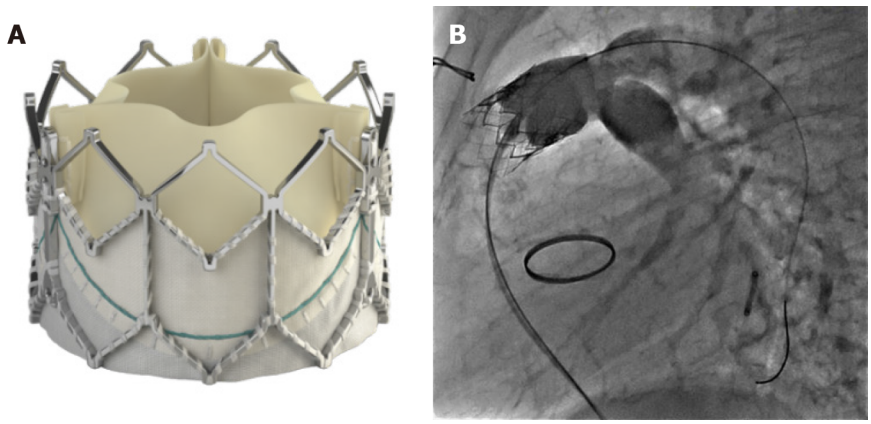


Figure 4 Edwards Sapien XT™. A: Edwards Sapien XT™ valve (Reproduced with permission of Edwards Lifesciences LLC, Irvine, CA, United States); B: Angiogram after placement of a 23 mm Edwards Sapien XT™ valve in a Contegra conduit stented with a stainless-steel stent up dilated up to 22 mm.

Experience from European centers with the Melody valve predates use in the United States–Lurz *et al*[26] reported their series of 155 implants with an excellent success rate of 96.7%, freedom from reoperation rates of 70% after 70 mo and lower re-operation rates with increasing familiarity/expertise with the valve system[26]. The United States Investigational Device Exemption trial reported its medium to long term results in 2015 enrolling a total of 171 patients with 148 successful implants and a re-intervention free rate of 76% at 5 years[27]. The Melody valve received Conformitè Europëenne Mark approval in 2006; the FDA granted HDE approval in 2010 and full post market approval in 2015. The United States post market approval study had 100 implants with 98% success rate and a 98% rate of freedom from catheter/surgical re-intervention[28].

The Edwards Sapien XT (Edwards Lifesciences, Irvine, CA, United States) transcatheter heart valve (THV) was approved by the FDA for use in the pulmonic position in 2016 (Figure 4). The valve is made of bovine pericardial tissue and

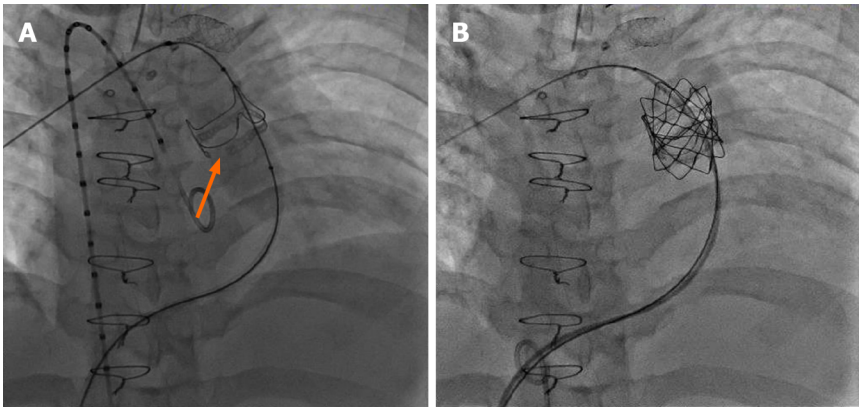


Figure 5 Transcatheter valve in valve with valve fracture: 21 years old with congenital pulmonary stenosis with a prior dysfunctional 21 mm Edwards Magna™ valve- 22 mm. A: Atlas balloon inflated to 20 ATM fractured the valve ring (orange arrow); B: placement of 22 mm Melody valve.

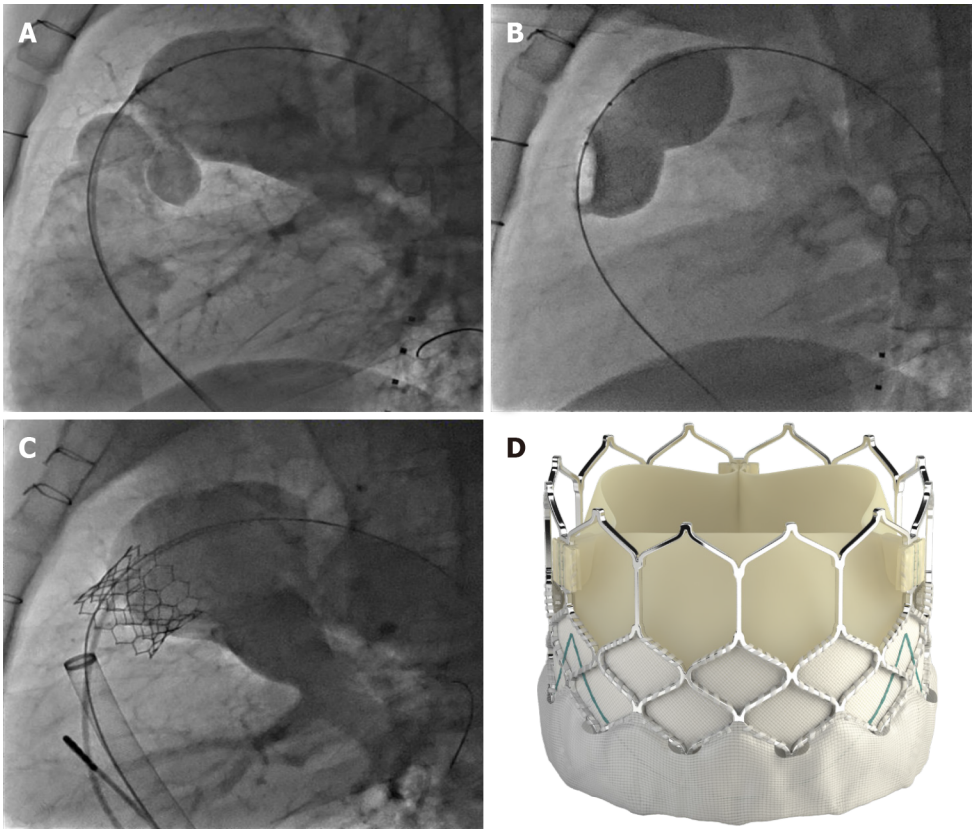


Figure 6 Native transcatheter pulmonary valve implantation. A and B: 46 years old with prior surgical pulmonary valvotomy as a child presenting with severe insufficiency (A), balloon sizing performed with 40 mm Numed sizing balloon demonstrated a narrowed landing zone of 27 mm (B); C: Native implant with a 29 mm Sapien 3™ valve was feasible through a 26 F 65 cm Gore DrySeal sheath; D: Edwards Sapien 3™ valve (reproduced with permission from Edwards Lifesciences LLC, Irvine, CA, United States).

mounted on a cobalt chromium stent with a fabric skirt on the outside lower part of the stent to minimize perivalvular regurgitation. The valve sizes are 23, 26 and 29 mm and delivered *via* the Edwards Novaflex delivery system. The COMPASSION clinical trial enrolled 81 patients and implanted the Sapien XT THV in 69 with a 93.7% freedom from re-intervention at 3 years[6]. There are ongoing clinical trials, for post market approval surveillance of the use of this valve and also for the evaluation of the Edwards Sapien 3 THV (Figure 4). The Sapien 3 expands the valve sizes with a 20 mm option–the Commander valve delivery system is also believed to be better suited for delivery into the RVOT. Data from a series of 56 patients from Germany suggests excellent procedural success and no reinterventions were needed up to 2 years of follow up[29].



Figure 7 Medtronic Harmony transcatheter pulmonic valve (Reproduced with permission from Medtronic, Inc, Minneapolis, MN, United States).

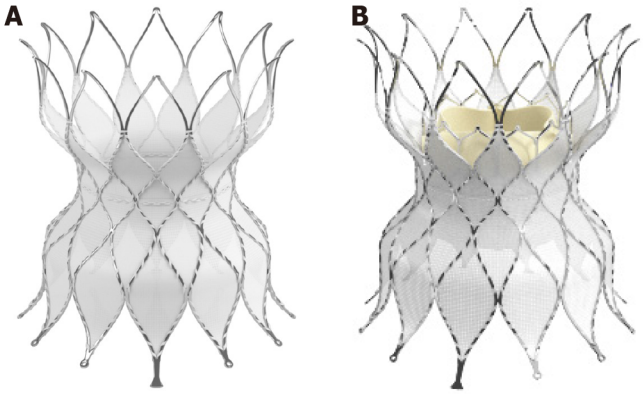


Figure 8 Edwards native outflow tract prestent. A: Alterra Adaptive Prestent™; B: Edwards Sapien 3™ valve implanted inside the Alterra prestent (Reproduced with permission from Edwards Lifesciences LLC, Irvine, CA, United States).

The venus *P* valve (Venus Medtech, Hangzhou, China) is a newer generation valve using porcine pericardium leaflets mounted inside the middle segment of a self-expanding nitinol stent. The middle segment measures 22-36 mm in diameter and 20-35 mm in length. The proximal and distal ends are flared to provide an hourglass shape that helps with anchoring in the RVOT and main pulmonary artery. The delivery system consists of a 19-24F capsule which houses the crimped stent valve and a 15F shaft. This system is designed keeping in mind the unmet need of treating PI in native RVOT which in most circumstances sizes out of approved valve systems' range in adults. Multiple small series report favorable outcomes with the venus *P* valve–in a 38-patient retrospective multi center report, 37 implantations were successful; 1 patient subsequently required surgical repositioning. With a median follow up of 25 mo, no significant valve dysfunction was reported. Stent fractures were reported in 27% patients but the significance of those with this valve system is not yet known[30].

Another valve system with a similar concept is the Pulsta valve (TaeWoong Medical Co, Gyeonggi-do, South Korea). It also has a knitted double strand Nitinol wire frame which is self-expanding with treated porcine pericardial tissue leaflets sutured on. The valve is available in 18-28 mm sizes (2 mm increments). The length of the stent frame is 28-38 mm depending on the valve size and the ends are flared 4 mm wider than the outer diameter for anchoring. The diameter of the "valve loading zone" is 18F while the shaft of the delivery system is 12F in caliber. There is a "hook block" to minimize chances of abrupt delivery and migration. In a Korean feasibility study, ten TOF patients with PR were treated with the Pulsta valve–five with 26 mm and other five with 28 mm valve. There were no major complications with all 10 implants showing good valve function and significant reduction in RV volumes[31].

OUTCOMES OF TPVI

Procedural success and complications

With growing experience, procedural success has improved remarkably–in a prior meta-analysis, we reported a success rate of 96.2% using observational reports, which is consistent with the 98% success rate reported in the Melody United States post market approval surveillance study[28,32]. The most dreaded complications for TPVI are conduit rupture and coronary compression. Conduit rupture is estimated in about 4.1% patients–more so in homografts[32,33]. In recent years, the practice of performing TPVI off label in conduits sized < 16 mm has increased, and the rate of conduit rupture is much more in this population. Varied estimates from 16% to 50% have been reported-however most of these ruptures are limited and can usually be managed with a covered stent implant[34,35].

Coronary compression was reported more frequently in the earlier TPVI experience and led to procedural mortality. In our pooled analysis of 1044 attempted TPVI, there were a total of five coronary complications. There were only two deaths in elective cases, and both were attributed to coronary compression[32]. However, with more experience and careful testing prior to stent/valve implant, these have become extremely rare. In the United States post market approval study, only 1 out of 100 implants had coronary compression was reported which required conversion to surgery. Five other patients out of the originally considered 120 patients had evidence of coronary compression on balloon testing[28]. It should especially be noted that anomalous origin of coronaries especially left coronary artery arising from the right cusp is a strong predictor of coronary compression[36].

Re-interventions

The issue of needing frequent re-interventions or re-operations has largely been deemed secondary to stent fractures of the Melody valve and the rates for same have vastly improved since the adoption of pre-stenting. The United States Investigational Device Exemption trial for example had only 10% pre-stenting in the first tertile of the study and reported a freedom from re-intervention rate of 76% after 5 years. The other factors leading to re-interventions were found to be implant in a homograft, a higher post implant gradient (> 25 mmHg) and pre-existing significant tricuspid regurgitation[27]. Conversely, in a French registry study with 96.9% pre-stenting only 3/62 (4.8%) patients needed re-operation for conduit re-stenosis at a median follow up of 4.6 years[37]. The other common cause for re-operation is endocarditis, which is discussed separately. The issue of re-operation/intervention has not been adequately answered for the Edwards Sapien THV because of smaller number of studies. The COMPASSION trial reported a freedom from re-intervention rate of 93.7% after 3 years with seven re-interventions in four patients[6].

Endocarditis

Endocarditis/blood stream infection has been described as a late complication after TPVI. There have been variable reports of endocarditis after Melody and Sapien valve implants, more for the former. McElhinney *et al*[38] used three patient cohorts in North America and Europe with a cumulative sample of 309 patients and a follow up of 5.1 years–Endocarditis was diagnosed in 46 patients with TPV related endocarditis occurring in 35 patients[38]. Median time to endocarditis was 3.1 years. At 5 years, 89% patients were free of endocarditis. However widely variable reports of endocarditis rates exist-Abdelghani *et al*[39] in their systematic review reported cumulative incidence ranging from 3.2%-25% with the median time from TPVI to onset of endocarditis being 18 mo[39]. 79% of these patients had evidence of RVOT obstruction with vegetations detected in 34% cases. They also did a patient level pooled analysis from 69 case reports, 8.7% patients died and 52% required surgical or transcatheter re-intervention. Less data exists for Edwards Sapien THV–97.1% freedom from endocarditis was reported in the COMPASSION study at 3 years[6]. There are also multiple reports with no endocarditis in the medium term after TPVI with Sapien THV. In a French cohort of 79 patients with a median follow up of 1.8 years, 8/32 Melody valve patients developed endocarditis compared to none for the 47 Sapien XT THV[40].

It is also interesting to note that there are differences in endocarditis rates amongst surgical PVR recipients–rates are much higher in patients receiving bovine jugular vein conduits as compared to homografts–20.4% *vs* 2.4%[41].

Comparison to surgical PVR

Very few head-to-head comparisons of SPVR and TPVI exist. Caughron *et al*[42] reported a study of 66 patients (SPVR 36; TPVI 30) and found no differences in mortality, cardiovascular re-admissions or repeat interventions in the two groups[42]. A recent meta-analysis of 1132 TPVI and 4939 SPVR patients also did not show any difference in mortality or repeat interventions. However, there were fewer procedure related complications and higher rate of endocarditis with TPVI[43]. A study using the Nationwide Inpatient Sample database also suggested the same–comparing an estimated 8449 SPVR and 555 TPVI admissions, it showed a higher in-hospital mortality with SPVR along with other iatrogenic cardiac complications. Also, TPVI predictably had less hospital length of stay decreasing the impact on societal loss of wages for patients/care givers[44].

CONCLUSION

TPVI has dramatically evolved over that past decade and has become a common procedure to manage many patients with dysfunctional RVOT. The short and midterm results are overall quite favorable with a low and acceptable morbidity and mortality. Ideally in the future, smaller and more flexible delivery systems will be developed. With native OTs, intervention becomes quite appealing if a new valve can be placed inside indefinitely thus avoiding surgery except for at the time of initial repair. As all the existing valves have been implanted for a short time with limited follow up, future data is necessary to understand their overall longevity and types of valve failure. Furthermore, as many patients have smaller and stenotic conduits even in a growing child, adoption of new surgical techniques to allow for further expansion of small and stenotic conduits could be of significant clinical benefit.

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ORIGINAL ARTICLE

Case Control Study

Correlation between soluble receptor for advanced glycation end products levels and coronary artery disease in postmenopausal nondiabetic women

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Author contributions: Ghosh S designed the research along with collection of samples and analysis; Kapoor D helped in analysis and writing of manuscript; Sangwan S performed the experiments; Study was conducted under the direct supervision of Vijayvergiya R, Wangkheimayum S and Dhawan V; Mehta S and Dhawan V edited and revised the manuscript.

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Abstract

BACKGROUND

The established cardiovascular risk factors cannot explain the overall risk of coronary artery disease (CAD), especially in women. Therefore, there is a growing need for the assessment of novel biomarkers to identify women at risk. The receptor for advanced glycation end products (RAGE) and its interaction with the advanced glycation end product (AGE) ligand have been associated with atherogenesis. The soluble fraction of RAGE (sRAGE) antagonizes RAGE signaling and exerts an antiatherogenic effect.

AIM

The study aim was to explore the association between plasma levels of sRAGE and CAD in nondiabetic postmenopausal women.

METHODS

This case-control study included 110 nondiabetic postmenopausal women who were enrolled in two groups. Group I included 55 angiographically proven CAD subjects with > 50% stenosis in at least one of the major coronary arteries and Group II included 55 healthy control women who did not have CAD or had < 50% stenosis of the coronary arteries. Stenosis was confirmed by invasive angiography. Plasma sRAGE was determined by an enzyme-linked immunosorbent assay.

RESULTS

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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We observed significantly lower plasma sRAGE concentrations in subjects with CAD *vs* healthy controls ($P < 0.05$). Univariate and multivariate logistic regression analysis also revealed a significant correlation between plasma sRAGE levels and CAD ($P = 0.01$). Multivariate odds ratios for CAD revealed that subjects with sRAGE concentrations below 225 pg/mL (lowest quartile) had a 6-fold increase in CAD prevalence independent of other risk factors.

CONCLUSION

Our findings indicated that low sRAGE levels were independently associated with CAD in nondiabetic postmenopausal women. Risk assessment of CAD in postmenopausal women can be improved by including sRAGE along with other risk factors.

Key Words: Coronary artery disease; Soluble receptor for advanced glycation end products; Postmenopausal status; Nondiabetic females; Correlation; Regression

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Core Tip: The growing need for the assessment of novel biomarkers led us to identify the risk in women. The receptor for advanced glycation end products (RAGE) and its interaction with the AGE ligand have been shown to play an important role in promoting atherosclerosis. The soluble fraction of RAGE (sRAGE) binds to ligands and antagonizes RAGE signaling, thereby exerting an antiatherogenic effect. This study established that low levels of sRAGE in plasma are independently associated with the presence of coronary artery disease in nondiabetic postmenopausal females.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality throughout the world. The incidence of CAD is rising rapidly in India, and it is projected that more than 50% of CAD cases in the world will in from India by 2025[1]. Atherosclerosis is the most common cause of CAD. It causes luminal narrowing, which creates an imbalance between supply and demand, thereby impairing the coronary reserve. The etiology of CAD is multifactorial. Traditional risk factors include diabetes, hypertension (HTN), hyperlipidemia, smoking, family history, physical inactivity, obesity, and others. Along with the classical risk factors, oxidative stress and inflammation are now considered as significant risk factors of CAD. Evidence in the literature supports significant positive correlations between various inflammatory mediators including high-sensitivity C-reactive protein (hsCRP), homocysteine, lipoprotein (Lp)-a, matrix metalloproteinases, and tissue inhibitor of matrix metalloproteinase and development of CAD[2]. Postmenopausal status is an important risk factor of CAD, and cardiovascular disease is more common in postmenopausal than in premenopausal women because of decreased endogenous estradiol in that age group[3]. Postmenopausal status is the strongest predictor in women, but it is the least studied factor compared with other traditional risk factors.

Numerous reports in the literature state that CAD occurs in the absence of major risk factors in about one-third of patients in India[4]. Therefore, the overall risk of CAD cannot be explained by traditional and established cardiovascular risk factors[4-6]. The elucidation of novel biomarkers is the need of the hour to identify women at risk. One of the candidate genes that potentially accounts for an inherited predisposition to CAD is receptor for advanced glycation end products (RAGE) together with its soluble circulating form, sRAGE, and an endogenous secretory form

called esRAGE.

RAGE is a transmembrane receptor of the immunoglobulin superfamily, and it is located in the major histocompatibility complex (gene 6 p21.3)[7]. It can interact with various ligands involved in inflammation, atherosclerosis, and vasoconstriction[8] and is highly expressed at the site of vascular pathology[9]. Activation of the RAGE-dependent pathway is followed by many deleterious effects occur like activation of nuclear factor-B, increased cytokines, and induction of oxidative stress[10,11]. Advanced glycation end products (AGEs) are RAGE ligands for RAGE and their interaction results in coronary atherosclerosis[12]. AGE-RAGE interaction and the subsequent effects are also of great importance in diabetic vasculopathy. Recent studies have shown the key role of this signaling pathway in nondiabetic atherosclerosis[13].

sRAGE is produced by the cleavage of membrane-bound RAGE. It consists of the extracellular ligand-binding domain only and lacks both cytoplasmic and transmembrane domains[14]. It circulates abundantly in blood and antagonizes RAGE signaling[15]. There are two schools of thoughts regarding the association of sRAGE and CAD. Some investigators believe that decreased levels of sRAGE increase the risk of CAD; others believe that increased levels of sRAGE increase the risk of CAD. Many experimental and clinical studies have assessed the association and correlation of the plasma levels of sRAGE and CAD, but whether increased or decreased levels of sRAGE are associated with CAD remains controversial. Moreover, very few of those studies were carried out in Indian populations, especially in postmenopausal women. In this study, we aimed to assess the correlation between plasma levels of sRAGE and CAD in postmenopausal women.

MATERIALS AND METHODS

Study design

This case-control prospective observational study was conducted at the Advanced Cardiac Center of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. After screening, we enrolled 110 nondiabetic postmenopausal women and assigned them to two groups. Group I included women with CAD and > 50% stenosis in at least one of the major coronary arteries (n = 55). and Group II included healthy women without CAD and with < 50% stenosis in the coronary arteries. Each study subject underwent coronary angiography following the cardiac center protocol. The indications for angiography were suspicion of CAD or preoperative screening for CAD in subjects with valvular disease. Exclusion criteria were patients with diabetes, premenopausal female, surgery or trauma during the month preceding the study, known cardiomyopathy, known malignant diseases, known febrile conditions, subjects using lipid lowering agents, acute or chronic inflammatory disease, connective tissue disorder, renal insufficiency (creatinine > 1.5 mg/dL), abnormal liver function, patients with heart failure or cardiogenic shock, refusal to give informed consent and patient with any neoplasm. Subjects having a concentration of hsCRP > 10 mg/L, a level considered to be indicative of clinically relevant inflammatory conditions, were also excluded from the study[16].

Ethical approval and informed consent: The study was conducted following the ethical standards detailed in the Declaration of Helsinki[17] and was approved by the Institute ethical committee. Informed consent was obtained from all the patients after explaining the protocol prior to their enrolment in the study.

Clinical examination and parameters

All participants underwent a standard clinical examination. All cardioactive drugs used by the patients were registered, with particular regard to beta-blockers, calcium-antagonists, ACE inhibitors, antiplatelet drugs, statins, and nitrates. Clinical characteristics including height, weight, smoking status, blood pressure (BP), waist circumference, family history of CAD, and body mass index (BMI, kg/m^2) were documented. According to the Asian classification, a BMI of < 18.5 kg/m^2 is underweight, 18.5-22.99 kg/m^2 is normal, 23.0-27.49 kg/m^2 is overweight and > 27.5 kg/m^2 is obese[18]. A waist circumference cutoff of 80 cm as applied for women[19]. Cigarette smoking was dichotomized into ever *vs* never, with ever smoking defined as having smoked daily for 1 year or more. Many patients had quit after the onset of CAD, hence the designation as ever smoking rather than current and former. HTN was defined as a systolic BP of > 140 and/or a diastolic BP of > 90 and/or on treatment with antihyper-

tensives, following the eighth Joint National Committee guidelines[20]. American Diabetes Association guidelines, diabetes was taken as either fasting blood sugar (FBS) > 126 mg/dL, 2 h postprandial glucose > 200 mg/dL, glycosylated hemoglobin (HbA1c) > 6.5% or Rutherford backscattering spectroscopy > 200 mg/dL, with symptoms of hyperglycemia in an oral glucose tolerance test[21]. The study protocol excluded subjects with diabetes.

Laboratory methods

All laboratory determinations were performed in a blinded fashion. Before angiography, A 14 mL blood sample was collected from antecubital vein after an overnight fast, and 10 mL were immediately sent to different laboratories in PGIMER for testing as described below. The remaining 4 mL was collected in ethylenediaminetetraacetic acid vials and was centrifuged at 1000 *g* for 30 min for collection of plasma and immediately divided into aliquots. Plasma was stored at −80°C until performing the Lp(a) and sRAGE assays.

Lipid profile: All components of the lipid profile were measured in an autoanalyzer. Subjects were classified as dyslipidemic if they had levels of low-density lipoprotein cholesterol (LDL-C) > 100 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL, triglycerides > 150 mg/dL or total cholesterol > 200 mg/dL[22].

Blood sugar: Plasma FBS and postprandial blood sugar (PPBS) were estimated by the glucose oxidase method. HbA1c was estimated by high-performance liquid chromatography.

hsCRP: hsCRP levels were estimated in samples of plasma containing suspensions of latex particles coated with monoclonal/polyclonal antibodies to human CRP. The plane polarized light passing through the solution was scattered in a manner proportional to the CRP concentration. The intensity of the scattered light was measured against a standard curve prepared using known concentrations of the CRP antigen.

Plasma homocysteine: Plasma homocysteine levels were determined in heparinized blood samples with an enzyme cycling assay.

Renal function tests: For renal function tests, urea levels were measured by Fearon reaction and creatinine levels were measured by Jaffe's alkaline picrate method in an autoanalyzer.

Lp(a): Lp(a) levels were estimated using a commercially available enzyme-linked immunosorbent assay kit (Assay Max Human Lp(a), Assaypro Catalog no: EL3001-1). This assay employed a quantitative sandwich enzyme immunoassay technique that measured human Lp(a) in less than 4 h. The normal Lp(a) value with this kit was 60-180 µg/mL.

sRAGE: Plasma sRAGE levels were determined using a commercially available enzyme-linked immunosorbent assay kit (BioVendor, Catalog No: RD191116200R) following the manufacturer's protocol. Briefly, a monoclonal antibody against sRAGE was used to capture sRAGE from plasma. Captured sRAGE was detected with a polyclonal anti-human sRAGE antibody. After washing, plates incubated with streptavidin-horseradish peroxidase, were developed with the appropriate substrate, and the OD_{450} was determined using an enzyme-linked immunosorbent assay plate reader. Measurements were performed in duplicate and the results were averaged and reported as pg/mL.

Coronary angiography

Coronary angiography was carried out in all the patients using a standard protocol. The catheter was inserted through femoral or radial artery and moved up to the coronary arteries. Radiocontrast was injected into the coronary arteries under X-ray guidance in order to display the coronary anatomy and possible luminal obstruction. Existing significant CAD was defined as stenosis in the major epicardial coronary arteries that reduced the lumen diameter by 50%.

Statistical analysis

The sample size of 55 in each group had a power of more than 90% and confidence intervals (CI) of 95%. The statistical analysis was carried out using the Statistical Package for Social Sciences version 20 (IBM Corp.) All quantitative variables were estimated using measures of central location (mean) and measures of dispersion

(standard deviation). Normality of data was checked by measures of skewness and Kolmogorov–Smirnov tests of normality. Normally distributed data in groups was expressed as means ± SD. For normally distributed data, differences of the case and control mean values were compared using Student's *t*-tests. Qualitative or categorical variables like smoking history, HTN, and family history of CAD were reported as frequencies and percentages. Frequencies were compared using χ^2 or Fisher's exact tests, whichever was applicable. Pearson's correlation was used to find the associations of variables like serum triglycerides, HDL-C, LDL-C, total cholesterol, Lp(a), and sRAGE. The CAD patients and controls were categorized in quartiles of the plasma sRAGE concentration in the entire study cohort. The interquartile cutoffs of sRAGE concentration were categorized into four categories: I < 225 pg/mL, II = ³225 to < 397.5 pg/mL, III = ³397.5 to < 730 pg/mL, and IV ³730 pg/mL. To evaluate the risk associated with decreasing levels of sRAGE, odds ratio (ORs) for each quartile in the entire study cohort relative to the fourth quartile were calculated. To determine independent predictors of CAD, univariate and multivariate logistic regression were performed for categorical variables like age, HTN, and family history of CAD, and for continuous variables like waist circumference, total cholesterol, triglycerides, LDL-C, HDL-C, Lp(a), hsCRP, and sRAGE. Lastly, Pearson's correlation was used to find any correlation between sRAGE levels and other biochemical parameters. All baseline variables related to CAD with $P < 0.01$ and $P < 0.05$ in simple logistic regression analysis were included in the multivariate model. Crude and multivariate adjusted ORs were reported with their 95%CIs. Values were considered statistically significant at the $P < 0.01$ and $P < 0.05$ levels.

RESULTS

Subject characteristics

The clinical and biochemical characteristics of the study subjects (Group I: Cases; Group II: Controls) are shown in Table 1. All the participants were postmenopausal women and with a similar socioeconomic status. All were never-smokers, 30 patients and 24 control subjects had HTN, and 26 patients and 14 control subjects had family histories of CAD. Student's *t*-tests found no significant differences in age, BMI, waist circumference, lipid profile, FBS, PPBS, HbA1c, creatinine, hsCRP, homocysteine, Lp(a), and sRAGE. Chi-square tests found no significant differences in HTN or family history of CAD. No significant differences in age, BMI, waist circumference, HTN, low physical activity, total cholesterol, LDL-C, HDL-C, sugar profile (FBS/ PPBS/ HbA1c), creatinine, and Lp(a) ($P > 0.05$) were observed among the study groups. Study subjects in Group I had significantly higher levels of triglycerides (TG), hsCRP, and homocysteine along with a significant factor, *i.e.* family history of CAD, than those in Group II ($P < 0.05$). However, sRAGE levels were significantly lower in Group I (subjects with CAD) compared with Group II (subjects without CAD, $P < 0.05$).

Logistic regression

Univariate logistic regression analysis: To evaluate the significance of each factor in Table 1, univariate logistic regression analysis was performed. We observed significant differences in family history of CAD, serum cholesterol, LDL-C, homocysteine, Lp(a), hsCRP, and plasma sRAGE levels in the two groups. The results are shown in Table 2.

Multivariate logistic regression analysis: After controlling for family history of CAD, serum cholesterol, LDL-C, homocysteine, Lp(a), hsCRP and plasma sRAGE, multivariate logistic regression analysis revealed significant differences in the two groups, thus indicating them as independent predictor of CAD ($P < 0.05$). However, no significant differences in association w observed with other parameters such as HTN, HDL-C and triglycerides. The results are shown in Table 3.

Quartiles of sRAGE and CAD

The plasma sRAGE concentration [mean: 474.89 (range: 30-4350) pg/mL] was significantly lower ($P < 0.02$) in CAD cases (Group I) compared with control subjects (Group II) [mean: 725.73 (range: 90-4800) pg/mL]. The study subjects were further categorized in quartiles of sRAGE concentration, which were found to be significantly different in the multivariate analysis. The interquartile sRAGE concentration cutoffs were Category I: < 225; Category II: ≥ 225 to < 397.5; Category III: ≥ 397.5 to < 730 and Category IV: ≥ 730. The numbers and percentages of subjects in each quartile of plasma sRAGE concentration, are shown in Table 4 and Figure 1. The number of CAD

Table 1 Baseline characteristics of the study subjects

Variable	Group I (*n* = 55)	Group II (*n* = 55)	*P* value
Age (yr)	57.58 ± 7.75	56.29 ± 7.69	0.38
BMI (kg/m²)	25.41 ± 3.05	24.81 ± 3.79	0.35
WC (cm)	83.02 ± 5.17	81.42 ± 6.11	0.14
Serum CHOL (mg/dL)	175.33 ± 40.68	180.12 ± 37.12	0.52
Serum TG (mg/dL)	175.16 ± 48.67	150.09 ± 42.67	0.05
Serum HDL-C (mg/dL)	38.57 ± 6.89	40.59 ± 8.17	0.16
Serum LDL-C (mg/dL)	123.68 ± 27.73	113.17 ± 31.58	0.06
FBS (mg/dL)	92.89 ± 8.81	95.71 ± 10.14	0.12
PPBS (mg/dL)	133.33 ± 5.53	133.15 ± 3.76	0.84
HbA1c (%)	5.24 ± 0.19	5.28 ± 0.14	0.14
Serum creatinine (mg/dL)	0.79 ± 0.16	0.85 ± 0.23	0.09
Serum hsCRP (μg/mL)	5.26 ± 1.94	1.41 ± 0.44	0.00[b]
Plasma HC (μmol/L)	18.13 ± 5.39	12.83 ± 3.99	0.00[b]
Lp(a) (μg/mL)	294.36 ± 202.22	251.22 ± 221.42	0.28
sRAGE (pg/mL)	285 (30-2490)	540 (90-3450)	0.02[a]
Category 1 (< 225)	24	4	0.00[b]
Category 2 (≥ 225-< 397.5)	8	19	0.01[a]
Category 3 (≥ 397.5-< 730)	13	15	0.66
Category 4 (≥ 730)	10	17	0.12
Hypertension	30	24	0.25
Family history	26	14	0.01[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
Data are means ± SD, median (interquartile range), or frequency counts, as appropriate. BMI: Body Mass Index; CHOL: Cholesterol; FBS: Fasting blood sugar; HbA1c: Glycosylated hemoglobin; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); PPBS: Post prandial blood sugar; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides; WC: Waist circumference.

cases was 6-fold higher in the first quartile (plasma sRAGE < 225 pg/mL), than in the control subjects ($P = 0.00$). In the second (sRAGE ≥ 225-< 397.5), third (sRAGE ≥ 397.5-< 730) and fourth (sRAGE ≥ 730) quartiles, the number of control subjects was 2.38 ($P = 0.01$), 1.15 ($P = 0.66$), and 1.7-fold higher ($P = 0.12$), respectively than the number of CAD patients.

Univariate and multivariate ORs

To evaluate the risk associated with decreasing levels of sRAGE, ORs for each quartile in all of the study groups relative to fourth quartile was calculated. As shown in Tables 5 and 6, the ORs of CAD was significantly higher in the first quartile of sRAGE level compared with the fourth quartile ($P = 0.001$), but no significant differences were observed between second and fourth and third and fourth quartiles.

Pearson's correlation

Pearson's correlation was used to evaluate the significance of the relationships between sRAGE levels and other biochemical parameters. We found no significant correlations between sRAGE levels and total cholesterol, triglycerides, HDL-C, LDL-C, hsCRP, homocysteine, or Lp(a) levels (Table 7).

Table 2 Univariate logistic regression analysis

Parameter	SE	*P* value	OR	95%CI for OR	
				Lower	Upper
Age (yr)	0.038	0.374	1.034	0.960	1.115
HTN	0.598	0.742	0.821	0.254	2.651
BMI (kg/m²)	0.202	0.354	1.206	0.812	1.791
WC (cm)	0.126	0.152	0.835	0.653	1.069
FH CAD	0.668	0.011[a]	0.184	0.050	0.680
S. CHOL (mg/dl)	0.017	0.001[b]	1.060	1.025	1.096
S.LDL-C (mg/dl)	0.024	0.008[b]	0.938	0.895	0.983
S.HDL-C (mg/dl)	0.041	0.963	1.002	0.924	1.087
S.TG (mg/dl)	0.008	0.350	0.993	0.978	1.008
HC (μmol/L)	0.079	0.00[b]	0.725	0.621	0.847
Lp(a) (μg/mL)	0.002	0.041[a]	0.996	0.993	0.999
sRAGE (pg/mL)	0.001	0.010[a]	1.002	1.001	1.003
hsCRP (μg/mL)	1.037	0.00[b]	0.023	1.001	0.178

[a]$P < 0.05$.
[b]$P < 0.01$.
BMI: Body mass index; CAD: Coronary artery disease; CHOL: Cholesterol; CI: Confidence interval; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein. HTN: Hypertension; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: Standard error; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides; WC: Waist circumference.

Table 3 Multivariate logistic regression analysis

Parameter	SE	*P* value	OR	95%CI for OR	
				Lower	Upper
FH CAD	0.639	0.014[a]	4.827	1.379	16.904
S. CHOL (mg/dL)	0.017	0.002[b]	1.055	1.020	1.091
LDL-C (mg/dL)	0.024	0.011[a]	0.941	0.898	0.986
HC (mg/dL)	0.074	0.00[b]	0.734	0.635	0.848
sRAGE (pg/mL)	0.001	0.011[a]	1.001	1.0001	1.003
Lp(a) (μg/mL)	0.001	0.052	0.997	0.994	1.000
HTN	0.571	0.755	1.195	0.390	3.662
HDL-C (mg/dL)	0.040	0.853	0.993	0.918	1.073
TG (mg/dL)	0.008	0.265	0.991	0.976	1.007
hsCRP (μg/mL)	1.037	0.00[b]	0.023	0.003	0.178

[a]$P < 0.05$.
[b]$P < 0.01$.
CAD: Coronary artery disease; CHOL: Cholesterol; CI: Confidence interval; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein; HTN: Hypertension; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: Standard error; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides.

DISCUSSION

CAD is a major cause of morbidity and mortality worldwide, and a large proportion of the cases of CAD occur in India. CAD mortality is declining in developed nations, but it is increasing in developing countries. In India, CAD prevalence has increased 4-fold over past two decades[23], and postmenopausal women are major contributors.

Table 4 Quartiles of soluble receptor for advanced glycation end products

Frequency distribution of CAD and control in sRAGE quartile categories					
sRAGE (pg/mL)		Group		Total	*P* value
		Case	Control		
< 225	*n*	24	4	28	19.16/0.00[b]
	%	43.6	7.3	25.5	
≥ 225-< 397.5	*n*	8	19	27	5.9/0.01[a]
	%	14.5	34.5	24.5	
≥ 397.5-< 730	*n*	13	15	28	0.19/0.66
	%	23.6	27.3	25.5	
≥ 730	*n*	10	17	27	2.4/0.12
	%	18.2	30.9	24.5	
Total	*n*	55	55	110	
	%	100.0	100.0	100.0	

[a]$P < 0.05$.
[b]$P < 0.01$ (χ^2 test).
CAD: Coronary artery disease; sRAGE: Soluble receptor for advanced glycation end products.

Table 5 Univariate odd ratios for prevalence of coronary artery disease in each category of soluble receptor for advanced glycation end products relative to category 4

Category	*P* value	OR	95%CI	
			Lower	Upper
Category 1 *vs* 4	0.001	0.098	0.026	0.365
Category 2 *vs* 4	0.564	1.397	0.448	4.355
Category 3 *vs* 4	0.481	0.679	0.231	1.994

CI: Confidence interval; OR: Odds ratio.

Table 6 Multivariate odd ratios for prevalence of coronary artery disease in each category of soluble receptor for advanced glycation end products relative to category 4

Category	*P* value	OR	95%CI	
			Lower	Upper
Category 1 *vs* 4	0.001	0.065	0.014	0.308
Category 2 *vs* 4	0.533	1.555	0.387	6.243
Category 3 *vs* 4	0.096	0.325	0.087	1.221

CI: Confidence interval; OR: Odds ratio.

Traditional risk factors like diabetes, HTN, hyperlipidemia and others cannot fully explain the occurrence of CAD in this population. Many studies have been done worldwide to find a correlation between emerging inflammatory risk factors like sRAGE and CAD. Such studies are lacking in India, especially in postmenopausal women. Postmenopausal women are more prone to CAD than premenopausal women because of decreased levels of protective estrogen[24]. Therefore, this study was undertaken in postmenopausal females to understand whether sRAGE, an emerging inflammatory risk factor, was independently correlated with CAD in postmenopausal women. To the best of our knowledge, our study is the first to demonstrate a

Table 7 Pearson's correlation

Parameter	CHOL	LDL-C	HDL-C	TG	hsCRP	HC	sRAGE	Lp (a)
CHOL	1	0.865[b]	−0.616[b]	0.491[b]	0.052	0.090	−0.179	0.227
LDL−C	0.865[b]	1	−0.606[b]	0.646[b]	0.082	0.094	−0.197	0.205
HDL−C	−0.616[b]	−0.606[b]	1	−0.529[b]	−0.157	−0.164	0.245	−0.169
TG	0.491[b]	0.646[b]	−0.529[b]	1	−0.182	−0.002	−0.127	0.174
hsCRP	0.052	0.082	−0.157	−0.182	1	0.761[b]	0.011	−0.235
HC	0.090	0.094	−0.164	−0.002	0.761[b]	1	0.067	−0.226
sRAGE	−0.179	−0.197	0.245	−0.127	0.011	0.067	1	0.158
Lp(a)	0.227	0.205	−0.169	0.174	−0.235	−0.226	0.158	1

[a]$P < 0.05$.
[b]$P < 0.01$.
CHOL: Cholesterol; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides.

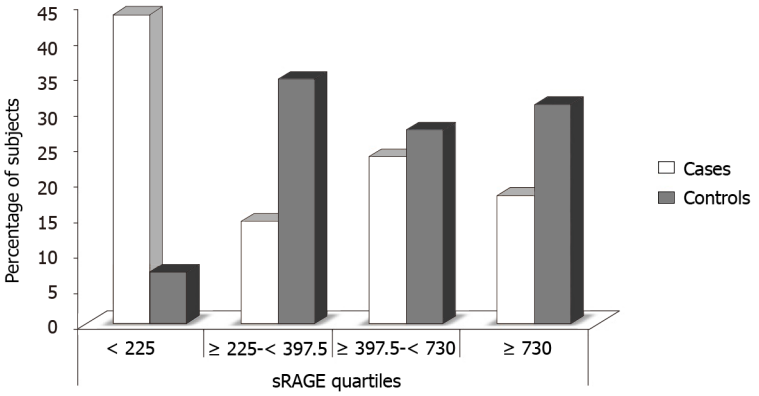


Figure 1 Plasma concentrations (pg/mL) of soluble receptor for advanced glycation end products. Group I included coronary artery disease cases and Group II included healthy controls. sRAGE: Soluble receptor for advanced glycation end products.

correlation between plasma sRAGE levels and CAD in nondiabetic postmenopausal women.

Amino groups of proteins bind non-enzymatically to carbonyl groups of reducing sugars to form glycated proteins known as AGEs. The altered proteins lose their normal functions. AGEs increase with ageing, but production is markedly accelerated in diabetes and with oxidative stress[26]. AGEs are associated with atherosclerosis in both diabetic and nondiabetic subjects and increases in the concentration of circulating AGEs are associated with the severity of CAD and adverse clinical outcomes[27]. In addition to extracellular interactions, some AGEs are as specific ligands RAGE, which is a membrane-bound receptor. It is a transmembrane receptor of the immunoglobulin superfamily and is expressed in endothelial, neuronal, smooth muscles, mesangial and mononuclear cells[7]. Bucciarelli *et al*[13] and Kislinger *et al*[28] demonstrated that even in the absence of diabetes, the ligand-RAGE axis plays an important role in vascular pathology and the development of atherosclerosis[28]. Again plaque instability and rupture occur when there is over-expression of RAGE and plaque stabilization can be achieved by blocking RAGE[29]. EsRAGE and sRAGE are soluble forms of RAGE that are abundantly present in the circulation. EsRAGE is produced by alternative splicing of the gene for RAGE and sRAGE is produced by cleavage of membrane-bound RAGE[15]. They competitively inhibit the ligand-RAGE interaction and subsequent downstream signaling. sRAGE also serves as a scavenger receptor for circulating AGEs and other RAGE ligands[29]. Park *et al*[30] and Bucciarelli *et al*[13] infused sRAGE in a mouse model and demonstrated that it retarded the development of atherosclerosis[30]. To date, few studies have been performed to evaluate the role of sRAGE in human atherosclerosis. In a pioneer study, Falcone *et al*[31] first demon-

strated an inverse association between levels of sRAGE and atherosclerosis in humans. In their case-control study, involving nondiabetic Italian men, plasma sRAGE levels were lower in subjects with CAD than in subjects without CAD. In addition, Kucukhuseyin *et al*[32] demonstrated that the sRAGE concentration was significantly associated with the presence and severity of CAD in nondiabetic Japanese subjects[32]. All those studies found an inverse association of sRAGE level and CAD. In this study, we investigated the correlation between sRAGE and CAD in postmenopausal nondiabetic Indian women. The study results are consistent with the earlier observations that decreased levels of sRAGE were significantly and independently associated with CAD.

The study included 110 nondiabetic postmenopausal women, 55 of whom had angiographically proven CAD (Group I) and 55 control subjects (Group II) who were proven by invasive angiography not to have CAD. Blood samples were collected and processed as described in the materials and methods and the results were systematically analyzed. Student *t*-tests and χ^2 tests were performed for continuous variables and categorical variables respectively. When compared with subjects without CAD, those with proven CAD had a significantly higher serum TG, hsCRP, and homocysteine levels and a significant family history of CAD. However, the opposite was found to be true for plasma sRAGE levels, which were found to be significantly lower in subjects with CAD compared with those without CAD ($P < 0.05$). Univariate and multivariate logistic regression analysis also revealed a significant correlation between plasma sRAGE levels and CAD ($P = 0.01$). Multivariate ORs for CAD revealed that the study subjects with sRAGE concentrations below 225 pg/mL had a 6-fold increase in CAD prevalence, independent of other risk factors. That finding is consistent with a study carried out by Falcone *et al*[31] that evaluated the correlation between sRAGE levels and CAD in Italian men, and found that low sRAGE levels (< 776 pg/mL, the first quartile) were associated with a 6.719-fold increase in CAD prevalence, independent of the other risk factors[16]. Similar results were obtained by Mahajan *et al*[2], who reported in 2009, that subjects with low sRAGE levels (< 607 pg/mL, the first quartile) were associated with a 13.6-fold increase in CAD prevalence, independent of other risk factors[2].

Pearson's correlation failed to find any significant correlations between sRAGE levels and other biochemical parameters like total cholesterol, triglycerides, HDL-C, LDL-C, hsCRP, homocysteine, or Lp(a) levels. That finding is in contrast to a report by Basta *et al*[33], who demonstrated a positive correlation between sRAGE and HDL levels in an Italian population[33]. Our finding that no correlation existed between sRAGE levels and HTN contradicts a study by Geroldi *et al*[34] finding that hypertensive subjects had lower levels of sRAGE compared with normotensive CAD subjects[34]. The cause for this discrepancy is not clear, but it could be explained by differences in the ethnicity and sex of the two studies. Our subjects were all postmenopausal Indian women. We also found that sRAGE levels were lower in women. A 2005 study in nondiabetic Italian men by Falcone *et al*[31] reported mean sRAGE levels of 966 pg/mL in cases and 1335 pg/mL in controls[16]. In our study population the means were 474.89 in cases and 725.73 pg/mL in controls. The observed differences could have resulted from different study populations and small sample size in our study.

In our study, we found a significant correlation between CAD and some biochemical parameters. Univariate and multivariate analysis revealed a significant correlation between hsCRP and CAD. ($P = 0.00$) Our finding is consistent with Mahajan *et al*[2] and Haidari *et al*[35], who reported a positive correlation between increased sRAGE level and severity of CAD. Pearson's correlation analysis found a strong positive correlation between hsCRP and homocysteine levels ($r = 0.76$, $P = 0.00$), which supports the observations of Liu and Ding[36], who also observed a positive correlation between serum homocysteine and hsCRP levels in CAD subjects. In our study, homocysteine emerged as an independent risk factor of CAD ($P = 0.00$), which supports the data of Schaffer *et al*[37] who also found a strong positive correlation between CAD and homocysteine levels[37].

Multivariate analysis revealed that a family history of CAD was an independent risk factor of CAD ($P = 0.014$). Our findings support Bachmann *et al*[38] reported in 2012 that a family history of CAD was associated with a persistent increase in CAD and related mortality across a long-term follow-up[38]. Our study also revealed a significant positive correlations of CAD and total cholesterol ($P = 0.002$) and CAD and LDL-C levels ($P = 0.011$) It is clear that high hsCRP, homocysteine, Lp(a) levels and decreased sRAGE levels, when considered together, are the best predictor of development and progression of CAD.

Our study has some limitations. First, the study population included only women from northern India. The results might not be obtained in other ethnic groups. Second, we determined only total sRAGE levels and not individual isoforms of sRAGE. Thus, it is possible that the observed reduction in sRAGE levels may reflect a reduction in a distinct circulating sRAGE isoform. Third, follow-up of the study subjects were not done. Therefore, the effects of drugs on the variables under consideration are not known. Last but not the least, the study sample size was small and might thus have been underpowered. Therefore, further studies in a larger number of subjects with CAD are warranted.

CONCLUSION

In conclusion, CAD in postmenopausal women cannot be fully explained by traditional risk factors. RAGE and its ligand, sRAGE play an important role in the development of atherosclerosis and CAD. Despite the limitations mentioned above, ours is the first study that included only postmenopausal nondiabetic women to demonstrate the correlation of decreased level of sRAGE with CAD. Our findings corroborate existing evidence that the pathogenesis of CAD involves many aspects of inflammation. Risk assessment for CAD in postmenopausal women can be further improved by considering sRAGE with other risk factors. Further studies in a large number of postmenopausal nondiabetic women from different geographical areas are needed to show that its correlation with the development of CAD is applicable to other ethnic groups.

ARTICLE HIGHLIGHTS

Research background

The overall risk assessment for coronary artery disease (CAD) in postmenopausal women cannot rely on traditional risk factors. Thus, assessment of novel markers is needed. Receptor for advanced glycation end products (RAGE) interaction is of great importance in diabetic vasculopathy and plays a key role in atherosclerosis.

Research motivation

The motivation was to add to what is known of the role of soluble fraction of RAGE (sRAGE**)** in Indian postmenopausal women.

Research objectives

The objective was to investigate the association and correlation between plasma levels of sRAGE and CAD in nondiabetic postmenopausal women.

Research methods

This case-control study included 55 angiographically proven CAD subjects with > 50% stenosis of at least one of the major coronary arteries and 55 healthy control women. Plasma sRAGE was determined with an enzyme-linked immunosorbent assay.

Research results

Plasma sRAGE concentrations were significantly lower in subjects with CAD than it was in healthy controls. A significant correlation between plasma sRAGE levels and CAD was observed using univariate and multivariate analysis.

Research conclusions

sRAGE was positively correlated with CAD independent of other traditional risk factors.

Research perspectives

sRAGE can be included in the assessment of CAD-risk in postmenopausal women.

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SYSTEMATIC REVIEWS

Efficacy and safety of distal radial approach for cardiac catheterization: A systematic review and meta-analysis

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Abstract

BACKGROUND

The traditional radial approach (RA) is recommended as the standard method for coronary angiography (CAG), while a distal RA (DRA) has been recently used for CAG.

AIM

To assess the efficacy and safety of the DRA *vs* RA during CAG.

METHODS

The following databases were searched through December 2020: MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, the World Health Organization International Clinical Trials Platform Search Portal, and Clinical-Trials.gov. Individual randomized-controlled trials for adult patients undergoing cardiac catheterization were included. The primary outcomes were the successful cannulation rate and the incidence of radial artery spasm (RAS) and radial artery occlusion (RAO). Study selection, data abstraction and quality assessment were independently performed using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

RESULTS

Three randomized control trials and 13 registered trials were identified. The two approaches showed similar successful cannulation rates [risk ratio (RR) 0.90, 95% confidence interval (CI): 0.72-1.13]. The DRA did not decrease RAS (RR 0.43, 95%CI: 0.08-2.49) and RAO (RR 0.48, 95%CI: 0.18-1.29). Patients with the DRA had a shorter hemostasis time in comparison to those with the RA (mean difference -

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6.64, 95%CI: -10.37 to -2.90). The evidence of certainty was low.

CONCLUSION
For CAG, the DRA would be safer than the RA with comparable cannulation rates. Given the limited data, additional research, including studies with standard protocols, is necessary.

Key Words: Radial artery; Cardiac catheterization; Coronary angiography; Snuff box; Systematic review; Meta-analysis

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Core Tip: No consensus is available in the literature about which technique for coronary angiography—distal radial approach (DRA) or radial approach (RA)—is more beneficial to patients. This is the first systematic review and meta-analysis to compare clinical data on the DRA and RA. We investigated the successful cannulation rate, the incidence of radial artery spasm and radial artery occlusion, the mean number of punctures, and the mean time for hemostasis with the two approaches. The present study indicated the DRA to be safer than the RA, with comparable procedure rates. Further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

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INTRODUCTION

Coronary angiography (CAG) is an invasive but essential part of the diagnosis and treatment for coronary artery disease (CAD). Annually, it is estimated that 1016000 inpatient diagnostic CAG and 480000 inpatient percutaneous coronary intervention (PCI) procedures are performed in the United States[1]. In European countries, it is estimated that 4500 diagnostic coronary angiograms per million people and 2000 PCI procedures per million people are performed each year[2]. Interventional cardiologists gain access *via* a peripheral artery, and the latest guidelines from the European Society of Cardiology, National Institute for Health and Care Excellence, and American College of Cardiology/American Heart Association recommended the radial approach (RA) over the transfemoral, transbrachial, and transulnar approaches, because it is associated with a reduced risk of cardiac death, all-cause mortality, bleeding, and access site complications[3-5].

The distal RA (DRA) was recently introduced, as this approach may have some potential advantages in comparison to the RA[6,7]. Previous observational studies showed that the two approaches were associated with similar successful cannulation rates[8], while the rates of vascular complications in the DRA, including radial artery occlusion (RAO) and radial artery spasm (RAS), were less frequent than the RA[9-16]. The DRA is assumed to be an alternative approach to the RA, but the efficacy of the two approaches has never been systematically reviewed and analyzed.

Therefore, the present study aimed to evaluate the efficacy and safety of the DRA in comparison to the RA. To achieve this aim, a systematic review and meta-analysis of only randomized-controlled trials (RCTs) were conducted to produce high-quality evidence that would inform clinical practice decisions for guidance of the cardiac catheterization procedures concerning these two approaches.

MATERIALS AND METHODS

Literature search

Our review protocol was registered in protocol.io (dx.doi.org/10.17504/protocols.io.bramm^{2}c6). Our study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement[17].

Individual RCTs were included to evaluate the efficacy and safety of the RA *vs* DRA for cardiac catheterization. All papers, including published and unpublished articles, abstracts of conferences, and letters, were included, regardless of language, country restrictions, or publication year. Non-RCTs were excluded. The inclusion criteria were adult patients (≥ 18 years of age) undergoing diagnostic CAG and PCI for CAD. Patients for whom a > 7-Fr sheath was used were excluded (available on a commercial basis)[18]. The DRA is a method of puncturing distal radial arteries at the proximal part of the anatomical snuffbox or the first intermetacarpal space. After successful artery puncture, a guidewire is smoothly passed through the needle and used to guide the sheath through the artery. After introduction of the sheath, interventional cardiologists perform diagnostic CA and PCI with the coronary catheters through the sheath[19]. The RA is a method of puncturing radial artery at the forearm, a few centimeters above the wrist joint[20]. The primary outcomes were the successful cannulation rate and the incidence of RAS and RAO. The successful cannulation rate was defined as completion of the procedure without cross-over to another access site or as defined by practitioners. RAS was diagnosed by angiographic evaluation of the radial artery. RAO was diagnosed based on the absence of flow on color Doppler ultrasound. The secondary outcomes were the mean number of punctures per patient and the mean time for hemostasis. The success of hemostasis was defined as no bleeding or hematoma formation after release. The total time was defined as the time from when the sheath was removed to when successful hemostasis was confirmed. All outcomes included the definitions of the authors of original studies.

The following databases were searched through December 2020: MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE (Supplementary material, Appendix 1). The World Health Organization International Clinical Trials Platform Search Portal and ClinicalTrials.gov databases were also searched for ongoing or unpublished trials (Supplementary material, Appendix 2). The original authors were asked for unpublished or additional data if necessary. The reference lists of studies, including international guidelines published by the European Society of Cardiology, National Institute for Health and Care Excellence, and American College of Cardiology/American Heart Association[3-5], as well as the reference lists of eligible studies and articles citing eligible studies, were checked.

Study selection

Two independent reviewers (Izumida T and Yoshida R) screened the titles and abstracts, then assessed the eligibility based on the full text. We contacted the original authors when relevant data were missing. Disagreements between the two reviewers were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Data extraction

Two reviewers (Izumida T and Yoshida R) performed independent data extraction of the included studies using a standardized data collection form. The form included information on the study design, study population, interventions, and outcomes. Any disagreements were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Risk of bias

Two reviewers (Izumida T and Yoshida R) evaluated the risk of bias independently using the Risk of Bias 2[21]. Disagreements between the two reviewers were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Statistical analysis

We pooled the relative risk ratios (RRs) and 95% confidence intervals (CIs) for the following binary variables: Cannulation success, RAS, and RAO. We pooled the mean differences and the 95%CIs for the following continuous variables: Mean time for hemostasis. An intention-to-treat analysis was performed for all dichotomous data (to the extent that was possible). For continuous data, missing data were not imputed based on the recommendation of the Cochrane handbook[22]. A meta-analysis was

performed using the available data in the original study. The Review Manager software program (RevMan 5.4.1) was used to perform the meta-analysis. A random-effects model was used. The statistical heterogeneity was evaluated by a visual inspection of forest plots and calculation of the I^2 statistic (I^2 values of 0%-40%: Might not be important; 30%-60%: May represent moderate heterogeneity; 50%-90%: May represent substantial heterogeneity; 75%-100%: May represent considerable heterogeneity)[22]. When there was substantial heterogeneity (I^2 > 50%), the reason for heterogeneity was assessed. The Cochrane chi-squared test (Q-test) was performed for the I^2 statistic, and P values of < 0.10 were considered statistically significant. A funnel plot was not created and the Egger test was not performed because < 10 trials were included in our analysis[22]. The following subgroup analyses of the primary outcomes were performed when sufficient data were available: For participants, the young- to middle-age group (< 65 years of age) *vs* the elderly group (≥ 65 years of age) and for intervention, right-side approach *vs* left-side approach[23,24] and diagnostic CA *vs* PCI. For the sensitivity analyses of the primary outcomes, studies using imputed statistics were excluded and participants were only included if they completed the study and their data were complete.

RESULTS

Study selection

Figure 1 shows the flow of the study selection of studies comparing the DRA *vs* RA for cardiac catheterization. We identified a total 752 records (MEDLINE 63 records, EMBASE 150 records, CENTRAL 36 records, ClinicalTrials.gov 132 records, and ICTRP 371 records) published prior to December 7, 2020. After the initial screening, 16 trials met the inclusion criteria. Among these trials, we identified eight ongoing trials (NCT03611725, NCT03986151, NCT04171570, NCT04194606, NCT04211584, NCT04232488, NCT04318990, KCT0004537), five protocols without results (NCT03373565, NCT04001764, NCT04023838, NCT04125992, NCT04238026), and three clinical trials.

Table 1 summarizes the characteristics of eligible studies. Three studies included 519 participants[16,25,26]. Table 2 and Supplementary Tables 1-4 show the risk of bias in each study. The overall risk of bias for the successful cannulation rate was similar in the three studies.

Primary outcomes

Successful cannulation rate: Three studies were eligible for the evaluation of the successful cannulation rate[16,25,26]. In one study, the operators were specialists, and in the other two studies, the operators' skills were unknown. The DRA resulted in little to no difference in the successful cannulation rate in comparison to the RA (RR 0.90, 95%CI: 0.72-1.13; I^2 = 93%) (Figure 2A).

Incidence of RAS: The incidence of RAS was measured in two of three studies[16,25]. The two studies used verapamil and nitrate, respectively[16,25]. The DRA did not reduce the incidence of RAS (RR 0.43, 95%CI: 0.08-2.49; I^2 = 29%) (Figure 2B).

Incidence rate of RAO: Two of the three studies were eligible for the evaluation of incidence of RAO[25,26]. The DRA did not reduce the incidence of RAO (RR 0.48, 95%CI: 0.18-1.29; I^2 = 0%) (Figure 2C).

We could not perform a pre-specified subgroup analysis or sensitivity analyses for the successful cannulation rate, the incidence of RAS, or the incidence of RAO.

Secondary outcomes

Mean number of punctures: We included one RCT for the evaluation of mean number of punctures[25]. In the study, the mean number of punctures per patient was 2.4 with the DRA and 1.6 with the RA.

Mean time for hemostasis: Two of the three studies were eligible for the evaluation of the mean time for hemostasis[16,26]. In one study, hemostasis was performed only by manual compression without using a device[16], and in the other study, it was unclear whether a device was used[26]. The DRA reduced the mean time for hemostasis in comparison to the RA (mean difference -6.64, 95%CI: -10.37 to -2.90; I^2 = 88%) (Figure 3).

Table 1 Summary of the characteristics of the eligible studies

Ref.	Country	Subject No.	Mean age in yr	Male, %	Right arm/left arm, *n*	CAG/PCI (*n*)	5-Fr sheath/6-Fr sheath, *n*	Operators	Medications to prevent radial artery spasm	Approach to hemostasis	Timing of assessment of radial artery occlusion
Mokbel *et al*[26], 2018	Romania	200	63.4	NS	NS	NS	NS	NS	Nitrate	NS	At discharge
Koutouzis *et al*[25], 2019	Greece	205	63.3	75.5	152/48	200/0	0/200	Specialists	Verapamil	Manual compression	At discharge
Vefalı *et al*[16], 2020	Turkey	114	60.4	69.3	33/172	156/49	205/0	NS	NS	Manual compression	NS

CAG: Coronary angiography; NS: Not stated; PCI: Percutaneous coronary intervention.

Table 2 Quality scores for the studies eligible for the evaluation of the successful cannulation rate

Ref.	Risk of bias 2 tool assessment					
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
Mokbel *et al*[26]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Koutouzis *et al*[25]	Low	Low	Low	Low	Some concerns	Some concerns
Vefalı *et al*[16]	Some concerns	Low	Low	Low	Some concerns	Some concerns

Certainty of evidence

The certainty of the evidence was low for the successful cannulation rate because of inconsistency due to substantial heterogeneity and imprecision due to the small sample size. The certainty of evidence was low for RAS, RAO, and the mean number of punctures because of imprecision due to small sample size and the small number of participants. The certainty of the evidence was very low for the mean time for hemostasis because of substantial heterogeneity, imprecision, and a high risk of bias (Table 3).

DISCUSSION

In the present review, the rate of cannulation failure with the DRA was suggested to be similar to that with the RA. Furthermore, the DRA might reduce the incidence of RAS and RAO in comparison to the RA. Additionally, the DRA had a shorter hemostasis time. These findings indicate the safe clinical practice analyses of the DRA to guide cardiac catheterization procedures.

The puncture of the distal radial artery has some caveats because of anatomical features such as the superficial position of the artery and the bone basement. The puncture site in the DRA is either the distal radial artery of the anatomic snuffbox or the more distal radial artery, which is located on the vertex of the angle between the tendon of the extensor pollicis longus and the second metacarpal bone[7]. Some studies showed that the diameter of distal radial artery was smaller and might have the increased tortuosity and angulations in comparison to forearm radial artery[25,27,28]. However, considering the similar results of successful cannulation rates and puncture counts for DRA and RA arms in our review, these anatomical factors might have little effect on the efficacy of the procedure.

Table 3 Summary of findings (the efficacy and safety of the radial approach *vs* the distal radial approach for diagnostic coronary angiography and percutaneous coronary intervention)

Patient or population: Adults; Setting: Diagnostic coronary angiography and percutaneous coronary intervention; Intervention: Radial approach (RA); Comparison: Distal radial approach (DRA)

Outcomes	Anticipated absolute effects[1] (95%CI)		Relative effect (95%CI)	Patient number (studies)	Certainty of the evidence, GRADE	Comments
	Risk with RA	Risk with DRA				
Successful cannulation rates	950 per 1000	798 per 1000 (532-1000)	RR 0.90 [0.72-1.13]	519 (3 RCTs)	Low[2,3]	DRA resulted in little to no difference in successful cannulation rates
Radial artery spasm	39 per 1000	16 per 1000 (4-56)	RR 0.43 [0.08-2.49]	405 (2 RCTs)	Low[3]	DRA may reduce incidence of radial artery spasm
Radial artery occlusion	32 per 1000	14 per 1000 (5-41)	RR 0.48 [0.18-1.29]	314 (2 RCTs)	Low[3]	DRA may reduce the incidence of radial artery occlusion
Mean number of punctures per patient	The mean number of punctures per patient were 2.4 in DRA in comparison to 1.6 in RA			200 (1 RCT)	Low[3]	DRA may reduce the mean number of punctures per patient
Mean time for hemostasis	-	MD 6.64 min lower (10.37 lower to 2.9 lower)	-	405 (2 RCTs)	Very low[2,3,4]	DRA reduced mean time for hemostasis

[1]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval). GRADE Working Group grades of evidence: High certainty: Very confident that the true effect lies close to that of the estimated effect. Moderate certainty: Moderately confident in the estimated effect. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the estimated effect is limited: The true effect may be substantially different from the estimated effect. Very low certainty: We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

[2]Downgraded because of inconsistency due to substantial heterogeneity.

[3]Downgraded because of imprecision due to small sample size and/or small number of participants.

[4]Downgraded due to imprecision because of high risk of bias.

CI: Confidence interval; MD: Mean difference; RCT: Randomized-controlled trial.

RAS is one of the most frequent complications in cardiac catheterization[29,30] and can be caused by mechanical stimulation by guide wires or catheters and increasing catecholamine levels, which are induced by pain and discomfort[28]. In previous systematic reviews, additional drugs, such as local anesthetics and vasodilatory medications, reduced RAS[31,32]. In the present review, the DRA arm was likely to reduce the incidence of RAS, despite the use of additional medications. Although the detailed mechanism remains unknown, a previous study reported that the DRA might be associated with more advantages in terms of patient satisfaction and the analgesic effect[16,33].

RAO is relatively common, with an incidence ranging from 0.6% to 2.2%; it occurs through the inflammation and endothelial dysfunction of the radial artery[34,35]. Regarding possible explanations for the lower incidence of RAO in the DRA arm, the first possibility seemed to be the anatomical features of the distal radial artery. The antegrade flow through the superficial palmar arch can be maintained during compression of the distal radial artery, resulting in a low risk of retrograde thrombus formation[6]. The second possibility was the shorter duration of hemostasis with the DRA[7], which appeared to be related to the structure of the anatomic snuffbox with a bony basement surrounded by tendons.

The mean number of punctures in the DRA could be mostly comparable to that in the RA. The operators were mainly specialists in the study setting; however, in the clinical setting, the DRA is associated with a learning curve because it involves the puncture of small and weak arteries[36]. Ultrasound is useful for increasing the rate of successful puncture and for reducing adverse events. The measurement of the diameter of the distal radial artery helps to select a suitable sheath, leading to reduced damage of the endothelium and reduced development of RAS and RAO[28]. The use of ultrasound may alter the results of similar studies in the future. Research is needed to evaluate the usefulness of ultrasound in the DRA.

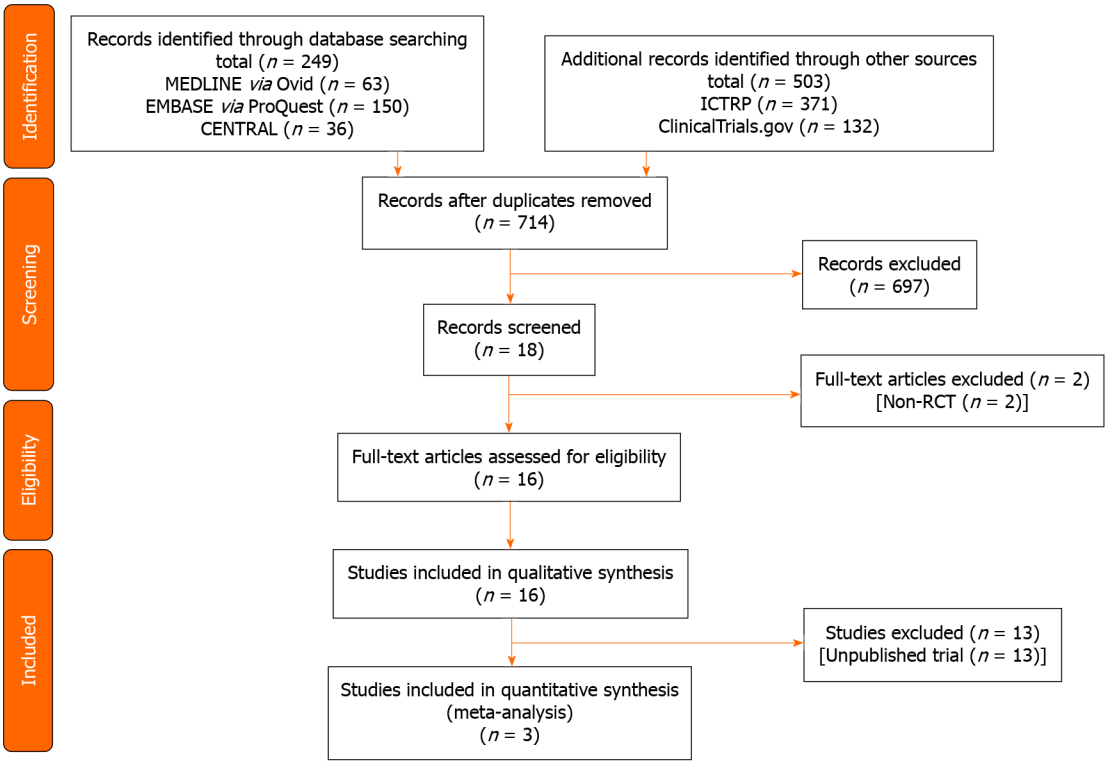


Figure 1 Study selection.

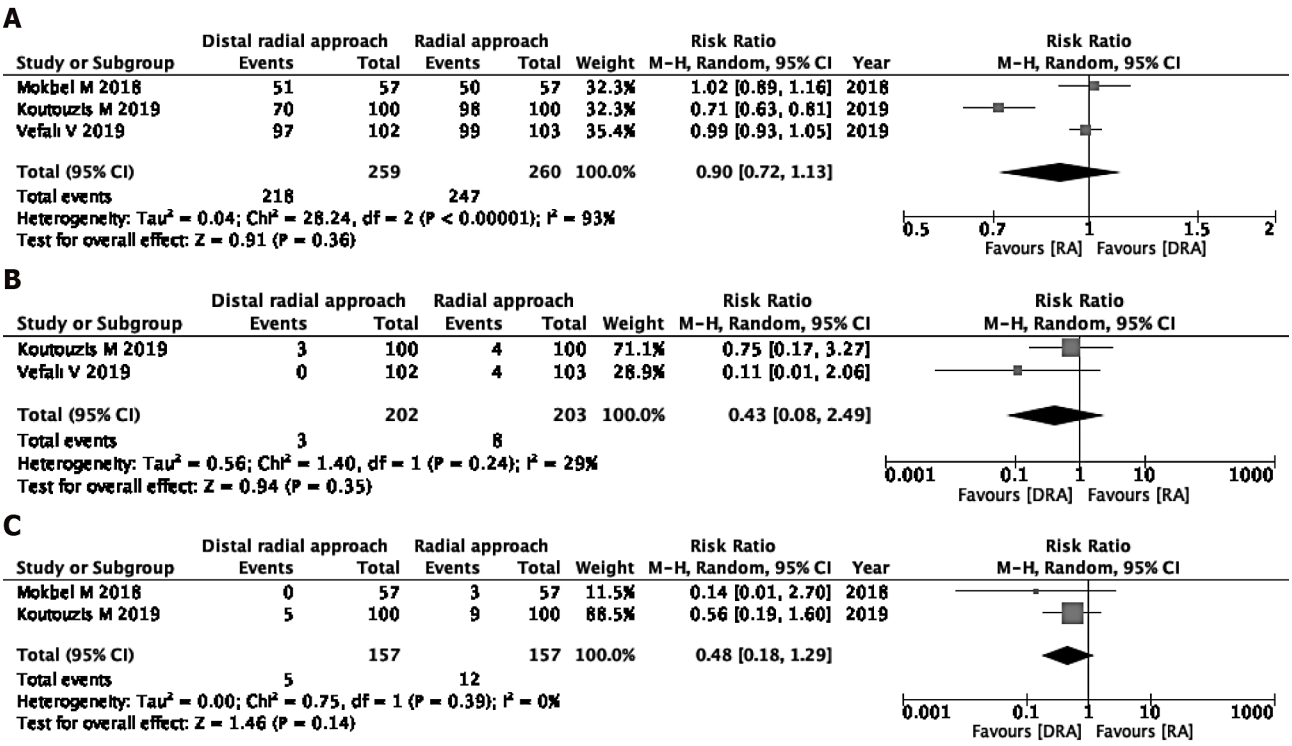


Figure 2 Forest plot. A: The successful cannulation rate; B: The rate of radial artery spasm; C: The rate of radial artery occlusion. CI: Confidence interval; RA: Radial approach; DRA: Distal radial approach.

The shorter time of hemostasis in the DRA, as found in the present review, is a useful aspect of this approach for the prevention of vascular damage. Due to the anatomical features of the distal radial artery, the DRA can reduce the hemostasis time. A new compression hemostasis device for the puncture site of the distal radial artery was also developed, and the safety and efficacy of the device were valida-

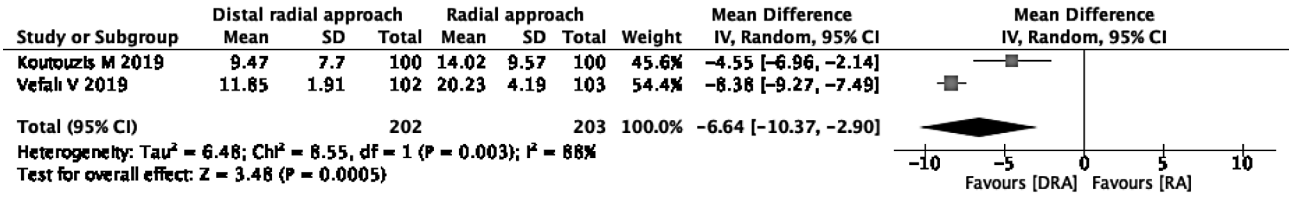


Figure 3 Forest plot of the mean time for hemostasis. CI: Confidence interval; RA: Radial approach; DRA: Distal radial approach.

ted[37]. Mechanical compression is more convenient and requires fewer human resources in comparison to manual compression[38]. In the present review, hemostasis was performed by manual compression. Further research is needed to evaluate the DRA using mechanical compression hemostasis.

The present review had some limitations. First, our review included a relatively small number of studies. Second, various definitions may have been applied for RAS, RAO, and hemostasis, because the protocols were not described. To improve the quality of evidence and draw convincing conclusions, it will be necessary to perform large cohort studies with standard protocols.

CONCLUSION

This first systematic review and meta-analysis to compare clinical data using the DRA and RA indicated that the DRA would be safer than the RA, with comparable procedure rates. Given the limited data, accumulating more knowledge by further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

ARTICLE HIGHLIGHTS

Research background

While the traditional radial approach (RA) is the gold standard method for cardiac catheterization, a distal RA (DRA) has been recently introduced.

Research motivation

The DRA may have some advantages compared to RA; however, it is not fully understood as to which technique for coronary angiography—DRA or RA—is more beneficial to the patients.

Research objectives

Via the systematic review and meta-analysis, we compared clinical data using the DRA and RA.

Research methods

The databases MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, the World Health Organization International Clinical Trials Platform Search Portal and ClinicalTrials.gov were searched. All randomized-controlled trials for adult patients undergoing cardiac catheterization until December 2020 were included. The primary outcomes were the successful cannulation rate and the incidence of radial artery spasm (RAS) and radial artery occlusion (RAO). The statistical analysis was performed on a random-effect model to pool the relative risk ratios (RRs) and 95% confidence intervals (CIs) for the binary variables, such as cannulation success, RAS, and RAO.

Research results

Three randomized-control trials including 519 participants and 13 registered trials were identified. The two approaches showed similar successful cannulation rates (RR 0.90, 95%CI: 0.72-1.13). The DRA did not decrease RAS (RR 0.43, 95%CI: 0.08-2.49) and RAO (RR 0.48, 95%CI: 0.18-1.29). The evidence of certainty was low.

Research conclusions

The present study indicated the DRA to be safer than the RA, with comparable procedure rates. Importantly, there are limitations, including the limited study numbers and no studies with standard protocols, that prevent definitive conclusions.

Research perspectives

Further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

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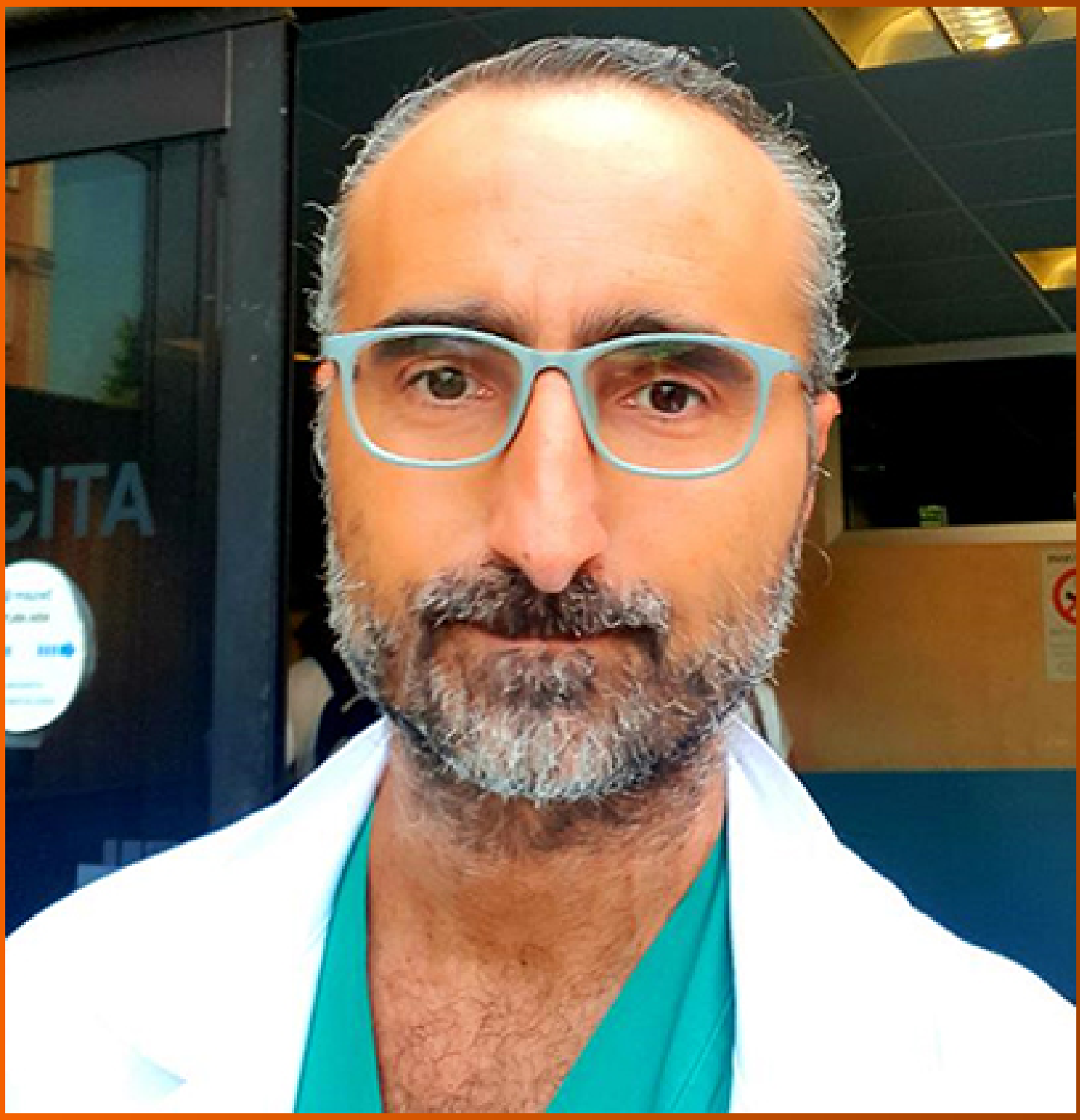
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FIELD OF VISION

A Novel guide extension assisted stenting technique for coronary bifurcation lesions

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Abstract

A challenging technical scenario frequently encountered in a percutaneous coronary intervention of a coronary bifurcation lesion (CBL) is stent implantation of only the stenosed segment without compromising the other two normal segments in non-true bifurcation lesions. Another is precise stent implantation covering the side branch ostium without leaving excessive stent metal at the other two segments of a bifurcation lesion in complex true bifurcation lesions. The aim of this study was to describe a novel stenting technique for both non-true and true CBLs by using a guide extension catheter (GuideLiner). With the assistance of a guide extension catheter mounted on both the main and the side-branch guidewires and with its intubation down to the bifurcation carina, a stent can be implanted in the side branch segment or distal main segment of the bifurcation lesion appropriately without compromising the other two segments of the coronary bifurcation. Stent implantation is described in three bifurcation lesions in three cases and shown in detail with illustrative figures. The technique facilitates side-branch only stenting in side-branch mono-ostial (medina 0, 0, 1) CBL or only the distal main segment in distal mono-ostial (medina 0, 1, 0) CBL without compromising the other two remaining segments when using the one-stent technique in non-true CBLs without leaving unnecessary excessive stent metal at the bifurcation site and when using a two-stent technique in complex true bifurcation lesions (tri-ostial or medina 1, 1, 1). Consequently, through optimizing stent deployment, the technique may have the potential to reduce the risk of subacute stent thrombosis and future in-stent restenosis. The most appropriate lesions suitable for the technique, and some other practical tips are also described.

Key Words: Coronary bifurcation lesion; GuideLiner stenting; Percutaneous coronary intervention; One- or two-stenting technique; Novel descriptive, intelligible and ordered

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Core Tip: A novel stenting technique for coronary bifurcation lesions (CBLs) is presented. With the help of a guide extension-assisted technique using a GuideLiner mounted on both guidewires in the branches of the bifurcation lesion and advanced to the carina of the bifurcation, a stent can be implanted at the most possible appropriate site of the side branch in side-branch mono-ostial (medina 0, 0, 1) or in the distal mono-ostial (medina 0, 1, 0) in non-true CBLs. The technique can also be used to stent the side branch in two-stent techniques for complex true CBLs (tri-ostial or medina 1, 1, 1).

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INTRODUCTION

Percutaneous coronary intervention (PCI) of a coronary bifurcation lesion (CBL) is a challenging procedure for interventionists[1]. The short- and long-term outcomes are closely related to the procedural success and optimization of the bifurcation stenting technique[2,3]. Several one- or two-stent techniques for PCI of CBLs have been described, depending on the type and location of the bifurcation lesions[1,4]. Stenting of the side branch in side-branch mono-ostial[5] (medina 0, 0, 1)[6] bifurcation stenoses is associated with difficulties in stent placement at the proper site with the risk of missing the side branch ostium or of excessive stent protrusion in the main branch. The same applies to stenting only the distal main segment in distal mono-ostial (medina 0, 1, 0) bifurcation stenoses. Consequently, the provisional stenting technique is typically employed in treating a distal mono-ostial stenosis (medina 0, 1, 0) but this requires "unnecessary" stenting of the normal proximal main segment of the bifurcation and the risk of compromising the side branch[1].

The provisional stenting technique is also recommended as the default strategy by most interventionists in tri-ostial (medina 1, 1, 1) or true bifurcation lesions[1]. However, this technique may lead to side-branch occlusion during stenting of the main branch and acute peri-procedural myocardial infarction. Improvements in the protection of the side branch have been reported with the jailed balloon protection of the side branch[7] or modified jailed balloon techniques[8]. The risk of side-branch occlusion is increased in complex tri-ostial (medina 1, 1, 1) bifurcation lesions where a two-stent technique should always be considered. However, the current two-stent techniques for the CBLs, such as crush[9] and culotte[10] stenting, leave multiple layers of stent struts at the bifurcation site causing difficulties in rewiring, balloon re-crossing, and the performance of sequential post-dilatation and final kissing balloon inflation. This may result in stent under expansion, and/or malapposition at the bifurcation site predisposing to acute and sub-acute stent thrombosis. Suboptimal stent implantation is also associated with an increased risk of future in-stent restenosis [1]. To overcome these challenges, the crush technique has evolved to mini-crush and double kissing (DK)-crush techniques[1]. The DK-crush stenting technique facilitates final kissing balloon inflation, but the technique has complex procedural steps and is time consuming. Other two-stent techniques include simultaneous kissing stenting, T-stenting and V-stenting techniques. The T-stenting technique does not leave multiple layers of stent struts, which facilitates final kissing balloon inflation, but has the potential of geographical miss at the side branch. These technical shortcomings highlight the need for a stent implantation technique that avoids unnecessary stenting of the normal segments and not leaving multiple layers of stent struts at the bifurcation site. A guide extension catheter can intubate the coronary arteries down to the carina of the bifurcation site. This may facilitate precise stent implantation at the ostium of the side branch or the distal main segment and thus enhance rewiring,

balloon re-crossing and final kissing balloon inflation in two-stent techniques.

METHODOLOGY

Description of the guide extension-assisted stenting technique using a GuideLiner catheter (Vascular Soutions Inc., Minneapolis, MN)

The GuideLiner is a guide extension catheter that is mounted coaxially on a monorail system extending through the guide catheter. It consists of a coaxial exchange system with a flexible extension of 20 cm and a radio-opaque marker 2 mm proximal to the tip of the catheter. The extension catheter has been used for deep vessel intubation to allow the smooth device delivery of balloons and stent platforms in calcified or tortuous vessel anatomy. Guide extension catheters have also been used to facilitate obtaining good angiographic and optical coherence tomographic (OCT) images by subselective injection of reduced contrast medium, and particularly useful in tortuous vessel or angulated bifurcation anatomy[11]. Further uses include stenting the main branch of a complex bifurcation lesion while retaining guide wires in both side branches of the bifurcation[12] and to facilitate side strut stenting technique for the treatment of right coronary artery ostial in-stent restenosis where there is ostial right coronary artery stent overhang into the aortic root[13].

In this novel technique, the coronary artery is engaged by conventional 6, 7, or 8F guide catheters, through radial (6 and 7F), or femoral (6, 7, and 8F) artery approaches. Two guidewires are placed in the branches of the bifurcation lesion, one in the main branch and one in the side branch (Figure 1A and B). The bifurcation lesion is pre-dilated, preferably with undersized 1.5 or 2 mm balloon, and the ostium of the side branch should be dilated with a cutting or scoring balloon, especially the left anterior descending artery (LAD) ostium or the left circumflex artery (LCx) ostium. The dilated but still stenosed bifurcation lesion helps to prevent to-and-fro movement of the stent during stent implantation especially in LAD. Dilatation of the ostium by a cutting or scoring balloon helps to avoid stent sliding distally during stent implantation. Thereafter, the appropriate (6, 7, or 8F) GuideLiner mounted on both guidewires is introduced and placed near the tip of the guide catheter (Figure 1C). The stent is introduced somewhat distal to the lesion (Figure 1D) and then the GuideLiner introduced to the carina of the bifurcation, and the stent is retracted while the GuideLiner is advanced carefully against the carina until the proximal radio-opaque marker of the stent balloon is overlapping the distal radio-opaque marker of the GuideLiner (Figure 1E). Being mounted on both main and side-branch guidewires, the guide extension catheter will stop at the carina of the bifurcation just adjacent to the ostium of the side branch or ostium of the distal main segment of the main branch. The stent is then implanted slowly to avoid stent displacement (Figure 1F). During stent implantation, the proximal part of the stent balloon pushes the GuideLiner catheter backward. In this way the stent is implanted at the ostial region and distally without compromising the other two segments of the bifurcation (Figures 1-4). The stent balloon catheter is pulled out first followed by the GuideLiner. The stent is then post-dilated, and the stent apposition is checked in the conventional way. In tri-ostial bifurcation lesions (medina 1, 1, 1), and after stenting the side branch by GuideLiner technique described above (Figure 4), the procedure is completed conventionally with stenting of the main branch, proximal optimization technique (POT), rewiring of the side branch, balloon re-crossing of the main branch stent struts, sequential balloon dilatation, and final kissing balloon inflation. The technique is further illustrated and described in three bifurcation cases treated with this guide extension technique in Figures 1-4.

Coronary artery bifurcation lesions suitable for the GuideLiner-assisted stenting technique

This novel guide extension assisted stenting technique is characterized by keeping the guidewire access to both branches of the bifurcation during the whole procedure in side-branch mono-ostial (medina 0, 0, 1), distal mono-ostial (medina 0, 1, 0) CBL, and stenting only the lesion site without compromising the other two segments of the bifurcation. The most appropriate bifurcation sites suitable are the bifurcation lesions situated proximally in the coronary artery trees as left main stem/LAD/LCx, proximal LAD/diagonal, and proximal LCx/marginal bifurcation lesions. The most suitable types of CBLs for this technique are the side-branch mono-ostial (medina 0, 0, 1), the distal mono-ostial (medina 0, 1, 0) and potentially distal bi-ostial (medina 0, 1, 1)

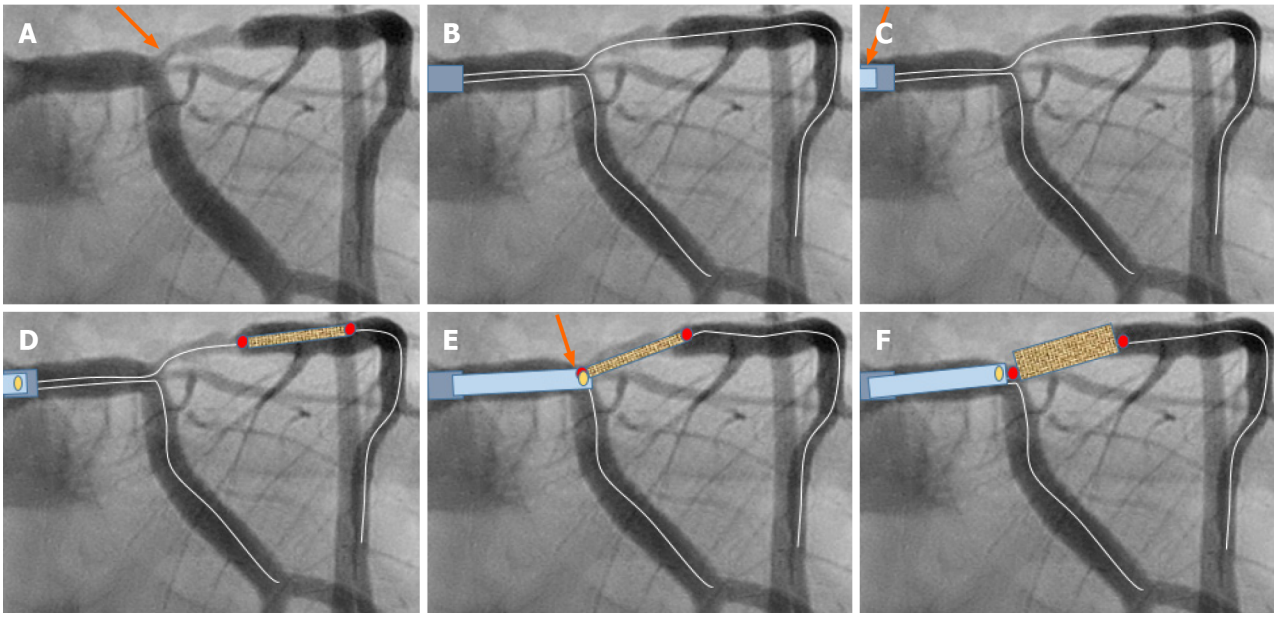


Figure 1 Schematic description of the guide extension-assisted technique in a coronary bifurcation lesion in the first case. A: Coronary angiography in a male patient admitted with unstable angina revealed a significant ostial and proximal left anterior descending artery (LAD) stenosis. It was classified as side branch mono-ostial (medina 0, 0, 1), left main stem/left circumflex artery (LCx)/LAD bifurcation stenosis (orange arrow). Evaluation by fractional flow reserve assessment was 0.76, indicating a significant stenosis. The guide extension-assisted percutaneous coronary intervention technique is demonstrated schematically. B: Two guide wires are placed in the left coronary artery (both LAD and LCx); C: After conventional pre-dilatation, the GuideLiner, mounted on both guidewires, is placed proximal to the tip of the mother guide catheter (orange arrow); D: The stent is introduced just distal to the stenosis; E: The GuideLiner is then advanced to the carina of the bifurcation and the stent is pulled back to a level where the proximal radio-opaque marker of the stent balloon overlaps the radio-opaque marker just proximal to the tip of the guide-liner (orange arrow). Because the GuideLiner is mounted on both wires, the carina of the bifurcation will prevent further introduction of the GuideLiner into the LAD or LCx; F: The stent is implanted slowly. Note that the GuideLiner is pushed backwards when the stent balloon is inflated.

bifurcation lesions when the proximal segment of the main branch is normal. The technique can also be utilized in tri-ostial bifurcation stenosis (medina 1, 1, 1) through stenting the side branch using the guide extension technique (Figure 4) and then conventional stent implantation in the main branch with the advantage of not leaving excessive stent metal at the carina and facilitation of the procedure by proximal optimization, rewiring, sequential balloon dilatation, and final kissing balloon inflation.

Side branch stenting

Side branch stenting is challenging for all interventionists. The crucial step is positioning the stent so that it covers the ostium of the side branch without protruding too much into the main branch. Achievement of geographical precision is more difficult when the bifurcation angle is of the "Y-type" and almost impossible when the ostium of the side branch cannot be visualized, which is the case in some bifurcation lesions as shown in Figure 3. One of the disadvantages of the T-stenting technique is that it may miss covering the ostium of the side branch. In contrast, the crush, mini-crush, and culotte stenting techniques[1] leave multiple strut layers in the main branch that may result major difficulty in rewiring the side branch and subsequent sequential and final kissing balloon inflations. The novel guide extension-assisted stenting technique of the side branch reduces the risk of missing the ostium substantially and avoids unnecessary stent protrusion into the main branch.

RESULTS

Three different types of CBLs in three cases that were successfully treated with PCI using a GuideLiner-assisted stenting technique. Two cases had non-true CBLs and one had a true CBL. The first case had left main stem/LCx/LAD bifurcation stenosis of a side-branch type mono-ostial (medina 0, 0, 1) bifurcation lesion. With a GuideLiner advanced to the carina of the bifurcation, the side branch (LAD) was stented successfully (Figure 2). The stent covered the ostium of the LAD without leaving stent struts in the left main stem or LCx, confirmed by StentBoost imaging (Figure 2F). The

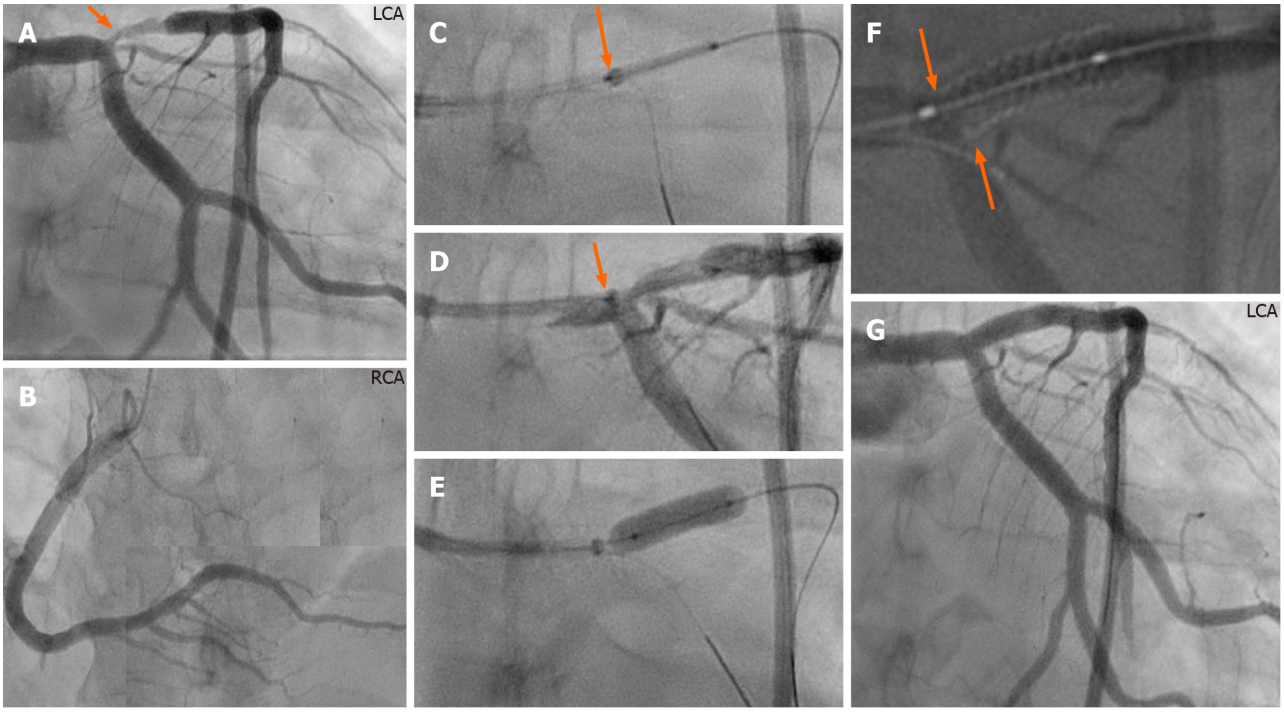


Figure 2 Annotated description of the guide extension technique in the bifurcation lesion in the first case. A and B: Left (A) and right (B) coronary angiography of the same patient in figure 1 showing stenosis at the ostium and proximal part of left anterior descending artery (LAD) (A, orange arrow); C and D: After engagement of the left coronary artery with 7F XB 3.5 guide catheter, a 7F GuideLiner, mounted on both guidewires, is advanced carefully against the carina of the bifurcation and the stent is placed at the stenosis site with the proximal radio-opaque marker of the stent balloon overlapping the radio-opaque marker just proximal to the tip of the GuideLiner (D, under contrast injection); E: A 3.5 mm × 15 mm stent was implanted with a pressure of 20 atm; note that the GuideLiner is pushed backwards during stent implantation. The stent is post-dilated in the conventional way; F: The proximal stent edge can be seen accurately placed at the ostium using StentBoost imaging (orange arrows); G: Final result, stent implanted in the LAD without compromising the left main stem or the left circumflex artery ostium. LCA: Left coronary artery; RCA: Right coronary artery.

bifurcation lesion in the second case treated with this novel technique was a LAD/diagonal bifurcation stenosis type distal mono-ostial (medina 0, 1, 0) where the stenosis was restricted to the distal main segment of the bifurcation. It is worth mentioning that visualization of the angle between the diagonal branch and the distal segment of the main branch (LAD) was ambiguous, making it especially suitable for this novel technique. With a GuideLiner intubated down to the carina of the bifurcation, the distal main segment was stented successfully (Figure 3). The stent covered the ostium of the distal main segment without leaving stent struts in proximal main segment or the side branch and this was confirmed by OCT (Figure 3E and F), which also showed a well-apposed stent to the vessel wall. The bifurcation lesion in the third case was a complex LAD/diagonal bifurcation stenosis of type tri-ostial (medina 1, 1, 1) (Figure 4). The side branch was stented by this novel technique after extending the GuideLiner to the carina of bifurcation. The stent covered the side-branch ostium without leaving stent struts at the bifurcation site. The main branch is then stented in the conventional way without leaving multiple layers of stent struts at the bifurcation site. Consequently, the procedure enhanced rewiring, balloon re-crossing and the performance of sequential post-dilatation and final kissing balloon inflations. StentBoost and optical coherence tomography confirmed well-apposed stents at the bifurcation site with no stent struts covering the ostium of the diagonal branch (Figure 4H and I)

DISCUSSION

The main advantage of the guide extension-assisted stenting technique is precise positioning of the stent at the side branch of a CBL especially in lesions where the side-branch ostium is challenging to visualize or ambiguous. The most appropriate CBLs suitable for this technique are the side-branch mono-ostial (medina 0, 0, 1), distal mono-ostial (medina 0, 1, 0), and potentially distal bi-ostial (medina 0, 1, 1) CBLs. In such lesions, the guide extension-assisted technique avoids stenting of the normal

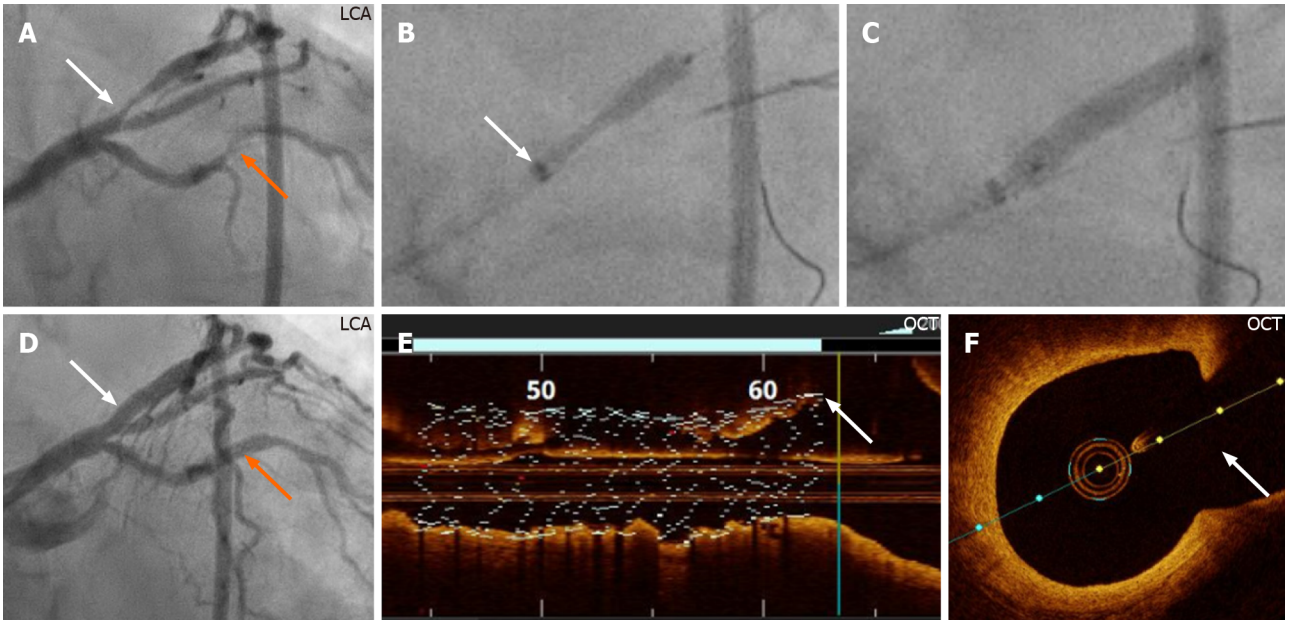


Figure 3 Demonstration of the guide extension technique during percutaneous coronary intervention of the bifurcation lesion of the second case. A: Left coronary artery (LCA) angiography reveals a stenosis in the obtuse marginal branch, (orange arrow) that was stented first after engagement of the left coronary artery with 7F-XB 3.5 guide catheter. There is also a distal mono-ostial (medina 0, 1, 0) left anterior descending artery (LAD)/diagonal bifurcation stenosis (white arrow), which was stented with the guide extension-assisted technique; B: Of note, angiography to visualize the angle between the diagonal branch and the distal segment of the main branch (LAD) was ambiguous, making it especially suitable for this novel technique. The GuideLiner, mounted on both the LAD and diagonal guidewires, was introduced to the carina site of the bifurcation. A Promus Premier 3.0 mm × 16 mm stent (Boston Scientific, Marlborough, MA, United States) positioned at the stenosis with the proximal stent balloon radio-opaque marker positioned on the GuideLiner radio-opaque marker just proximal to the tip of the GuideLiner (white arrow); C: The stent was implanted at a pressure of 22 atm; D: Angiographic final result (white and orange arrows); E and F: The implanted stent, checked by using OCT, is well-apposed to the vessel wall; the proximal stent edge can be seen positioned at the ostium of the distal segment of the main branch (E, white arrow), and no stent struts are seen to cover the diagonal branch ostium (F, white arrow). OCT: Optical coherence tomography.

proximal segment of the bifurcation with its subsequent risk of compromising the other branch of the bifurcation, and the subsequent need for re-crossing the stent struts for final kissing balloon inflation. The guide extension assisted technique can also be utilized for stenting the side-branch lesion in complex tri-ostial (medina 1, 1, 1) bifurcation lesions as demonstrated Figure 4.

The bifurcation PCI principle of "keep it open" for the side branch and the provisional side-branch stenting, is currently regarded as the default procedure in the majority of bifurcation lesions, in part attributable to the fact that the two-stent techniques (crush and culotte) are more complex and may leave stent struts under expanded or malapposed, with increased risk of acute or subacute stent thrombosis and future in-stent-restenosis. However, in complex bifurcation lesions, the risk of compromising the side branch is substantial with a provisional approach. The incidence of side-branch occlusion was 13.4% for true bifurcation and 4.0% for non-true bifurcation lesions in a bifurcation stenting registry enrolling 2227 cases of bifurcation PCIs treated by the one-stent approach[14]. For this reason, a two-stent technique is frequently necessary for complex true bifurcation lesions. The DK-crush technique has been shown to be superior to the provisional side-branch stenting as well as to culotte techniques in terms of efficacy and safety[1,3]. Nonetheless, it must be recognized that the DK-crush technique is technically demanding and time consuming.

A simplified two-stent technique, which does not leave excess layers of stent struts at the bifurcation site, is thus highly desirable. The guide extension-assisted stenting technique for the side branch does not leave unnecessary stent metal in the main branch as may occur with crush and culotte techniques and consequently avoids the subsequent risks of subacute stent thrombosis and difficulties in performing rewiring, balloon re-crossing the stent strut toward the side branch, sequential balloon dilatation, and final kissing balloon inflation.

Limitations

The main limitation of the technique is that in Y-shaped side branch angulation, it is impossible to implant a stent covering the whole side-branch ostium circumferentially; in such cases the stent either protrudes somewhat into the main branch at the lower

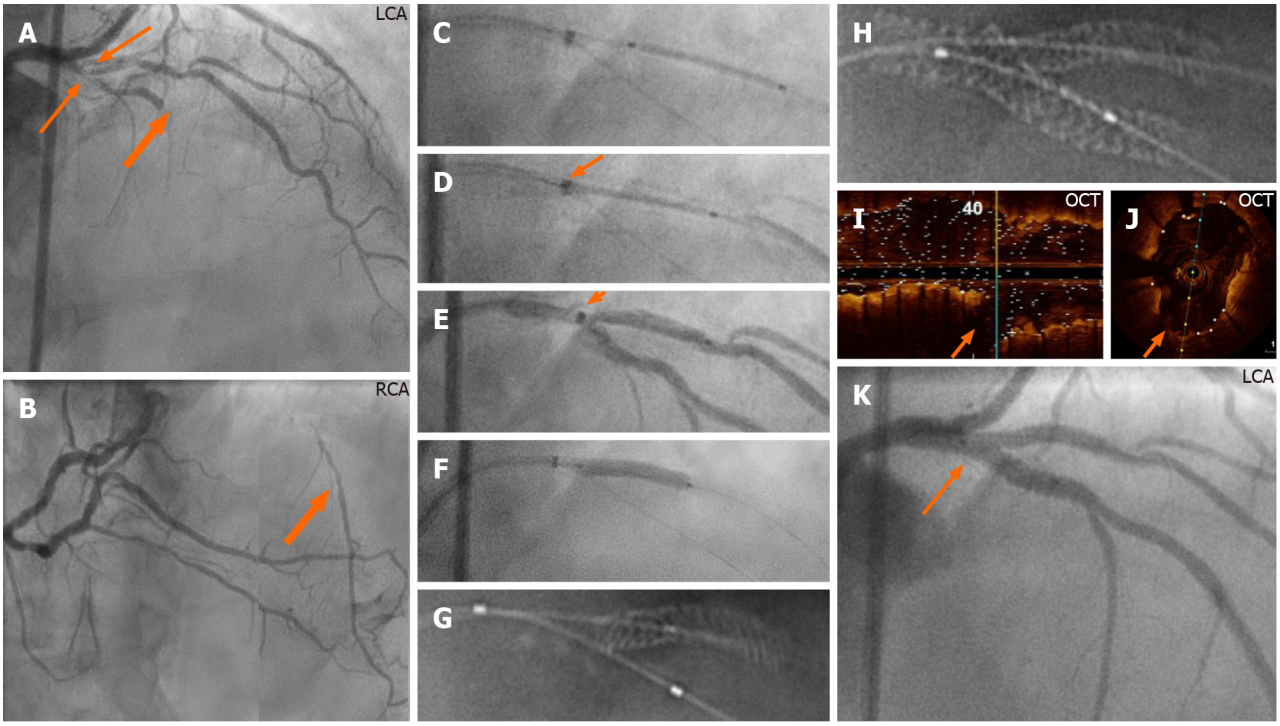


Figure 4 Demonstration of the guide extension technique in a complex true bifurcation lesion in the third case. A and B: Left (A) and right (B) coronary angiography. The left anterior descending artery (LAD) system reveals a proximal tri-ostial (medina 1, 1, 1) LAD/diagonal bifurcation stenosis where the LAD is subtotally occluded (thick orange arrows); B: The distal part of the LAD is filled by collateral circulation from the right coronary artery (thick orange arrow); C: The left coronary artery engaged with 7F-XB 3.5 guide catheter. After placing two guidewires, one in the LAD and another in the diagonal artery, and then conventional predilatation of both the main and the side branches, the GuideLiner, mounted on both guidewires, is positioned at the bifurcation carina. A Promus Premier (Boston Scientific, Marlborough, MA, United States) 2.5 mm × 16 mm stent is placed in the diagonal artery; D and E: The stent is retracted so that the proximal stent balloon radio-opaque marker overlaps the radio-opaque marker just proximal to the tip of the GuideLiner (D: Without contrast; E: With contrast; orange arrows); F: The stent was implanted at a pressure of 22 atm; the stent balloon pushes the guide extension catheter backwards; G: StentBoost imaging (Philips Medical Systems, Eindoven, the Netherlands) shows that the proximal stent edge is positioned at the side-branch ostium. After stent implantation in the main branch with a Promus Premier (Boston Scientific, Marlborough, MA, United States) 3.0 mm × 24 mm stent post-dilated with a 3.5 mm high pressure balloon, rewiring of the side branch, sequential balloon dilatation, proximal optimization technique, and final kissing balloon inflation; H: StentBoost imaging reveals a precisely stented bifurcation lesion without unnecessary layers of struts; I and J: Optical coherence tomography confirmed a well-apposed stent and no struts covering the ostium of the diagonal artery (orange arrows); K: Final result (orange arrow). LCA: Left coronary artery; RCA: Right coronary artery.

edge of the side-branch ostium or misses somewhat the upper edge of the side-branch ostium. Care must also be taken to ensure that the proximal stent balloon marker is not proximal to the guide extension radio-opaque marker during stent implantation to avoid inadvertent "trapping" of the guide extension.

In addition, the use of guide extensions is associated with complications such as proximal dissection due to deep intubation, air embolism due to insufficient de-airing, and ischemia, which may limit the length of time that the equipment can be kept in place.

Finally, other guide extension catheters are currently available, including Guidezilla (Boston Scientific), Telescope (Medtronic), and Gudion (IMDS). The technique should be applicable to these platforms even though they were not tested in this reported experience.

CONCLUSION

A novel guide extension-assisted stenting technique for selected CBLs is described. This technique facilitates stenting only the diseased side branch or distal main segment in non-true bifurcation lesions without compromising the other branches. It may also facilitate precise stenting implantation in the side branch when using two-stent techniques in complex true bifurcation stenoses without leaving excess stent struts at the bifurcation site, which facilitates easier rewiring, balloon re-crossing, and performing final kissing balloon inflation. The technique may potentially reduce the risks of acute and subacute stent thrombosis as well as future in-stent restenosis and is worthy of further investigation.

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MINIREVIEWS

Is branched-chain amino acid nutritional supplementation beneficial or detrimental in heart failure?

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Abstract

Sarcopenia or cachexia is often complicated in heart failure. Nutritional support, particularly branched-chain amino acid (BCAA) supplementation, is a candidate treatment for improving sarcopenia or cachexia in elderly patients. However, the efficacy of BCAA supplementation in patients with heart failure has not been established, and the issue is comparatively more complex. Indeed, there are conflicting reports on the efficacy of BCAA supplementation. The evidence for including BCAA supplementation in treating patients with heart failure was reviewed, and the complexity of the issue was discussed.

Key Words: Branched-chain amino acid; Heart failure; Sarcopenia; Cachexia; Nutrition; Branched-chain a-ketoacids

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Core Tip: The pros and cons of branched-chain amino acid (BCAA) supplementation can vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

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INTRODUCTION

Sarcopenia or cachexia is often complicated in heart failure, which aggravates the clinical course of the disease. Sarcopenia and cachexia were reported to be present in approximately 20% of patients with heart failure; however, there were differences in their percentages among different studies[1]. Also, both of them sometimes coexist in approximately 10% of patients with heart failure[2]. Low physical performance and reduced cardiopulmonary capacity influence sarcopenia and cachexia[3]. These comorbidities are independent predictors of the clinical course of patients with heart failure[4]. Therefore, the therapeutic strategy for sarcopenia or cachexia is a critical issue in managing heart failure. However, there is no standard management strategy at this time.

Nutritional support might be one candidate treatment for the improvement of sarcopenia or cachexia. Amino acid supplementation was effective for sarcopenia in elderly patients. Rondanelli *et al*[5] demonstrated nutritional supplementation with whey protein, essential amino acids, and vitamin D for twelve weeks, significantly increasing fat-free mass and muscle strength. Among several amino acid supplementation types, branched-chain amino acids (BCAAs) were beneficial in forming skeletal muscles because they account for a large part of the essential amino acids that form these skeletal muscles[6]. Ottestad *et al*[7] reported that BCAA levels decreased by 10% in sarcopenic adults, whereas nonessential amino acid levels did not change, suggesting the importance of BCAAs in skeletal muscle maintenance.

BENEFICIAL EFFECT OF BCAA IN PATIENTS WITH HEART FAILURE

Several reports about BCAA's effect on cardiopulmonary performance in other populations exist (Table 1). Chang *et al*[8] demonstrated that BCAA and arginine supplementation improved performance in intermittent sprints by reducing perceived exertion. Other reports on experimental and clinical conditions, according to the effect of improvement in exercise capacity by BCAA supplementation, were also presented [9-11]. Additionally, BCAA supplementation also reduced the muscle damage associated with endurance exercise[12]. Therefore, BCAA supplementation might have favorable effects on improving and maintaining exercise capacity, which might help patients with heart failure and reduced exercise capacity. Furthermore, several reports about the efficacy of BCAA supplementation for the improvement of sarcopenia also exist. Ko *et al*[13] demonstrated that BCAA administration for five weeks improved several parameters, including bioelectrical-impedance-analysis-derived skeletal mass index by approximately 10% and grip strength by about 10%. BCAA supplementation before and after exercise has shown beneficial effects in decreasing exercise-induced muscle damage and promoting muscle-protein synthesis[14]. Leucine supplementation also enhances myofibrillar protein synthesis, leading to increased muscle strength[15,16]. These effects could be partly explained by the shift to anabolic signaling of the skeletal muscle through the mammalian target of rapamycin complex 1 pathway[17]. Indeed, the anabolic pathway decreased because of alterations in the insulin-like growth factor 1/growth hormone axis and increased catabolism, induced by proinflammatory cytokines, in the presence of heart failure with sarcopenia[18]. There were several reports of the impact of BCAA on the treatment of sarcopenia.

Nichols *et al*[19] performed a systematic review of the effect of amino acid supplementation in heart failure. They demonstrated that essential amino acid supplementation could improve important outcome measures related to sarcopenia. For instance, amino acid supplementation increased the six-minute walk test distance by approximately 20%. In contrast, few reports demonstrated BCAA efficacy in the improvement of heart failure[20,21]. Oral intake of AAs is presumed to improve exercise capacities through its beneficial effect on the skeletal muscle in patients with heart failure. Furthermore, BCAA treatment decreased the heart rate, preserved cardiac function, and prolonged survival in heart failure with reduced ejection fraction model rats[20]. Uchino *et al*[21] reported that in-hospital heart failure patients with hypoalbuminemia showed increased serum albumin, decreased cardiothoracic ratio (CTR), and increased cholinesterase after BCAA supplementation. Another beneficial effect of BCAA is that it activates rapamycin's mammalian target (mTOR), promoting albumin synthesis[22]. The increase in serum albumin might favorably affect the clinical course of heart failure. The improvement in CTR could be due to decongestion efficiently induced by BCAA administration.

Table 1 Outcomes of branched-chain amino acid administration in clinical trials

Ref.	Study design	Sample size	Subjects	Dose	Length	Outcome
Chang *et al*[8]	Double-blind, randomized	22	Well-trained handball players	0.17 g/kg BCAA and 0.04 g/kg arginine together	1 d	Improve the performance in intermittent sprint
Watson *et al*[11]	Double-blind, randomized	8	Healthy male	12 g/L BCAA	Every 15 mins during exercise	Exercise capacity change observed between subjects in response to BCAA ingestion
Coombes and McNaughton [12]	Prospective, assigned to one of two groups	16	Males	12 g/d BCAA	14 d	Supplementary BCAA decreased serum concentrations of the intramuscular enzymes
Ko *et al* [13]	Quasi-experimental single-arm intervention	33	Middle-aged and elderly	Leucine 0.54 g, isoleucine 0.43 g, valine 0.36 g, glutamine 0.65 g, arginine 0.61 g and other amino acids 1.01 g	Twice daily for 5 wk	Short-term positive effects on sarcopenic parameters
Komar *et al*[15]	Systematic review and meta-analysis	999	-	Each reference	Each reference	Beneficial effects on body weight, body mass index, and lean body mass in older persons
Murphy *et al* [16]	Randomized, single-blind, parallel-group, placebo-controlled crossover study	20	Men, 65-85 yr of age, BMI (in kg/m^2) from 20 to 35, nonsmokers, and generally healthy	Higher protein intake group (1.2 g/kg/d) or lower protein intake group (0.8 g/kg/d)	9 d	Enhances the anabolic effect of resistance exercise
Glynn *et al*[17]	Prospective	14	Young participants (6 men, 8 women)	10 g essential amino acids	180 min post ingestion	Induce a maximal skeletal muscle protein anabolic response
Nichols *et al*[19]	Systematic review and meta-analysis	167	-	Each reference	Each reference	Increase lean body mass and 6-minute walk test distance in patients with heart failure
Uchino *et al*[21]	Randomized, controlled trial	18	In-hospital heart failure patients with serum albumin < 3.5 g/dL	One pack of BCAA granules containing 1144 mg of l-valine, 1904 mg of l-leucine, and 952 mg of l-isoleucine	28 d, 3 time a day	Increased serum albumin and decreased ctr in-hospital hf patients with hypoalbuminemia

BCAA: Branched-chain amino acid.

DETRIMENTAL EFFECT OF BCAA IN PATIENTS WITH HEART FAILURE

A clinical trial on the efficacy of BCAA supplementation in cardiac rehabilitation was conducted[23]. However, the issue might be more complex. Conversely, there are reports of BCAA's pathological role in heart failure. In clinical studies, several reports about the link between the high level of circulating BCAA and the risk of cardiovascular diseases, including heart failure, are present[24-27]. For instance, in the study of type 2 diabetes patients free of cardiovascular and renal diseases, patients with incident heart failure had 5.6% higher serum BCAAs than those without heart failure (HF). Serum BCAAs had a positive linear association with incident HF, adjusting for age, sex, and duration of diabetes. They demonstrated that high levels of BCAA corresponded to the increased event risk of atherosclerotic diseases and heart failure. Recent studies reported that BCAA catabolism is impaired in a failing heart, downregulating catabolic enzyme expression[28,29]. This catabolic derangement increases the levels of BCAAs and branched-chain a-ketoacids (BCKAs), which reportedly have a direct effect on cardiac remodeling and dysfunction through mTOR activation and reactive oxygen production (Figure 1)[30]. In basic experiments, incubation with BCKAs led to decreased cell survival and increased apoptosis in primary cardiomyocytes[31]. Moreover, increased BCAA concentration in the heart was shown to suppress glucose metabolism, enhancing ischemia-reperfusion injury by enhancing the GCN2/ATF6/PPAR-α pathway[32]. BCKA dehydrogenase (BCKD) activity, a critical step in BCAA catabolism, is regulated by the phosphorylation of regulatory subunit E1a. BCKD kinase (BCKDK) phosphorylates E1a to inhibit BCKA dehydrogenase activity, increasing BCKDK expression in defective hearts[33]. From these findings, the additional increase of BCAA through BCAA supplementation might exacerbate BCAA

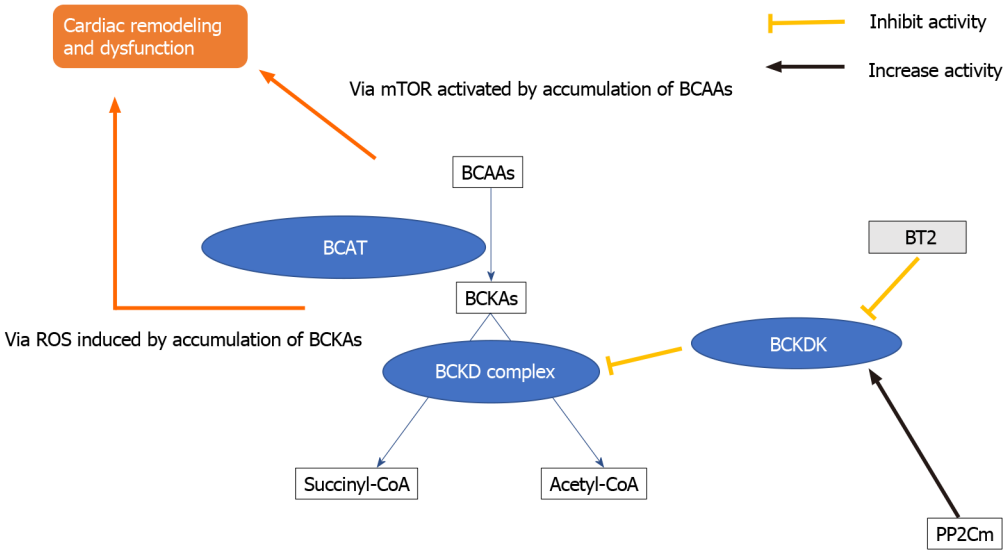


Figure 1 Branched-chain amino acid and its catabolic pathway in patients with heart failure. Branched-chain amino acid (BCAA) are degraded into their final products of acetyl-CoA and succinyl-CoA, however the decrease of branched-chain keto acid (BCKA) dehydrogenase leads to the increase of BCKA. The increases of BCAAs and BCKAs potentially exacerbate heart failure. mTOR: Mammalian target of rapamycin; BCAA: Branched-chain amino acid; BCKA: Branched-chain keto acid; BCAT: Branched chain aminotransferase; ROS: Reactive oxygen species; BCKD: Branched-chain keto acid dehydrogenase; BCKDK: Branched-chain keto acid dehydrogenase kinase; BT2: 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid; PP2Cm: Protein phosphatase 2C in mitochondria.

metabolites' burden in a failed heart, worsening the clinical course further in heart failure.

By contrast, some hopeful hints about the BCAA metabolic pathway in heart failure therapy might exist. In BCKDK regulation, 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid (BT2), a small-molecule BCKDK inhibitor, blocks BCKD phosphorylation, leading to increased BCAA catabolism[34]. Moreover, BT2 might alleviate oxidative stress by reducing BCKA or mTOR complex 1 activity by lowering BCAA concentrations, thereby improving cardiac function[35]. A study of BT2 administration to mice suggested that BT2 treatment improved cardiac function and led to remodeling without apparent toxicity[34].

The transcriptional factor Kruppel-like factor 15 (KLF15) also has a critical role in cardiac BCAA catabolic regulation[28]. KLF15-deficient hearts displayed reduced BCAT2 expression, another critical step in BCAA catabolism, whereas intramyocardial BCKA levels were elevated in KLF15-null hearts. KLF15 is reportedly a direct transcriptional activator of BCAT2[36]. KLF15 expression is lower in human cardiomyopathy. Therefore, the loss of KLF15 is a critical molecular mechanism underlying stress-induced BCAA catabolic defects in the diseased heart[37,38]. The modification of the KLF15 pathway could help the diseased heart in the BCAA metabolic pathway; however, its overexpression evoked arrhythmia due to its regulatory role in the potassium channel[39].

Additionally, the mitochondrial matrix-targeted 2C-type ser/thr protein phosphatase 2C family member (PP2Cm) is the endogenous phosphatase of the BCKD and functions as a key regulator of BCAA catabolism and homeostasis. The PP2Cm expression in the heart is dynamically regulated in the failing heart[40]. A study on PP2Cm-deficient mice revealed that PP2Cm deficiency led to heart failure signs, including weight gain, reduced left ventricular ejection fraction (LVEF), and chamber dilation[30]. The study findings suggested the impact of BCAA metabolism on the pathogenesis of heart failure. Furthermore, BT2 overturned the dysfunction induced in PP2Cm-knockout mice, significantly preserved LVEF, and reduced chamber dilation. The efficacy of BT2 treatment for the reinforcement of the BCAA metabolic pathway might be more than expected for the dysfunctional heart[41]. These basic findings would present some hints for treating heart failure, which is associated with the BCAA pathway.

CONCLUSION

Studies have shown that BCAAs are beneficial in heart failure. Conversely, BCAAs

could act as exacerbators of heart failure. Nevertheless, improving BCAA metabolism might lead to an effective treatment strategy for the disease. In conclusion, the pros and cons of BCAA supplementation could vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

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MINIREVIEWS

Cardiogenic shock in the setting of acute myocardial infarction: Another area of sex disparity?

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Abstract

Cardiogenic shock in the setting of acute myocardial infarction (AMI) carries significant morbidity and mortality, despite advances in pharmacological, mechanical and reperfusion therapies. Studies suggest that there is evidence of sex disparities in the risk profile, management, and outcomes of cardiogenic shock complicating AMI. Compared with men, women tend to have more comorbidities, greater variability in symptom presentation and are less likely to receive timely revascularization and mechanical circulatory support. These factors might explain why women tend to have worse outcomes. In this review, we highlight sex-based differences in the prevalence, management, and outcomes of cardiogenic shock due to AMI, and discuss potential ways to mitigate them.

Key Words: Cardiogenic shock; Myocardial infarction; Sex; Morbidity

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Core Tip: Sex disparities exist among different cardiovascular diseases and therapies. Cardiogenic shock is a leading cause of death among patients with acute myocardial infarction. Although some studies suggest that cardiogenic shock is more prevalent among women, women are less likely to receive guideline-recommended management including revascularization, which might explain why are more likely to experience worse outcomes.

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INTRODUCTION

Acute myocardial infarction (AMI) is the one of the leading causes of death in the United States and worldwide[1]. In recent years, there has been a decline in the incidence and case fatality of AMI, which is partly attributed to the advancements in management including timely reperfusion and medical therapies[2,3]. Despite these improvements, sex disparity still has an impact on AMI management and outcomes[3].

Cardiogenic shock is the most common cause of death in patients with AMI, resulting from left ventricular pump failure or as a consequence of post-MI mechanical complications such as papillary muscle rupture, ventricular septal rupture, free wall rupture or right ventricular failure[4,5]. Cardiogenic shock affects 5%-10% of AMI cases and is associated with high mortality (up to 30%-40%), despite advances in pharmacological, mechanical and reperfusion endeavors[6,7]. Similar to AMI without cardiogenic shock, sex differences exist in management and outcomes among those with cardiogenic shock[8]. In this review, we discuss the sex disparities in the risk profile, management, and outcomes of cardiogenic shock in the setting of AMI, and present few solutions to the existing challenges.

SEX DISPARITY IN AMI

Women with AMI tend to have a higher cardiovascular risk profile on presentation, as they are likely older and have a higher prevalence of traditional cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and obesity, compared with men[9,10]. Women also have greater variability in symptom presentation, since they often present with fatigue, dyspnea, dizziness, nausea, and upper back pain, while men usually complain of chest pain and diaphoresis[11]. This difference in presentation partly explains why the diagnosis of AMI is sometimes delayed or missed among women[12]. Women are also less likely to receive guideline-directed medical therapies or undergo timely pharmacological and mechanical reperfusion, as well as other invasive procedures[10,13]. Consequently, women are at a higher risk of AMI-related complications including cardiogenic shock and have a higher unadjusted mortality[10]. Indeed, some studies have indicated that female sex does not confer an additional risk of mortality after accounting for the differences in revascularization [14].

SEX DIFFERENCES IN THE PREVALENCE AND PRESENTATION

Some studies have suggested that cardiogenic shock in the setting of AMI occurs more frequently among women[9,15,16]. For example, data from the French Registry of acute ST-elevation or non-ST-elevation myocardial infarction (FAST-MI), that included > 10000 patients between 1995 and 2010, showed that the rate of cardiogenic shock was significantly higher among women compared with men (8.2% *vs* 4.8%; $P < 0.001$)[9]. Female sex was independently associated with an increased risk of developing cardiogenic shock after adjusting for age, type of AMI, and other baseline characteristics [odds ratio (OR) 1.20, 95% confidence interval (CI): 1.00-1.45][9]. Data from a prospective registry in Germany, The Maximal Individual Therapy of Acute Myocardial Infarction PLUS registry, that included 36643 patients with ST elevation myocardial infarction also showed that women are more likely to develop cardiogenic shock (12.9% *vs* 9.3%; $P < 0.001$), even after adjusting for other confounding variables (OR 1.19, 95%CI: 1.09-1.30)[15]. Another study that examined 9750 patients with cardiogenic shock in the setting of AMI between 1992 and 2008 from the Ontario Myocardial Infarction Database revealed that the rate of cardiogenic shock was also higher among women (3.7% *vs* 2.7%; $P < 0.001$)[16].

Similar to AMI without cardiogenic shock, women with cardiogenic shock tend to have a higher cardiovascular risk profile than men. Women usually have a higher comorbidity burden including hypertension, diabetes, hyperlipidemia, and metabolic syndrome[9,16]. Women are less likely to have a history of prior MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft[15]. These findings have

also been observed even among younger patients. An analysis of the National Inpatient Sample (NIS) (the largest inpatient administrative database in the United States) of AMI complicated by cardiogenic shock admissions aged 18-55 years, between 2000 to 2017, found that younger women also tend to have higher burden of comorbidities[17]. Table 1 summarizes the studies comparing the prevalence and risk profile between women and men.

SEX DISPARITY IN MANAGEMENT

Timely reperfusion remains the cornerstone in the management of AMI complicated by cardiogenic shock[18]. Studies examining AMI complicated by cardiogenic shock reveal that significant sex-based differences still exist. In an analysis of the NIS database, including > 134000 older (≥ 75 years) patients who were hospitalized between 2000 and 2014, women were less likely to undergo coronary angiography (55.4% *vs* 49.2%; $P < 0.001$), PCI (36.3% *vs* 34.4%; $P < 0.001$), and receive mechanical circulatory support devices (34.3% *vs* 27.2%; $P < 0.001$) compared with men[8]. Similar results were reflected in another NIS analysis of younger adults (18-55 years), which showed that women less frequently received coronary angiography (78.3% *vs* 81.4%), early coronary angiography (defined as angiography performed on the day of admission) (49.2% *vs* 54.1%), PCI (59.2% *vs* 64.0%), and mechanical circulatory support devices (50.3% *vs* 59.2%; all $P < 0.001$) compared with younger men[17]. The Canadian-based Ontorio Myocardial Infarction Database also showed that women were less likely to be revascularized (12.6% *vs* 17.6%; $P < 0.001$) and less likely to be transferred when they presented to non-revascularization sites (11.3% *vs* 14.2%; $P < 0.001$)[16].

Notably, some sex disparities were observed in randomized trials of interventions for patients with cardiogenic shock in the setting of AMI. An exploratory analysis of the Should we emergently revascularize occluded coronaries for cardiogenic shock? (SHOCK) trial of 1190 patients showed that although the rates of thrombolytic treatment, PCI and surgical revascularization were not different between both sexes, intra-aortic balloon pump (IABP) use was less frequent among women (48% *vs* 55%; $P = 0.05$), despite exhibiting lower cardiac index[19]. In another trial, Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) that included 600 patients undergoing early revascularization with or without IABP, although there was no evidence of interaction for IABP treatment based on sex, women were less likely to have undergone resuscitation before randomization[20]. Lastly, a secondary analysis of the CULPRIT SHOCK trial (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) showed that although the use of mechanical circulatory support was not different between women and men, women were less likely to receive therapeutic hypothermia[21]. Table 2 depicts the differences in in-hospital procedures between women and men.

SEX DISPARITY IN OUTCOMES

Many studies have indicated that women have higher unadjusted mortality rates compared with men, primarily explained by older age, higher co-morbidity burden and lower likelihood of receiving reperfusion therapy and mechanical circulatory support devices. Data from the NIS database for older patients (≥ 75 years) revealed that despite a steady decrease in in-hospital mortality during the study period between 2000 and 2014, adjusted trends showed consistently higher in-hospital mortality among women compared with men[8]. Female sex remained an independent predictor of higher in-hospital mortality (adjusted OR 1.05; 95%CI: 1.02-1.08; $P < 0.001$) [8]. Similarly, NIS data for younger patients (18-55 years) also showed that women experienced higher hospital mortality, and that female sex was an independent predictor of in-hospital mortality (adjusted OR 1.11, 95%CI: 1.07-1.16; $P < 0.001$)[17] (Figure 1). The timely use of reperfusion strategies could potentially improve survival among women. For example, data from the French FAST-MI registry showed that although 1-year mortality was significantly decreased for both men and women due to primary PCI, primary PCI was an independent predictor of 1-year survival among women (hazard ratio [HR] 0.55, 95%CI: 0.37-0.81), but not men (HR 0.85, 95%CI: 0.61-1.19)[9]. Although these studies showed that women were less likely to receive reperfusion therapy and mechanical circulatory support devices, data about the angiographic findings and other clinical variables were not available in these studies.

Table 1 Sex differences in the prevalence and risk profile

Ref.	Country	Prevalence of cardiogenic shock (%)		Mean age, yr		Hypertension (%)		Diabetes (%)		Prior myocardial infarction (%)		Prior percutaneous coronary intervention (%)		Smoking (%)	
		Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Isorni *et al*[9]	France	4.8	8.2	68.9	80.2	57	80	31	44	21	18.5	21	13	25	7
Koeth *et al*[15]	Germany	9.3	12.9	68	76.3	37	45.3	25.2	39.1	25.6	19.9	13.2	6.7	36	17.9
Abdel-Qadir *et al*[16]	Canada	2.7	3.7	71.1	75.5	NA	NA	24.4	26.9	NA	NA	NA	NA	NA	NA
Vallabhajosyula *et al*[8]	United States	NA	NA	82	83.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vallabhajosyula *et al*[17]	United States	NA	NA	48.8	48.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wong *et al*[19]	United States, Canada	NA	NA	66.8	71.4	45.6	62.1	28.3	40.8	44.7	32	7.6	5.1	57.5	40.7
Fengler *et al*[20]	Germany	NA	NA	68	74	66	76	29	40	25	16	31	15	39	25
Gimenez *et al* [21]	Switzerland, Germany, Poland, Austria, France, Italy	NA	NA	67	75	58.3	66.7	30.3	39.4	18.5	11.3	20.2	14.4	29	18.1

NA: Not available.

Table 2 Sex differences in in-hospital procedures

Studies	Percutaneous coronary intervention (%)		Coronary artery bypass graft (%)		Mechanical circulatory support (%)	
	Men	Women	Men	Women	Men	Women
Isorni *et al*[9]	76.5	68.5	NA	NA	NA	NA
Koeth *et al*[15]	18	11	NA	NA	NA	NA
Abdel-Qadir *et al*[16]	14	10.6	4.3	2.3	NA	NA
Vallabhajosyula *et al*[8]	36.3	34.4	12	8.1	34.3	27.2
Vallabhajosyula *et al*[17]	64	59.2	20.1	18.3	59.2	50.3
Wong *et al*[19]	31.1	35.4	17.3	12.1	55.2	48.1
Fengler *et al*[20]	96.6	94.1	0.7	1.6	52	48
Gimenez *et al*[21]	100	100	-	-	28.6	27.2

NA: Not available.

Secondary analyses of randomized trials of cardiogenic shock in the setting of AMI have also suggested that there was no difference in treatment effect based on sex[19-21]. As such, these findings support the notion that women should be treated similar to men (*i.e.* timely reperfusion, and consideration of mechanical circulatory support devices if indicated). Noteworthy, despite the higher prevalence of cardiogenic shock among women in many studies, women have consistently been underrepresented in these interventional trials. While women in the SHOCK and IABP-SHOCK-II trials comprised 32% and 31% of the participants, respectively, women constituted only 24% of the study population in the CULPRIT SHOCK trial that was conducted about 2 decades later.

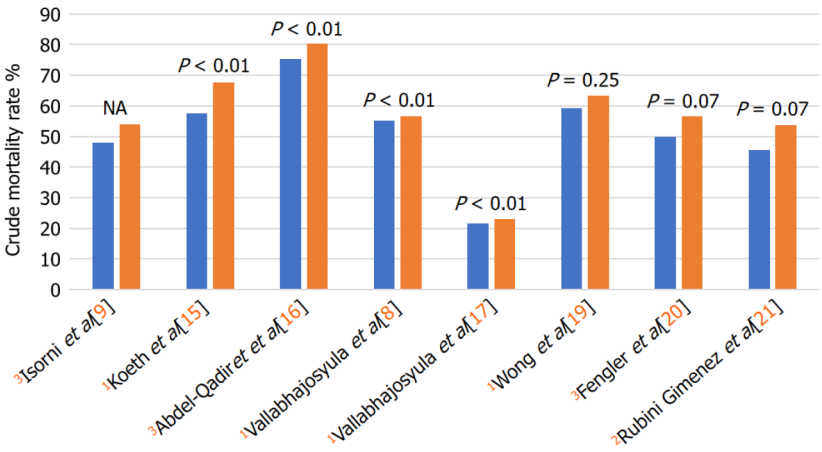


Figure 1 Studies showing crude mortality rates among women *vs* men. [1]In-hospital mortality; [2]30-d mortality; [3]1-year mortality. NA: Not available.

CHALLENGES AND POTENTIAL SOLUTIONS

Sex-based differences exist in the clinical presentation of AMI and might subsequently result in treatment delays. Women often present late and with non-classical symptoms of AMI and thus are often misdiagnosed resulting in delays in care, and potentially preventable adverse outcomes. This highlights the importance of using objective measures of risk stratification among patients with suspected AMI. Minimizing provider bias together with focusing on educating women at risk about the symptoms of AMI warrant priority.

With regards to clinical trials pertinent to cardiogenic shock in the setting of AMI, women continue to be underrepresented despite a higher incidence of cardiogenic shock among women in many studies. Clinical trials form the foundation for guidelines that shape our clinical practice, and the underrepresentation of women can result in some important information deficits with regards to management and outcomes. Well-designed clinical research studies with adequate women representation will ensure unbiased and reliable findings to guide clinical decision. An adequate representative sample is necessary for sex-based comparative analysis of the interventional strategy/therapy, as well as the outcomes. In this regard, there is a need to examine the role of sex-based differences in socioeconomic, logistic and enrollment barriers that might impede a proportionate representation of women[22].

CLINICAL IMPLICATIONS AND CLINICAL PRACTICE

Women, despite having higher comorbidity and varied symptom manifestation, derive similar benefit with guideline-directed management as men. This important message needs to be translated into action and reflected in our clinical practice, where unfortunately women are seen more often to be misdiagnosed and undertreated than men, resulting in worse outcomes. In the real world, there is a need to identify and address individual-based and system-based factors that trigger unconscious biases and impede the provision of high-quality and equitable healthcare irrespective of the sex differences. Since women with AMI have a higher cardiovascular risk profile and sometimes delayed presentations than men, clinicians are encouraged to keep a lower threshold for initiating work-up for diagnosis, and institute prompt delivery of care and employ aggressive treatment strategies when indicated.

In the meantime, there is a need to increase awareness among women to identify symptoms, and to seek immediate care. It is essential to emphasize both primary and secondary preventative strategies that are appropriate for women from numerous backgrounds, and could be applicable in various clinical settings. The foremost step towards personalized medicine involves paying attention to sex-specific details and recognizing sex-disparity in the clinical settings, which will help improve awareness, diagnosis, treatment and eventually outcomes in women.

CONCLUSION

Cardiogenic shock is the leading cause of death among AMI patients. Sex disparity in the management and outcomes of patients with cardiogenic shock in the setting of AMI exist. Although some studies indicate that cardiogenic shock occurs more frequently among women, women do not receive adequate management as evidenced by the lower rates compared of revascularization and mechanical circulatory support devices. Given these differences, women continue to experience worse outcomes. Future studies are needed to understand the reasons behind these differences and efforts are needed to minimize these disparities.

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CASE REPORT

Novel economic treatment for coronary wire perforation: A case report

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Author contributions: Egred M conceived and delivered the idea and performed the procedure; Abdalwahab A, McQuillan C, and Farag M were assisting during the procedure and have written and edited the manuscript and produced the schematic figure.

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Abstract

BACKGROUND

Coronary artery perforation is a rare but potentially life-threatening complication of percutaneous coronary intervention (PCI), however if recognized and managed promptly, its adverse consequences can be minimized. Risk factors include the use of advanced PCI technique (such as atherectomy and chronic total occlusion interventions) and treatment of severely calcified lesions. Large vessel perforation is usually treated with implantation of a covered stent, whereas distal and collateral vessel perforations are usually treated with embolization of coils, fat, thrombin, or collagen. We describe a novel and cost-effective method of embolisation using a cut remnant of a used angioplasty balloon that was successful in sealing a distal wire perforation. we advocate this method as a simple method of managing distal vessel perforation.

CASE SUMMARY

A 73-year-old male with previous coronary Bypass graft operation and recurrent angina on minimal exertion had undergone rotablation and PCI to his dominant left circumflex. At the end of the procedure there was evidence of wire perforation at the distal branch and despite prolonged balloon tamponade there continued to

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be extravasation and the decision was made to seal this perforation. A cut piece of an angioplasty balloon was used and delivered on the original angioplasty wire to before the perforation area and released which resulted in sealing of the perforation with no unwanted clinical consequences.

CONCLUSION
The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

Key Words: Percutaneous coronary intervention; Coronary perforation; Coronary guide wire; Collagen; Coronary angioplasty balloon; Coil; Case report

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Core Tip: The use of a remnant balloon for sealing a coronary perforation can be a cost-effective method of treating this complication using a readily available material. In cases where the sealing of the perforation is indicated, a careful and controlled approach for delivering the balloon remnant will ensure the safe and effective delivery and the sealing of the perforation which in turn will help stabilize and safe the patient by controlling any further bleeding.

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INTRODUCTION

The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

CASE PRESENTATION

Chief complaints

A 73-year-old male presented with recurrent angina on minimal exertion with poor functional capacity despite optimal medical treatment.

History of present illness

He suffered with recurrent angina for 3 mo before the procedure.

History of past illness

He has a history of previous coronary artery bypass grafting 16 years earlier, bronchiectasis, chronic kidney disease, Barrett's esophagus and hypertension.

Personal and family history

No family history of ischemic heart disease.

Physical examination

Within normal limits.

Laboratory examinations

Blood tests were normal.

Imaging examinations

Echocardiogram showed normal left ventricular function. He underwent coronary angiography which showed patent left internal mammary artery graft to left anterior descending artery (LAD), patent saphenous vein graft to right coronary artery (RCA), occluded LAD and RCA, severe long and calcific lesion in proximal to mid co-dominant left circumflex artery (LCX) with no visualized patent graft.

FINAL DIAGNOSIS

The final diagnosis of the presented case is distal wire coronary artery perforation sealed with an embolized cut angioplasty balloon.

TREATMENT

The procedure was performed from the right radial artery with planned rotablation. The proximal LCX was wired with a Gladius wire to the distal left posterior descending artery (LPDA) (Figure 1A). A Turnpike microcatheter was advanced over the Gladius wire and the wire exchanged for an extra-support rotablation wire. Rotablation was then performed with 1.25 mm then 1.75 mm burrs then a Sion black introduced with subsequent predilatation with 3.5 mm non-compliant balloon (Figure 1B). Following on a synergy drug eluting stent (DES) 4.0 mm × 24 mm was deployed and post dilated with 4.5 mm non-compliant balloon with excellent results (Figure 1C).

There was evidence of contrast staining and extravasation distally in the LPDA territory which appeared as a wire perforation. There was no evidence of hemodynamic compromise. In addition, there was dissection in the obtuse marginal (OM) branch.

A prolonged inflation of 2.0 mm balloon distally just before the site of perforation failed to stop the extravasation. Echocardiogram showed no evidence of tamponade.

At this stage, coil delivery was planned however and instead of delivering a coil, the operator thought that any compatible particle that can be delivered and block the distal artery should be helpful. The distal tip of the already used 2.0 mm balloon was cut (Figure 1D) and mounted on to the wire in the LPDA and then pushed with another intact balloon to the distal LPDA (Figure 1E) just before the perforation area then the wire and the pushing balloon were removed. There was no evidence of any further increase in the contrast staining. The OM branch was treated with 2 DES with excellent final angiographic results.

OUTCOME AND FOLLOW-UP

The patient had an uneventful postoperative clinical course and he was allowed home in a stable condition. He was doing well and asymptomatic on follow up 3 mo later.

DISCUSSION

Coronary perforations (large, distal, and collateral vessels) remain relatively rare[1,2], but have potentially increased with the higher use of adjunctive devices in calcified lesions[3-6]. Immediate recognition and rapid action will help prevent potential catastrophic outcome[3,7]. The balloon part, as was used in this case, is readily available and would substitute expensive equipment, and requires no specific expertise.

Rapid and clear management algorithms should be adopted. The first step is balloon tamponade with a 1/1 ratio for 5-10 min proximal or at the site of perforation. Repeated 5-10 min balloon inflation can be done till either successful sealing of the perforation or evidence of significant ischemia. Intravenous fluids and vasopressor may be needed and beneficial on occasions. Echocardiogram is important to rule out

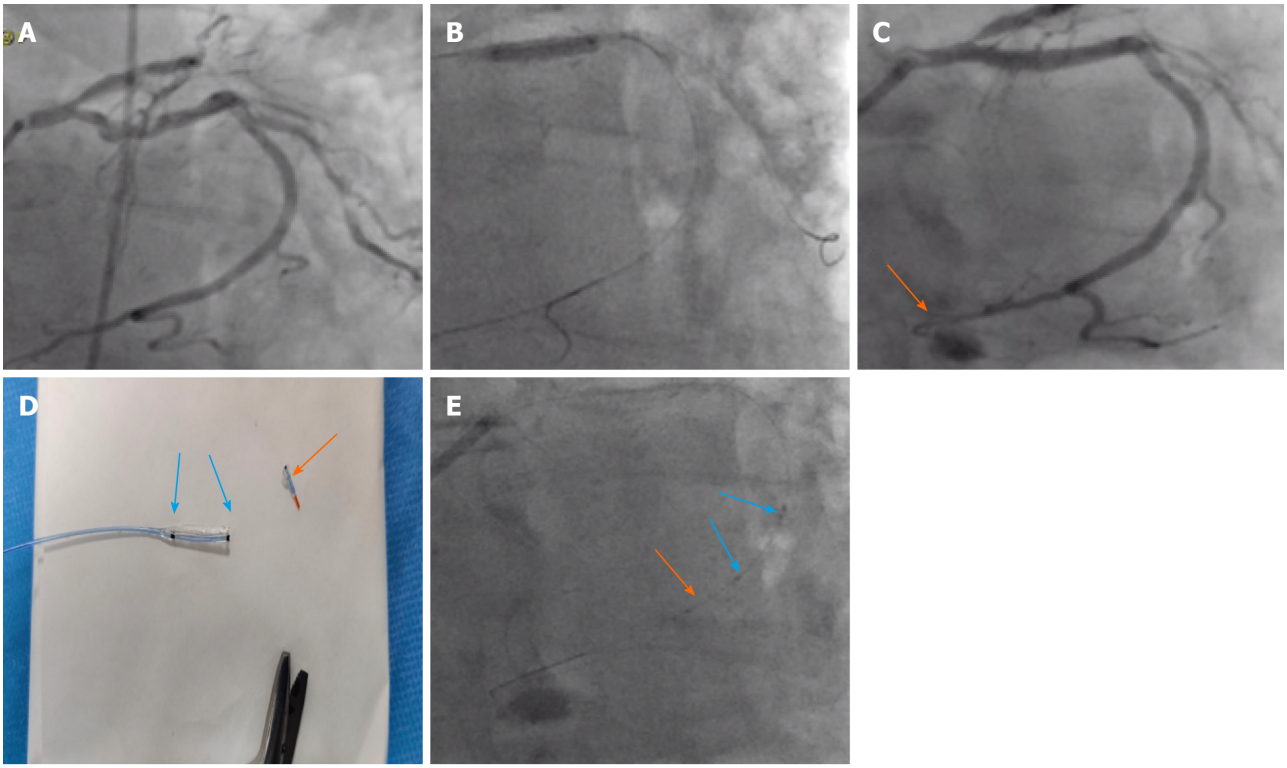


Figure 1 The proximal left circumflex artery. A: Calcific proximal dominant left circumflex artery (LCX) lesion; B: Distal wire position when predilatation; C: Distal wire perforation in the LCX (orange arrow); D: Tip of the balloon cut for embolization; E: The cut balloon tip with the marker for X-Ray visibility (orange arrow) pushed by another intact balloon with two markers (blue arrows).

cardiac tamponade where pericardiocentesis should be performed immediately. X-Ray Fluoroscopy can show pericardial collection as the dye escapes into the pericardium. In our experience, pericardiocentesis can be performed under fluoroscopy using the pericardial dye collection as a guide without the use of echocardiography.

Furthermore, follow up echo is crucial especially in wire induced perforation as delayed pericardial effusion can occur hours later.

A crucial aspect of this complication is anticoagulation reversal which seems to be put forward as a first step approach. Perforation is a mechanical problem and reversal of anticoagulation will not solve it. It is not recommended to reverse anticoagulation as a first approach and should only be considered once the perforation is sealed and equipment removed from the coronary arteries. This is important to avoid any intracoronary thrombosis. The reversal is usually accomplished by protamine sulphate and occasionally with platelets transfusion[6].

More specific treatment lines may be needed if the previous measures were unsuccessful. In large vessel perforation, covered stents or occasionally even surgery may be needed[8]. Due to their bulkiness, deployment of covered stent may be difficult or may fail in tortuous and small vessels. In addition, these covered stents can also be used in the management of distal perforation by deployment across the side branch ostium. In distal vessel perforation, embolization or deployment of a covered stent across the ostium of the perforated branch to occlude it from the origin can be used[9].

Distal embolization can be done by different materials such as subcutaneous fat, thrombin and coils[5]. In addition, less commonly methods have been used such as injection of fibrin or synthetic glue through the lumen of microcatheter or an over-the-wire balloon[10]. Embolization of collagen, which is available commercially in femoral occlusion angioseal devices, can be used to occlude distal perforation[11]. Injection of polyvinyl alcohol particles through the lumen of inflated over the wire balloon has also been used to seal distal vessel perforation. Furthermore, injection of autologous blood clot or autologous subcutaneous fat particles through the micro catheter can occlude distal perforation.

The mechanism by which embolic material stop the bleeding is by the formation of artificial clot which trigger more clotting and occlude the vessel. After that, this embolic material will cause a foreign body granuloma which differs in its nature according to the embolized material.

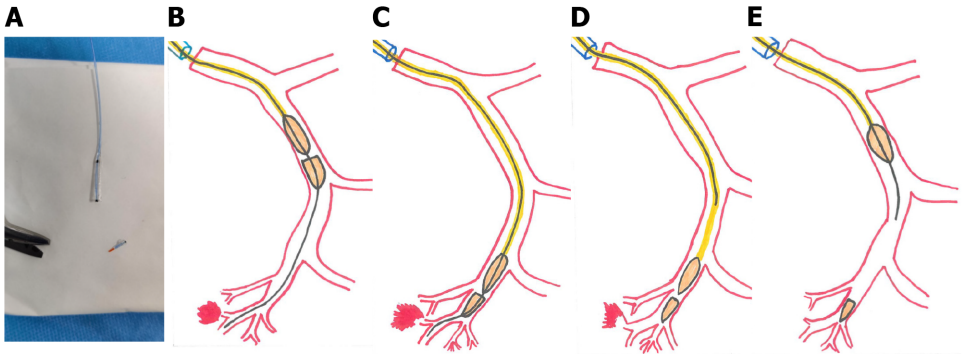


Figure 2 Schematic steps for sealing distal wire perforation using balloon remnant. A: Distal half of already used balloon is cut by scissors; B and C: The remnant piece is mounted on to the wire in the perforated vessel and pushed with another intact balloon to the distal vessel before the perforation; D and E: Withdrawal of the wire and the intact pushing balloon with the remnant part left distally as the embolization materials.

In our case, we used part of a PCI balloon that is readily available in all PCI cases. This offers a rapid, simple and cost-effective way for managing coronary perforations.

There are several important points and cautions to be highlighted and considered.

Most wire perforations are self-contained and require no significant treatment. If the decision is made to treat, then this balloon remnant method can be considered.

It can be argued that fat embolization is cheaper and not a foreign material, but it is not as easy or straight forward to use as any other method and particularly this newly described balloon remnant method.

The delivery of the balloon remnant can be perceived as uncontrolled and if there is resistance and inability to deliver it, then it cannot be retrieved. Furthermore, it could also be perceived that this remnant can be advanced too distal and may exit through the perforation and cause more bleeding. This in fact is not the case. (Figure 2) The balloon remnant would be delivered after another normal balloon has passed and has been used and inflated to temporarily block the artery and stop the extravasation. This would indicate that the remnant balloon will pass too. In addition, the anatomy and the site of perforation would be clear to any experienced operator which in turn ensures that the release of the remnant is well before the perforation site itself and will have no chance of exiting through the perforation and making matters worse.

Since this case, we have used this method in a second wire perforation case that needed embolization with sealing of the perforation and excellent outcome. The patient in this case was seen in the outpatient clinic 3 mo later and he was angina free and doing well.

CONCLUSION

The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

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REVIEW

Current concept in the diagnosis, treatment and rehabilitation of patients with congestive heart failure

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Abstract

Heart failure (HF) is a major public health problem with a prevalence of 1%-2% in developed countries. The underlying pathophysiology of HF is complex and as a clinical syndrome is characterized by various symptoms and signs. HF is classified according to left ventricular ejection fraction (LVEF) and falls into three groups: LVEF ≥ 50% - HF with preserved ejection fraction (HFpEF), LVEF < 40% - HF with reduced ejection fraction (HFrEF), LVEF 40%-49% - HF with mid-range ejection fraction. Diagnosing HF is primarily a clinical approach and it is based on anamnesis, physical examination, echocardiogram, radiological findings of the heart and lungs and laboratory tests, including a specific markers of HF - brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide as well as other diagnostic tests in order to elucidate possible etiologies. Updated diagnostic algorithms for HFpEF have been recommended (H2FPEF, HFA-PEFF). New therapeutic options improve clinical outcomes as well as functional status in patients with HFrEF (*e.g.*, sodium-glucose cotransporter-2 - SGLT2 inhibitors) and such progress in treatment of HFrEF patients resulted in new working definition of the term "HF with recovered left ventricular ejection fraction". In line with rapid development of HF treatment, cardiac rehabilitation becomes an increasingly important part of overall approach to patients with chronic HF for it has been proven that exercise training can relieve symptoms, improve exercise capacity and quality of life as well as reduce disability and hospitalization rates. We gave an overview of latest insights in HF diagnosis and treatment with special emphasize on the important role of cardiac rehabilitation in such patients.

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Core Tip: Diagnostic methods and treatment of heart failure (HF) are evolving rapidly. Making a firm diagnosis of HF with preserved ejection fraction is a challenge, and although diagnostic algorithms have been recommended further research is needed for better classification. Therapeutic options improve morbidity, mortality, as well as functional status of patients with HF with reduced ejection fraction and the new term - HF with recovered left ventricular ejection fraction is a result of successful therapy. Only a small part of patients with chronic HF participates in cardiac rehabilitation programs. Cardiac rehabilitation in patients with HF is an important part of care and should be implemented as a part of holistic approach because it improves exercise capacity and quality of life, reduces disability and hospitalization rates.

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INTRODUCTION

Heart failure (HF) is one of the major public health problems with a prevalence of 1-2% in developed countries (varies by definition and region), and it increases with age (rising to over 10% in people over 70 years of age)[1]. Approximately 33% of men and 28% of women at the age of 55 have a lifetime risk of developing HF[1].

The pathophysiology of HF is complex and it is therefore a clinical syndrome characterized by various symptoms and signs, which is caused by structural and/or functional abnormalities of the heart. HF can be a terminal stage of many cardiovascular diseases, including myocardial infarction, heart valve disease, tachyarrhythmias, congenital heart defects, and cardiomyopathies[1]. Most commonly, HF develops as a consequence of a myocyte injury caused by coronary artery disease, uncontrolled arterial hypertension, valvular heart diseases and diabetes mellitus, and it is important to consider pulmonary disorders such as chronic obstructive pulmonary disease or pulmonary arterial hypertension as causes that can lead to HF[1-3].

The main pathophysiological mechanisms leading to HF are increased hemodynamic overload, ischemia, myocardial dysfunction and remodelling, excessive neurohumoral stimulation - chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms (in the acute phase, this upregulated sympathetic activity is an essential compensatory response initiated in order to compensate for reduced contractility, and cardiac output but in the long-term, it contributes to cardiac dysfunction as it leads to cardiac hypertrophy and cell dysfunction), activation of the renin-angiotensin-aldosterone system (RAAS), excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations[3-6] (Figure 1). HF is associated with a variety of complications, such as frequent hospitalizations, fatal arrhythmias, and death in the advanced stage of the disease.

CLASSIFICATION

As mentioned, HF is caused by a number of conditions, causing left and right ventricular dysfunction[6-8]. The most common classification of HF refers to the left ventricular ejection fraction (LVEF). Accordingly, HF is classified into three groups: with preserved left ventricular ejection fraction LVEF ≥ 50% - HFpEF, with reduced ejection fraction LVEF < 40% - HFrEF, and patients with a mid-range ejection fraction are between these two groups LVEF 40%-49% - HF with mid-range ejection fraction

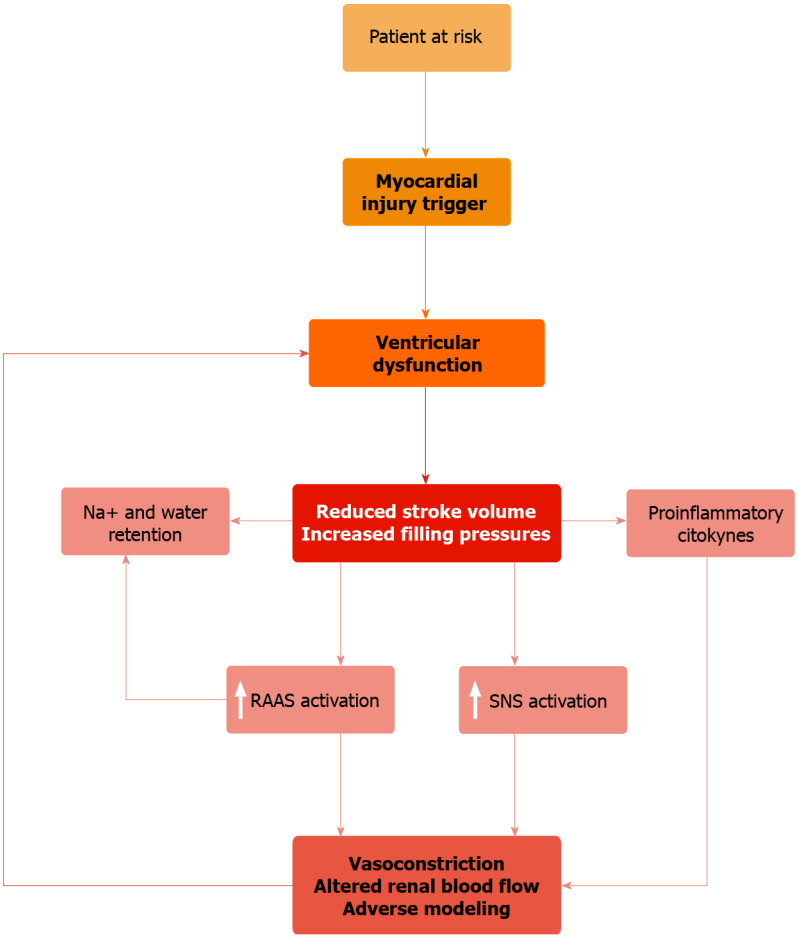


Figure 1 Pathophysiological mechanisms in chronic heart failure (data from[3]). RAAS: Renin-Angiotensin-Aldosterone System; SNS: Sympathetic nervous systems.

(HFmrEF)[1,2].

HF is often considered as a left-sided failure when caused primarily by left heart pathologies (*e.g.*, left ventricular, mitral valve, or aortic valve dysfunction). The ventricle fails in its ability to eject blood, or can do so only at the cost of high filling pressures[6,7]. Right-sided or right ventricular HF also has a complex pathophysiology and it is influenced by multiple factors (such as volume status, pulmonary vascular resistance, right ventricular, pulmonic valve, or tricuspid valve dysfunction, left ventricular function) and usually occurs as a result of left ventricular HF[8,9]. Left and right ventricular HF may overlap or occur separately and most patients with right HF have some elements of left HF.

Considering the clinical presentation, HF is divided into acute and chronic[1,2]. Patients with a low LVEF and no symptoms or signs of HF are characterized as asymptomatic patients with a reduced left ventricular systolic function. Those who have signs and symptoms of HF belong to the group of patients with chronic HF, and those who do not experience worsening of symptoms within at least a month are considered stable patients with chronic HF[6]. Acute HF includes the worsening of chronic HF, pulmonary oedema, and cardiogenic shock. There are a number of factors that can trigger acute HF, *e.g.*, myocardial disfunction, pericardial tamponade, and acute valve insufficiency, which are among the most frequent primary cardiac causes of acute HF[1,2]. Decompensation of chronic HF can occur without known precipitant factors, but infection, uncontrolled hypertension, rhythm disturbances, exacerbation of chronic obstructive pulmonary disease, or non-adherence to medicaments can be the cause of decompensation[1,2].

Chronic HF is a complex of multiorgan dysfunction, characterized by the impaired function of the heart, kidney, and skeletal muscles, with increased stimulation of the sympathetic nervous system and numerous humoral and neuroendocrine disorders. The severity of symptoms in chronic HF is classified according to the New York Heart Association (NYHA)[10] and American College of Cardiology/American Heart Association (ACC/AHA)[11] in four stages[2] (Table 1). The NYHA functional classi-

Table 1 Comparison of American College of Cardiology/American Heart Association Stages of HF and New York Heart Association Functional Classifications (data from[2])

ACC/AHA Stages of HF		NYHA Functional Classification	Restriction of physical activity
A At high risk for HF but without structural heart disease or symptoms of HF (*e.g.*, diabetes, arterial hypertension)		/	/
B Structural heart disease but without symptoms of HF	I	Regular physical activity does not cause dyspnea and fatigue – asymptomatic	No limitation of physical activity
C Structural heart disease with prior or current symptoms of HF	I	Regular physical activity does not cause dyspnea and fatigue – asymptomatic	No limitation of physical activity
	II	Moderate physical activity results in milder dyspnea and fatigue	Slight limitation of physical activity
	III	No difficulty at rest; minimal physical activity leads to exhaustion, dyspnea, and fatigue	Marked limitation of physical activity
	IV	Symptomatic at rest	Unable to carry on any physical activity without symptoms of HF
D Refractory HF requiring specialized interventions	IV	Symptomatic at rest	Unable to carry on any physical activity without symptoms of HF

ACC/AHA: American College of Cardiology/American Heart Association; HF: Heart failure; NYHA: New York Heart Association.

fication is an independent predictor of mortality and it is widely used in clinical practice[12].

CLINICAL PRESENTATION

Clinical signs and symptoms of HF include shortness of breath, dyspnoea (initially with severe physical exertion, and in the advanced stage at rest and worsening in the supine position), orthopnoea (dyspnoea in the supine position), paroxysmal nocturnal dyspnoea (sudden onset of shortness of breath at night), poor mobility, dizziness, lack of appetite, fatigue, and muscle weakness due to early fatigability. Due to compensatory mechanisms, in the early phase of HF patients do not have to present with all the specific symptoms and physical signs, such as those related to fluid retention. In the advanced stages, physical examination and auscultation can reveal abnormal pulmonary phenomena (wheezing, crepitation), the third heart murmur (S3 gallop) that can rarely be heard, presence of an oedema (generalized or localized), and cardiac cachexia (loss of muscle mass). The signs of predominantly right-sided HF are distended jugular veins, ascites, hepatojugular reflux (pressing the hands on the abdomen leads to a more pronounced filling of the jugular veins), and oedema of the legs[1-4].

DIAGNOSIS

The cornerstone in the diagnosis of HF is primarily established by a clinician's assessment and it is based upon a careful medical history (coronary heart disease, arterial hypertension, diabetes, valve disease, cardiotoxic drugs, irradiation, *etc.*), a physical examination, an electrocardiogram (ECG), an ultrasound of the heart (echocardiography), radiological findings of the heart and lungs, laboratory tests, including a specific markers of HF - brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as other diagnostic tests, in order to elucidate possible aetiologies [*e.g.*, invasive coronary angiography, magnetic resonance (MR), or computed tomography (CT)][1,6-8].

Even though a decreased left ventricular ejection fraction identifies patients with HFrEF, the echocardiogram alone does not establish or exclude the diagnosis of HF, since approximately half of the patients with HF have a preserved left ventricular ejection fraction. The most common patients with HFpEF are elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease[13]. Echocardiography is important in revealing findings that go along with HF and in verifying possible causes of HF (*e.g.*, left

ventricular diastolic dysfunction, left ventricular systolic dysfunction, valve dysfunction, regional wall motion abnormalities, left ventricular hypertrophy, left atrial enlargement).

Two algorithms, Heavy, 2 or more Hypertensive drugs, Atrial Fibrillation, Pulmonary hypertension, Elder age > 60, elevated Filling pressures (H2FPEF)[14] and HF Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF)[15] may facilitate a HFpEF diagnosis[13]. The H2FPEF score, which relies on simple clinical characteristics and echocardiography, enables the discrimination of HFpEF from noncardiac causes of dyspnoea and assists in the determination of the need for further diagnostic testing[14]. Elevated natriuretic peptides support a diagnosis of HFpEF[16] but normal levels do not exclude it. Echocardiography has a relevant role in HFpEF and is used for the non-invasive hemodynamic assessment of high LV filling pressures (indirectly pulmonary capillary wedge pressure, PCWP). Early (E) transmitral filling velocities that are measured at the mitral leaflet tips by pulse wave Doppler, Tissue Doppler echocardiography which is performed to measure early (e') diastolic tissue velocities at the septal and lateral mitral annulus, and the mean of the septal and lateral E/e' ratio is used to estimate the PCWP[16,17]. Other important measures include the left atrial volume index, the LV mass index, the LV relative wall thickness, tricuspid regurgitation velocity, and the LV global longitudinal systolic strain[15]. According to the consensus recommendation from the HF Association (HFA) of the European Society of Cardiology (ESC) and the definition of HFA-PEFF score, the major (2 points) and minor (1 point) criteria were defined from these measures[15]. The score has functional, morphological, and biomarker domains (Figure 2). Within each domain, a major criterion scores 2 points or a minor criterion 1 point. If several major criteria within a single domain are positive, this domain still contributes 2 points. If no major but several minor criteria are positive the contribution still is 1 point. Major and minor criteria are not additive in a single domain and points are added only when they come from different domains[15].

Patients with mild or moderate HF may appear normal on physical examination, with normal vital signs. Euvolemic patients with chronic dyspnoea, symptoms of HF, and normal cardiac filling pressures at rest may have abnormal hemodynamic responses during exercise, suggesting that the chronic symptoms are related to HF[18-21]. These patients with normal cardiac output at rest have an inability to increase cardiac output during exercise without an excessive increase in filling pressures, resulting in fatigue and intolerance. Elevated resting E/e' strongly supports the presence of high PCWP and thus HFpEF, but a normal resting E/e' does not exclude HFpEF[15,18]. Exercise stress echocardiography on a bicycle or a treadmill with imaging during exercise is recommended, but there are no universally adopted protocols[15]. Exercise echocardiography should be considered abnormal if the average E/e' ratio at peak stress increases to ≥15, with or without a peak tricuspid regurgitation (TR) velocity of >3.4 m/s[15]. An increase in only TR velocity should not be used to diagnose HFpEF because it might be a result of the normal hyperdynamic response to exercise (with increased pulmonary blood flow) without the LV diastolic dysfunction. For selected patients with suspected HF with uncertain diagnosis despite the evaluation, as described above, the clinical gold standard for the diagnosis of HF is the identification of an elevated PCWP on an invasive hemodynamic test (right heart catheterization with the PCWP assessed at rest or during exercise)[15,18]. The patient must have symptoms consistent with HF and PCWP ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise for establishing a diagnosis of HF[18]. If these criteria are not fulfilled, further evaluation for other causes of dyspnoea is required. To summarize, echocardiography may help rule out HFpEF, although approaches to exclude HFpEF based solely on data at rest are of questionable accuracy, and furthermore, there is evidence that reinforces the value of exercise testing using invasive and non-invasive hemodynamic assessments to definitively confirm or rule out the diagnosis of HFpEF[18].

TREATMENT

The therapy for HFrEF aims to improve quality of life, reduce the rate of hospitalizations, as well as morbidity and mortality. Care for patients with HFrEF includes an overall approach - the treatment of possible causes and associated conditions (*e.g.*, hypertension, diabetes mellitus, and thyroid dysfunction, anemia) of HF, pharmacologic therapy, monitoring, education and cardiac rehabilitation, palliative care, device therapy and cardiac transplantation.

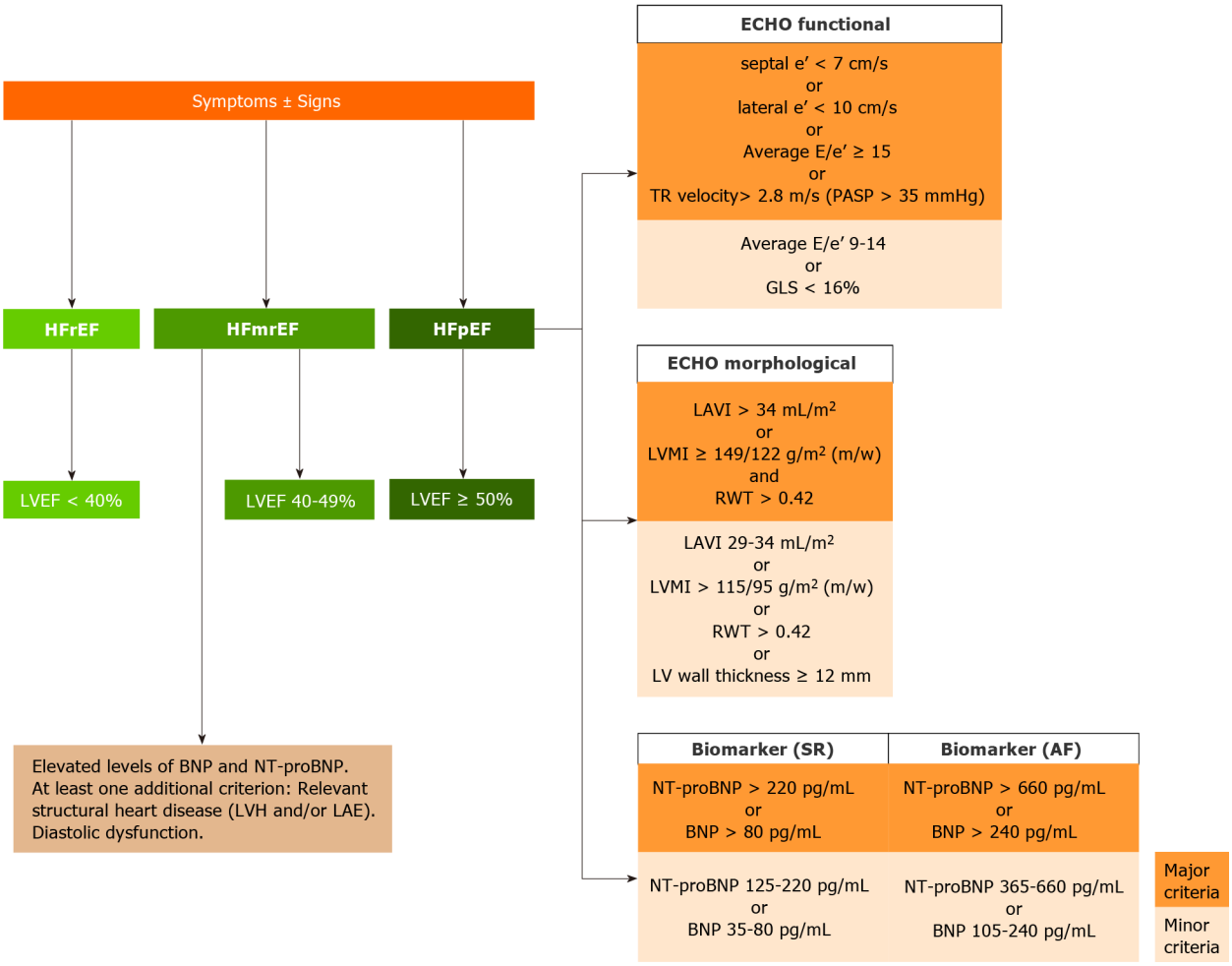


Figure 2 Heart failure – classification and criteria in diagnosis (data from[1,15]). HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy; LAE: Left atrial enlargement; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; LV: Left ventricle; TR: Tricuspid regurgitation; GLS: Global longitudinal strain; LAVI: Left atrial volume index; LVMI: Left ventricular mass index; RWT: Relative wall thickness; ECHO: Echocardiography.

Antagonism of neurohormonal activation is the foundation of the modern HF therapy. The pharmacological treatment aims to alleviate the symptoms and to improve the quality of life, prevent complications and the need for hospitalization, and thereby reduce high mortality. Diuretics are used to facilitate the symptoms of congestion. Meta-analyses show that diuretics, compared with placebo, appear to reduce the risk of death and reduce symptoms, and compared with an active control, appear to improve the functional capacity of patients with HFrEF[22,23]. The progression of the disease of the heart muscle itself can be prevented by acting on the reflex mechanisms that are activated in the body when HF occurs.

The first line of treatment is angiotensin converting enzyme inhibitors (ACEi) and beta-adrenergic receptor blockers (beta-blockers), regardless of the aetiology of HF[1,2,24]. If the patient does not tolerate ACEi or they are contraindicated, then angiotensin receptor blockers (ARBs) are used. ACEi have been shown to reduce morbidity and mortality in patients with HFrEF[25-27], and data suggests that there are no differences among the available ACEi regarding their effects on symptoms or on survival[28]. The usage of beta-blockers showed an improvement of LVEF and a reduction of mortality and the number of hospitalizations[29]. Unlike ACEi, beta-blockers have no class effect and evidence of beneficial effects in the treatment of HF has been reported for bisoprolol, prolonged-release metoprolol, carvedilol, and nebivolol[30,31]. Therapy with ACEi and beta-blockers is complementary and can be started together. Beta-blockers are recommended as a start for clinically stable patients at a low dose, followed by titration to the maximum tolerated dose[1].

Mineralocorticoid receptor/aldosteron antagonists (MRA) - spironolactone and eplerenone are recommended in all symptomatic patients (who are on ACEi and beta-blocker therapy) with LVEF ≤ 35%[1,2]. Inhibition of aldosterone action results in

decreased endothelial inflammation and decreased stimulation of the sympathetic system and RAAS systems with an antifibrotic effect. Studies show reduction of all-cause mortality (for spironolactone 30%[32]) and lower rate of hospitalization in patients treated with MRA[33-35]. Possible side effects are hyperkalemia, hyponatremia, reversible increase in blood urea and creatinine levels in patients with impaired renal function, hypotension in patients with low blood pressure (although recent study shows that MRA treatment had little effect on systolic blood pressure in patients with HFrEF and therefore low systolic blood pressure is not a reason to withhold MRA therapy in patients with HFrEF[36]). Spironolactone binds to both androgen and progesterone receptors, so men can experience breast enlargement - gynecomastia, while women can develop excessive farsightedness - hirsutism, and postmenopausal bleeding[8]. Due to its selective binding to the mineralocorticoid receptor, eplerenone has no endocrine side effects, has a lower risk of hyperkalemia, and it is a better choice in diabetics[8]. Caution should be exercised in the use of MRA in patients with impaired renal function and serum potassium level greater than 5.0 mmol/L[1].

If symptomatic HF persists (NYHA class II or III), replacement of ACEi (or ARB if used) by angiotensin receptor neprilysin inhibitor (sacubutril) - ARNI (angiotensin receptor neprilysin inhibitor) is recommended to further reduce morbidity and mortality[1,24,37]. Neprylisin inhibits natriuretic peptides (NP), bradykinin, adrenomedullin, and the β-amyloid (Aβ) peptide[37]. The combination of the renin–angiotensin system and neprilysin inhibition showed to be superior to a separate approach [38], but in clinical trials, the combination of ACEi and neprilysin was associated with serious angioedema[39,40]. Combined molecule LCZ696 consisting of sacubutril and valsartan minimizes the risk of serious angioedema, and the mechanism of action is inhibition of the neprilysin *via* the active metabolite of sacubitril and blocking of the angiotensin II receptor *via* valsartan[41,42]. There is an increase in the number of peptides that neprilysin degrades, such as A-type natriuretic peptide (ANP) and BNP, which bind to NP receptors. This results in vasodilation, the enhancement of natriuresis and diuresis, increased glomerular filtration, the inhibition of renin and aldosterone release, decreased sympathetic activity, as well as antihypertrophic and antifibrotic effects[43]. Considering described mechanism of action, BNP concentrations rise with neprilysin inhibition and the clinical validity of measuring BNP in patients treated with sacubitril/valsartan has been questioned. The use of NT-proBNP is preferred and recommended in assessing the effectiveness of therapy, although either biomarker predicts the risk of major adverse outcomes in patients treated with ARNI[44]. Monitoring of blood pressure and renal function is necessary in these patients and accordingly the dose increases to the maximum tolerated dose. The long-term use of ARNI has possible side effects such as amyloid deposition and cognitive disfunction, and these side effects may be associated with specific polymorphisms in individuals[45,46]. One small study on healthy individuals showed increase of β-amyloid protein in the soluble rather than the aggregable form, which may indicate cerebral safety[47]. Long-term safety, especially in patients at risk of Alzheimer disease, needs to be assessed[1,46].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication that are used in the treatment of type 2 diabetes. They reduce blood glucose by the inhibition of glucose reabsorption at the proximal tubule of the kidney which results in glycosuria and natriuresis[48]. Effects in lowering body weight and decreasing systolic blood pressure, as well as side effects such as genital tract infections, lower leg amputations, electrolyte disturbances, bone fractures are noted[48]. According to the latest recommendations on HF, empagliflozin should be considered in patients with type 2 diabetes mellitus (T2DM) in order to prevent or delay the onset of HF or prolong life, and canagliflozin and dapagliflozin should also be considered for patients with T2DM and either established cardiovascular (CV) disease or at high CV risk[49]. Newest studies show that SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalization in patients with HFrEF regardless of the presence or absence of diabetes[50,51]. Beneficial effects of SGLT2 inhibitors may complement and improve the effects of first line HF therapy (increase in natriuresis, decreasing LV wall stress, preload, afterload and interstitial oedema), alongside with clinically important benefit such as improving renal function in HF patients[50,51]. Therefore, compelling evidence suggest that SGLT2 inhibitors should be added to the current recommended treatments of HFrEF, even in the absence of diabetes (Figure 3).

In addition to the maximum tolerated dose of betablocker, ACEi (or ARB), and the MRA, ivabradine should also be considered in symptomatic patients with increased heart rate (more than 70 / min), in sinus rhythm and EFLV < 35%, to reduce the risk of HF hospitalization or cardiovascular death (or in patients who are unable to tolerate or have contraindications for a beta-blocker)[1,24].

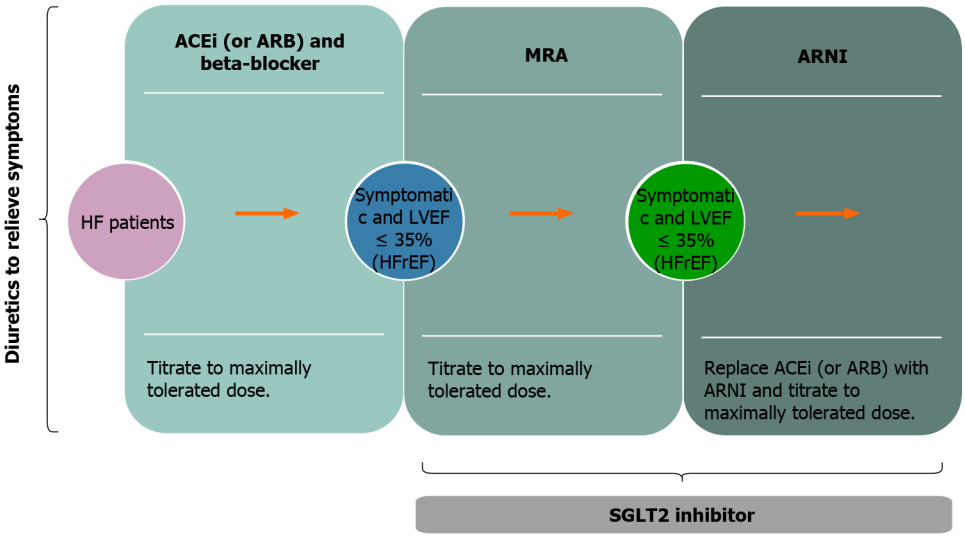


Figure 3 Heart failure medication therapy (data from[1,51]). HFrEF: Heart failure with reduced ejection fraction; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonist; ARNI: Angiotensin receptor neprilysin inhibitors; SGLT2: Sodium-glucose co-transporter-2; LVEF: Left ventricular ejection fraction.

In symptomatic patients (NYHA Class II-IV) with HFrEF who cannot tolerate ACEi nor ARB (or they are contra-indicated), hydralazine and isosorbide dinitrate may be considered to reduce the mortality[1,52]. Digoxin may be considered in symptomatic patients in sinus rhythm despite optimal medical therapy to reduce the risk of hospitalizations[1,53]. It is also used in patients with HF and atrial fibrillation (AF) to slow a rapid ventricular rate, but it is only recommended when adequate heart rate is not achieved with other therapeutic options[54,55]. Optimal ventricular rate for patients with HF and AF has not been well established but resting ventricular rate of 70-90/min is recommended based on current opinion (acceptable up to 110/min), rather than insisting on strict lower ventricular heart rate[56].

Non-dihydropyridine calcium-channel blockers (CCBs) are not recommended for the treatment of patients with HFrEF[1] (diltiazem and verapamil are considered to be unsafe in patients with HFrEF[57]). In case of compelling indications amlodipine and felodipine can be used in patients with HFrEF[1].

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce the mortality and morbidity in patients with atherosclerotic disease, but there is no evidence of benefit or improvement of the prognosis in patients with HFrEF[58]. Patients who already receive statin because of coronary artery disease or hyperlipidemia should continue to use this therapy[1]. The n-3 polyunsaturated fatty acid (PUFAs) is not a routinely used supplement in patients with HFrEF since the randomized trial demonstrated minimal to no benefit[59].

Novel therapeutic approaches

The effect of a novel oral soluble guanylate cyclase stimulator – vericiguat was tested in patients with HFrEF and the result of the new randomized trial showed that the incidence of death from cardiovascular causes or hospitalization for HF was lower among subjects who received vericiguat in comparison to those who received placebo (HF hospitalizations were significantly reduced, while cardiovascular deaths were not significantly diminished)[60].

Omecamtiv mecarbil is a cardiac-specific myosin activator that improves cardiomyocyte contraction which is being studied for a potential role in the treatment of left ventricular systolic HF[61]. The latest trial showed a significant reduction of HF event or death from cardiovascular causes in subjects who received omecamtiv mecarbil twice daily in contrast to those who received the placebo[62].

The effect of the anticoagulant therapy in HF patients in sinus rhythm is being assessed since HF is associated with activation of thrombin-related pathways, which predicts a poor prognosis. Studies with rivaroxaban (factor Xa inhibitor) hypothesized that the treatment could reduce thrombin generation and improve outcomes for patients with worsening chronic HF and underlying coronary artery disease[63,64]. Rivaroxaban did not reduce HF hospitalization but did reduce the rate of stroke[63]. Thromboembolic events occurred frequently in patients with HF, coronary artery

disease, and sinus rhythm. A post-hoc analysis revealed that rivaroxaban may reduce the risk of thromboembolic events in this population, but these events are not the major cause of morbidity and mortality in patients with recent worsening of HF where rivaroxaban had no effect[64]. Rivaroxaban at dose 2.5 mg twice daily in addition to aspirin may be considered for ambulatory patients with coronary artery disease (CAD) and chronic HF in NYHA class I/II with an LVEF > 30%, in order to reduce the risk of stroke and CV death[49,64]. For chronic HF patients in NYHA class III/IV and recent HF hospitalization, initiation of treatment with rivaroxaban is not recommended, as no benefit was shown[49].

The treatment of comorbidities that are present in chronic HF patients is an important part of holistic approach and improves outcomes of these patients. Iron deficiency is common in patients with and without anemia and has unfavorable clinical and prognostic consequences in patients with HFrEF. Important clinical trials have been conducted with ferric carboxymaltose (FCM)[65-67], and the treatment with FCM may result in the improvement of functional capacity, symptoms and quality of life (whether FCM is associated with an improved outcome in these high-risk patients needs further study). The trial including iron deficient patients hospitalized for acute HF showed that intravenous FCM compared to placebo was associated with reduction of total HF hospitalizations and CV death[68].

To conclude, there are important advances in the medicament treatment of HFrEF and therapeutic development is accelerated. These new therapeutic options improve clinical outcomes and functional status[69]. Accordingly, new working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed[69,70]. HFrecEF is a complex clinical entity and definition includes: (1) Documentation of a LVEF < 40% at baseline, combined with (2) a ≥ 10% absolute improvement in LVEF; and (3) A second measurement of LVEF > 40%[69,70]. The proportion of patients with HFrecEF varies widely (10%-40%) and should be followed every 6 mo to 1 year, with imaging obtained every 3-5 years to monitor LV function[70]. HFpEF has a significant morbidity and mortality and so far, no treatment has clearly demonstrated an improvement of outcome in HFpEF, but rather it is limited to symptom relief, which effectively improves the quality of life[13,71,72]. The emphasis is on treatment of comorbidities - hypertension, atrial fibrillation, obesity, diabetes mellitus, renal disease, obstructive lung disease, or ischemic heart disease. Regular exercise program is an important part in the treatment of these patients[13].

Device therapy

Implantable cardioverter-defibrillator (ICD) is effective in correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, however they do not reduce overall mortality and may even increase it[1]. An ICD is recommended in secondary prevention to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for more than one year with good functional status[1,73,74]. ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in selected patients at least 40 days after myocardial infarction with LVEF of 35% or less, symptomatic while receiving optimal medical therapy, and who have reasonable expectation of survival for more than one year with good functional status[1,24,75,76]. There is no benefit in patients who had an ICD implanted within 40 d after a myocardial infarction[77]. Decision about ICD implantation should be made for each patient individually, taking into consideration patient's opinion and their quality of life, the LVEF (survival benefit) and other diseases that can be cause of death within the following year[1,73,74]. ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy if they are not candidates for CRT, a ventricular assist device, or cardiac transplantation[1,78,79].

Cardiac resynchronization therapy (CRT) is recommended for symptomatic patients in sinus rhythm, with left bundle branch block (LBBB) QRS morphology, QRS ≥ 150 ms (and in patients with QRS duration of 130–149 ms) and EFLV ≤ 35% despite optimal medical therapy to improve symptoms and reduce morbidity and mortality[1,2,80-82]. For patients with ECG non-LBBB QRS morphology and QRS ≥ 150 msec CRT should be considered and CRT may be considered in patients with QRS 130–149 ms non-LBBB QRS morphology (in sinus rhythm)[1,2,80,83]. CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed (this also includes individualized decision for patients with atrial fibrillation)[84-86].

Patients with severe symptoms despite optimal medical and device therapy are potentially eligible for mechanical circulatory support - mechanical ventricular assist VAD); left - sided (LVAD) or right - sided (RVAD), biventricular (BiVAD)[1,87]. Heart transplantation is the last line of treatment for patients with the end-stage chronic HF [1,88]. These patients need to be motivated, well informed, emotionally stable, capable of complying with the intensive treatment required postoperatively and in order for transplantation to be successful and increase survival, proper selection criteria need to be applied[88].

ROLE OF CARDIAC REHABILITATION IN PATIENTS WITH CHRONIC HF

Although survival after diagnosis of HF has improved, the prognosis in such patients remains poor and quality of life severely reduced. The meta-analysis (2019), including over 1.5 million all-type HF patients, estimated the 1, 2, 5 and 10-year survival to be 87%, 73%, 57% and 35%, respectively[89]. Analysis about long-term outcomes among patients hospitalized with HF (including all three groups – HFrEF, HFmrEF, HFpEF; 2017) shown very high 5-year mortality rate of 75%, regardless of LVEF[90].

Chronic HF reduces the ability of physical activity in patients, which has detrimental effects on their daily life activities and reduces quality of life. Patients with HF have limited exercise capacity because of dyspnea and fatigue, so these symptoms make patients fearful of being active, moreover because exercise-induced dyspnea can be interpreted as worsening of their disease. In patients with stable HF, exercise training can relieve symptoms, improve the exercise capacity and quality of life, as well as reduce disability, hospitalization and mortality[91-93]. The Cochrane systematic review (2014) reported that exercise-based cardiac rehabilitation (CR) compared to no exercise control shows improvement in health-related quality of life (HRQoL) and hospital admission among people with HF, as well as possible reduction in mortality over long term[94]. A single large randomized controlled trial (RCT) with medically optimized and stable patients with systolic HF (LVEF ≤ 35%) showed a modest and non-significant reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization, but improvement in self-reported health status compared with usual care without training that persisted over time[95,96]. Recent systematic review and meta-analysis (2019)[97], a meta-analysis of randomized trials (2018)[98] and the Cochrane meta-analysis (2019)[99] that included a total of 5783 patients, predominantly HFrEF (NYHA class II and III receiving center-based exercise-based CR programs) but also patients with HFpEF, showed that exercise rehabilitation reduced hospital admissions overall, as well as for HF, and clinically important improvement in HRQoL was shown. In patients with HFpEF clinically relevant improvements in exercise capacity can be achieved, without significant changes in LV function or structure[100,101], regardless of training modality[102].

In practice, it is reasonable to advise patients to avoid stimuli that cause worsening of the disease symptoms. There are many pathophysiological mechanisms of exercise intolerance in HF: cardiac (systolic and/or diastolic dysfunction, reduced stroke volume, elevated filling pressures, secondary pulmonary hypertension and right ventricle disfunction, mitral regurgitation, reduced chronotropic reserve), ventilatory system (exaggerated minute ventilation relative to CO_2 production, ventilation/perfusion mismatch, alveolar edema), skeletal muscle (reduced muscle mass, reduced enzymes for oxidative metabolism and generation of ATP), endothelial function (reduced nitric oxide, increased reactive oxygen compounds, reduced vasodilatory response), neurohumoral system (increased sympathetic activity, low vagal activity, increased levels of pro-inflammatory cytokines)[103]. However, in chronic HF, poor exercise tolerance and quality of life can be successfully improved by dosed and tailored exercise training (ET)[96,104-107]. ET reduces sympathetic tone and increases the influence of the parasympathetic tone at rest, restores baroreflex sensitivity and decreases chemoreflex sensitivity in HF which is important in term of autonomic nervous system imbalance and chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms in HF leading to vasoconstriction, altered renal blood flow and adverse remodeling – hypertrophy and cell disfunction. ET in HF also results in reduction of reactive oxygen species and a concomitant increase in nitric oxide signaling, a reduction in Angiotensin II type 1 receptor signaling and a restoration of the imbalance of Angiotensin converting enzyme (ACE) and ACE2 expression, as well as a decrease in circulating pro-inflammatory cytokines, all of which contribute to the improvement of autonomic imbalance[103,108].

The guidelines of the European Society of Cardiology[1], American College of Cardiology/American Heart Association[2] and Canadian Cardiovascular Society[109] have included evidence-based recommendations for the use of exercise training in the management of chronic HF. Exercise training (or regular physical activity) is safe and effective in the improvement of symptoms and functional capacity (Class I, level of evidence A)[1,2,109], the reduction of the risk of hospitalization from HF (Class I, level of evidence A)[1] and in the improvement of exercise duration, HRQoL and reduction of mortality (Class IIa, level of evidence B)[2].

A consensus document of the HF Association and the European Association for Cardiovascular Prevention and Rehabilitation[110] emphasizes that cardiac rehabilitation program for patients with HF should include multiple components such as medical evaluation and baseline patient assessment, appropriate evaluation of many risk factors associated with such patients (*e.g.*, concomitant diseases -anaemia, valvular heart disease, renal function, patients age), education concerning medication adherence, psychosocial support, as well as exercise training and physical activity counseling. In addition to adopting a change in lifestyle that includes daily life activities (*e.g.*, housework, gardening, walking, recreation, proper nutrition), conducting structured physical activity and ET is important for further maintenance of stable condition of these patients. Implementation of ET requires appropriate patient selection, training protocol identification, intensity level determination, and progression monitoring. ET is recommended for stable New York Heart Association (NYHA) class I–III HF patients[110]. Early mobilization of patients after an episode of acute HF is also recommended. At this stage, gradual mobilization, respiratory exercises, and small muscle groups exercises is needed to establish clinical stability and help patients to achieve a sufficient level of functional capacity and trust prior to conducting a symptom-limited cardiopulmonary exercise test (CPET) and initiating regular ET. Exercise modalities are known to be safe for HF patient when given at the right intensity and duration. The overall concept in ET is to be done gradually and individualized. When clinical stabilization is achieved, it is necessary to assess whether there are contraindications for conducting rehabilitation (Table 2). This includes reassessment of the patient's condition and functional evaluation (history, clinical examination, electrocardiogram, ultrasound of the heart and CPET, and if the patient is unable to perform, then six-minute walking test)[110].

The choice of exercise modality should take into account patients associated diseases, work habits, preferences and abilities, limitations as well as the availability of rehabilitation itself. Determining the appropriate level of ET intensity is key in achieving the desired effects, while simultaneously having control over the potential risks associated with these patients. There is no general agreement on modalities of exercise, instead an individual approach is recommended, with careful clinical assessment, taking into consideration patient's preferences[110,111]. Exercise protocols can be different depending on the variables: intensity (aerobic and anaerobic), type (endurance, resistance, strength), method (continuous and intermittent/interval), application (systemic, regional area, respiratory muscles), control (supervised and non-supervised), setting (hospital and rehabilitation center or home-based). Three exercise modalities in different combinations have been proposed[110,111].

Aerobic/endurance training

Metabolic function can be assessed by maximum oxygen uptake which depends on the ability of the respiratory and cardiovascular systems to deliver oxygen from the atmosphere to the muscle and the ability of the working muscles to utilize oxygen. The volume of oxygen (VO2) measured in patients with chronic HF at the end of the exercise test is not the maximum VO2 value because such patients cannot reach it. Instead of the term VO2max we use the term VO2peak, by symptom-limited CPET. The CPET will give insight into the degree of cardiac impairment and will objectively measure VO2peak and help to determine training intensity and perform training adjustments[110]. The most used and evaluated exercise modality, the cornerstone of cardiac rehabilitation programs, is moderate continuous exercise (MCE)[112-114]. The intensity of training is thus usually prescribed relative to VO2peak, and the recommended intensity is 40%-50% at the beginning, with an increase during the exercise process to 70%-80% of VO2peak[110]. CPET is not always available in everyday clinical practice, so indirect methods have been proposed to assess the intensity of ET. In practice, heart rate (HR) reserve (HRR) - the difference between the basal and peak HR (the training in the range of 40%-70% HRR is recommended), and rating of perceived exertion (RPE) (training of 10/20–14/20 of the Borg RPE is recommended) are used. The intensity of physical training of 60% VO2peak corresponds to RPE from 12 to 13, and from 85% VO2peak corresponds to RPE 16[110]. High-intensity interval

Table 2 Contraindications for exercise training and screening for increased risk for exercise training (data from[110])

Contraindications to exercise training	Increased risk for exercise training
Progressive worsening of exercise tolerance or dyspnea at rest over previous 3–5 d	> 1.8 kg increase in body mass over the previous 1-3 d
Significant ischemia during low-intensity exercise (< 2 METs, < 50 W)	Concurrent, continuous, or intermittent dobutamine therapy
Uncontrolled diabetes	Decrease in systolic blood pressure with exercise
Recent embolism	NYHA functional class IV
Thrombophlebitis	Complex ventricular arrhythmia at rest or appearing with exertion
	Supine resting heart rate > 100 b.p.m.
	Pre-existing co-morbidities limiting exercise tolerance

NYHA: New York Heart Association.

training (HIIT) programs have been considered as a valuable exercise modality for low-risk HF patients[111,115]. HIIT is not superior to moderate continuous training (MCT) in changing left ventricular remodeling or aerobic capacity[115] but the recent meta-analysis showed that improves VO2peak and should be considered as a component of care of HFrEF patients[116]. Aerobic training dominates among cardiac rehabilitation programs, as in patients with chronic HF because it has the highest level of evidence, and proven beneficial effects for this type of activity[110,111].

Resistance/strength training

Muscle contraction is performed against a specific opposite force and thus generating resistance (*e.g.*, lifting weights). It gradually overloads the musculoskeletal system, strengthens and tones the muscles and it is suggested as an anabolic intervention due to the risk of muscle mass loss[110]. A meta-analysis showed that resistance exercise as a single intervention can increase muscle strength, aerobic capacity, and quality of life in HFrEF patients, and may offer an alternative approach, especially for those unable to participate in aerobic training[117]. It can be used as an adjunct to aerobic training which is the mainstay in HF patients.

As HF patients suffer from easy fatiguability, the initiation of a resistance/strength training (RST) program must be individually adjusted to the patient under medical supervision and each patient must be individually introduced into the training regimen. The amount of cardiovascular stress expected during RST depends on the magnitude of the resistance [% of one repetition maximum (% 1-RM)], the size of the working muscle mass and the relation between the duration of the muscle contraction and rest period between repetitions[110]. The minimum recommendations for implementation of an RTS in three progressive steps are: 1. "Instruction phase" – pre-training to learn and practice slow conduction, without or at very low resistance (RPE < 12, < 30% 1-RM). 2. "Resistance/endurance phase" – start of training with a high number of repetitions and a low intensity (RPE 12-13, 30%-40% 1-RM). 3. "Strength phase" – higher intensity (RPE < 15, 40%-60% 1-RM), increasing muscle mass[110]. Surveillance over each step is necessary because of the possibility of abdominal straining and consequent blood pressure elevations so prescribing the appropriate level of training according to the patient's clinical stability, motivation, and experience with RST is of great importance.

Respiratory training

The review of trials using inspiratory muscle training in patients with chronic HF suggested that such an intervention may improve the functional capacity and quality of life, especially in those with inspiratory muscle weakness[118]. Such additional exercises in combination with standard aerobic training might be useful.

There are limited data about ET for a special group of patients with chronic HF and implanted ICD or CRT. Evidence show that physical activity and exercise can be safely applied with adequate supervision[119,120] and it was confirmed in the larger RCT analysis of patients with ICD and HF[121]. It has been shown that physical activity can almost double the improvement in functional capacity and quality of life in CRT patients[122,123] and ET resulted in reduction of a number of ICD activations in the exercise group[120,121]. Moreover, non-sustained ventricular tachycardia in the presence of an ICD is not a contraindication for aerobic training[121]. Patients with an

ICD should begin training under medical supervision, and the HR must be monitored if it is possible to reach a HR close to the programmed intervention zone of the device. Patients who have symptomatic arrhythmias or ICD discharge should be directed to exercise modalities in which brief loss of consciousness due to ICD discharge may be less harmful (*e.g.*, avoiding swimming or climbing)[110]. Medical staff caring for such patients should be specially educated in understanding the possible challenges and problems associated with such patients.

Although progress has been made in rehabilitating patients with chronic HF, further RCT with large number of patients are needed to assess the effect and benefit from each training modality. Education of medical staff on the beneficial effects of physical exercise in patients with chronic HF and involvement of more patients in cardiac medical rehabilitation programs are crucial in order to provide complete care to chronic HF patients. A small part of patients with chronic HF participates in cardiac rehabilitation programs (the data vary, only 2.6% retrospectively[124], and in one observational study only 10% of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF[125]), and this is partly due to the fact that chronic HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis. Developing adequate and effective training methods and highlighting the beneficial effects of such an approach will result in improving the quality of life and providing better medical care to patients with chronic HF.

CONCLUSION

New diagnostic methods and treatment options of HF are evolving rapidly. Accordingly, the number of patients with recovered LVEF (HFrecEF) and improved functional status is increasing. Beside medicament options to maintain future stable state of the patients with HF, cardiac rehabilitation is an important part of care, ET is proved to be safe in HF patients and should be implemented as a part of overall approach. Nowadays it is important to emphasize the role of cardiac rehabilitation in patients with chronic HF, raise consciousness that HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis, and nurture a holistic approach to patients with HF.

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MINIREVIEWS

Large eustachian valve fostering paradoxical thromboembolism: passive bystander or serial partner in crime?

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Abstract

Catheter-based closure of patent foramen ovale (PFO) is more effective than medical therapy in the prevention of recurrent stroke[1]. It is likely that a proportion of patients evaluated for potential transcatheter PFO closure has actually different anatomical variants particularly common in the right atrium such as eustachian valve, Chiari network, Thebesian valve and Crista Terminalis. Notably, the eustachian valve may represent an increased risk factor for left circulation thromboembolism beyond that associated with PFO size and shunting. Such patients may benefit the most from percutaneous closure procedure.

Key Words: Eustachian valve; Chiari's network; Patent foramen ovale; Right-to-left shunt; Paradoxical embolism; Echocardiography

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Core Tip: Eustachian valve is usually considered to be a benign finding in the absence of associated cardiac anomalies. Moreover, eustachian valve is frequently found in adult patients with septal abnormalities mainly patent foramen ovale. It may actively facilitate the mechanism of paradoxical embolism by directing the blood from the inferior vena cava towards the interatrial septum *via* patent foramen ovale into the left atrium. Therefore, the presence of such anatomic variant may represent per se an increased risk factor for left circulation thromboembolism.

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INTRODUCTION

Bartolomeo Eustachio (San Severino Marche, Macerata 1507 (?)–Fossato di Vico, Perugia, Italy, 1574), also known by his latin name of Eustachius, was an Italian anatomist and one of the founders of human and comparative anatomy. He had a comprehensive humanistic education, in the course of which he acquired an excellent knowledge of Greek, Hebrew and Arabic. Eustachio's greatest contributions to anatomical science passed through many vicissitudes which kept his real merit from being recognized until long after his death. His greatest work, which he was unable to publish, is the "De dissensionibus et controversiis anatomicis" illustrated in the Anatomical Engravings (Tabulae). Engraved on copper plates, these tables illustrated the results of the dissections of Eustachio and were completed in 1552 but discovered only in the early eighteenth century-after 162 years-in the possession of a descendant of Pier Matteo Pini to whom Eustachio had bequeathed them. They were later purchased by Pope Clement XI for 600 scudi and presented to Giovanni Maria Lancisi, his physician and the successor to Eustachio in the chair of anatomy at the Sapienza in Rome. Lancisi published the plates in 1714, together with the eight smaller ones that had already appeared in 1564[2,3] (Figure 1). Although devoid of Eustachio's planned text, the plates alone assured him a distinguished position in the history of anatomy. The fact that his book became a bestseller more than a century after his death shows the extent of the religious restrictions on anatomists all through the Renaissance. In his work on the azygos vein and its ramifications (Opuscula Anatomica, 1564), Eustachio described the thoracic duct and particularly the "valvula venae cavae inferioris" (known as Eustachian Valve) that lies at the junction of the inferior vena cava and right atrium which serves to direct the blood through the foramen ovale into the left atrium, indicating a careful and relatively advanced knowledge of heart's structure. His description of the fetal circulation was the most complete up to his time. This constitutes the most important distinctive structural difference between the circulatory apparatus of the adult and the child.

Incomplete regression of the right sinus valve of sinus venosus results in a spectrum of vestiges such as Chiari network, eustachian valve (EV), Thebesian valve of the coronary sinus and crista terminalis.

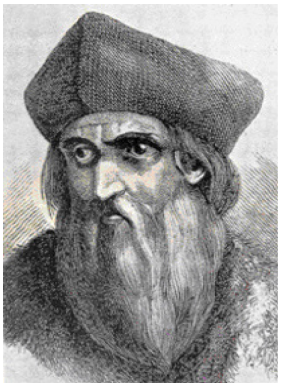
In particular, EV is a remnant of the embryonic valve of inferior vena cava (IVC), which in fetal heart directs oxygenated blood (by the placenta) towards the foramen ovale into the systemic circulation. It appears as a crescent-like membrane which extends from the IVC to the lower part of the fossa ovalis. There is a large variability in size, shape, thickness, texture and in the extent to which EV encroaches on neighboring structures such as the atrial septum. Its average length is 3.6 mm ranging from 1.5 to 23 mm[4]. Over time, EV disappears completely represented only by a thin ridge or, most commonly, it appears as a crescentic fold of endocardium arising from the anterior rim of the IVC orifice. The lateral horn of the crescent tends to meet the lower end of the crista terminalis, while the medial horn joins the thebesian valve, a semicircular valvular fold at the orifice of the coronary sinus (Figure 2). Sometimes, EV may persist as a mobile, elongated structure projecting deeply into the right atrial cavity, showing an undulating motion in real time echocardiography and, when it is quite large, it may be confused with right atrial tumors, thrombi, or vegetations.

The superior vena cava, on the contrary, does not have any homologous valve.

WHAT IS THE EUSTACHIAN VALVE PREVALENCE AND THE ANATOMICAL PATTERNS?

The prevalence of EV in the general population is not known, as the diagnostic criteria vary in different studies. Yater[5] reported a rate of approximately 60% of persisting EV in adults in a group of 120 consecutive necropsies. Limacher *et al*[4] found an incidence of approximately 70% in children of various ages. On transoesophageal echocardiography (TEE) a persisting EV was found in 4.2% of the patients and its prevalence was similar in men and in women[6]. The features and the physiology of the EV have been well described by 2D/3D echocardiography[7,8].

Three different anatomical patterns have been described: (1) Chiari network, found in 2%-3% of normal hearts at autopsy[9], is a reticolous and filamentous membrane with attachment to the upper wall of the right atrium along the ridge connecting the vena cava and atrial septum; it often appears as a web-like structure with a variable number of thread-like components[10]; (2) Eustachian ridge (ER), also known as ''sinus septum'' is prominently located between the fossa ovalis and the coronary



Bartolomeo Eustachio

San Severino Marche (Macerata), 1507? –
Fossato di Vico (Perugia), August 27 1574

Figure 1 Bartolomeo Eustachio, also known by his latin name of Eustachius, was a distinguished physician of the Renaissance period, professor of anatomy at the medical faculty of Collegio della Sapienza in Rome and one of the founders of the science of modern human anatomy.

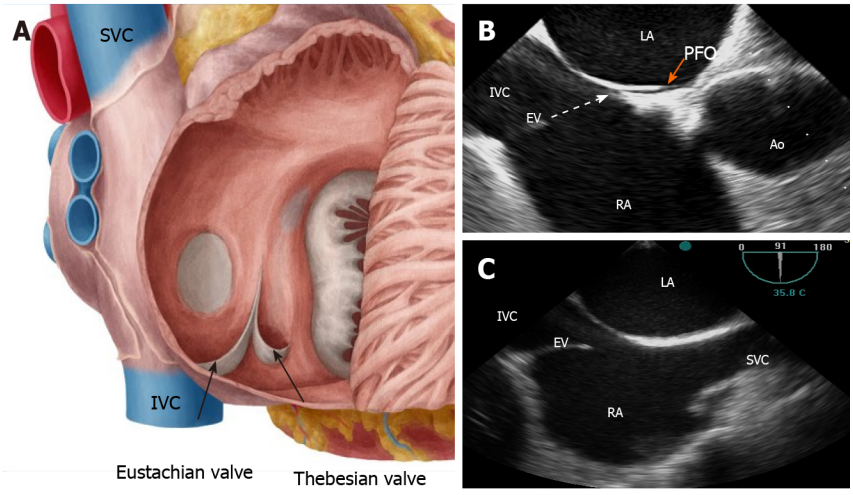


Figure 2 Anatomical illustration (A) and two-dimensional transesophageal echocardiogram in sagittal (B) and in bicaval (C) views showing the specific orientation of the eustachian valve directing the blood (white dotted arrow) toward the interatrial septum and patent foramen ovale (orange arrow). SVC: Superior vena cava; IVC: Inferior vena cava; RA: Right atrium; LA: Left atrium; EV: Eustachian valve; Ao: Aorta; PFO: Patent foramen ovale.

sinus ostium; the medial portion of the EV takes insertion on this structure and continues in the tendon of Todaro, which runs on the ER towards the central fibrous body[11]; and (3) EV, so called "valvula venae cavae inferioris", which is characterized by a mobile and fenestrated membrane without any anatomic connection[12] (Figures 3, 4 and Supplementary Videos 1, 2), often misdiagnosed as an intra-atrial thrombus.

CLUES FROM CLINICAL FEATURES ASSOCIATED WITH INCREASED RISK OF PARADOXICAL EMBOLISM

A persisting EV in the absence of other structural heart diseases is believed to have no pathological importance.

Nevertheless, EV is frequently found in adult patients with septal abnormalities, mainly patent foramen ovale (PFO) but also atrial septal defect (ASD) and it may participate in the mechanism of paradoxical embolism, by maintaining an embryonic right atrial flow pattern into adult life and directing the blood from the IVC *via* PFO into the left atrium (LA). Therefore, the presence of a prominent and large EV may increase the chance of paradoxical embolization beyond that associated with PFO size and the amount of shunting.

There are several reports documenting cyanosis in patients with ASD without an increase in right heart pressures but in whom the congenital defect was associated

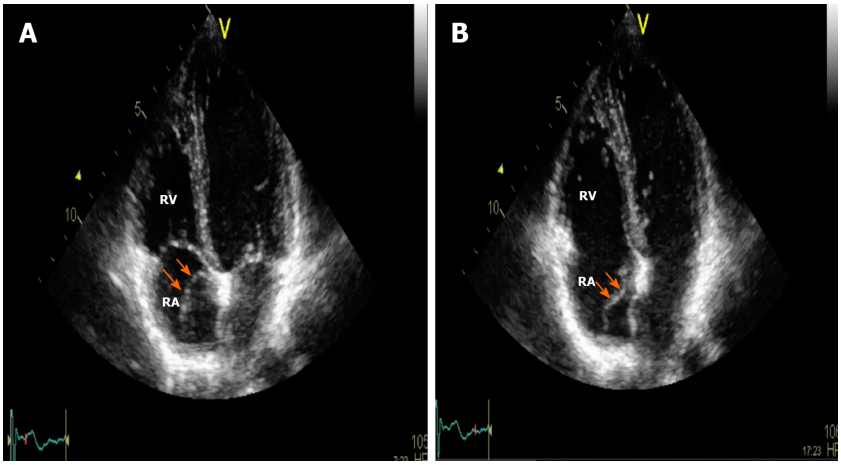


Figure 3 Two-dimensional transthoracic echocardiogram in apical four-chamber views showing the eustachian valve as a mobile, elongated structure (orange arrows) projecting into the right atrial cavity, showing an undulating motion during cardiac cycles. A: Systole; B: Diastole. RA: Right atrium; RV, right ventricle.

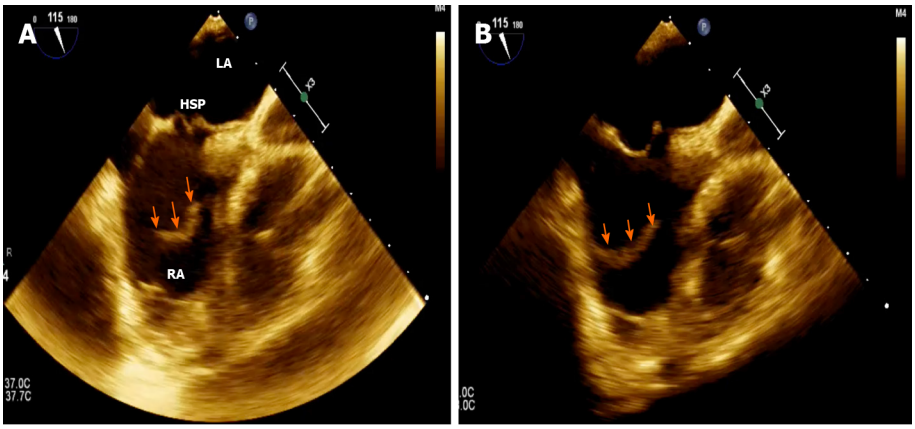


Figure 4 Two-dimensional transesophageal echocardiogram bicaval views. A: systolic frame; B: diastolic frame showing a prominent elongated eustachian valve (orange arrows) without any anatomic connection pointing towards the hypermobile septum primum. RA: Right atrium; LA: Left atrium; HSP: hypermobile septum primum.

with a prominent EV, the valve thus being implicated as the possible source of the right to left shunt[13]. The findings support the hypothesis that patients with a cryptogenic stroke (CS) and ASD or PFO combined with a prominent EV may benefit from interventional closure of the interatrial communication.

A persistent EV, particularly a prominent one, has been frequently observed in cases of platypnea-orthodeoxia syndrome[14,15].

Furthermore, a large ER or a prominent EV may pose issues with device placement because those right atrial structures limit the space available over the fossa ovalis on the right atrial side and may cause a PFO device to sit away from the fossa ovalis. The disc may rest on the ER or EV and result in the PFO tunnel being held open with a persistent residual shunt. Comprehensive assessment on 2D/3D TEE imaging is needed to accurately assess how such structures will impact on device choice and size.

In addition, EV has the potential to interfere with manipulation of the guidewire and it can be caught in the device during deployment, interfering with the occluder position or enhancing an embolic risk if drawn across the septum into the LA. A report of a case series showed the practicability of using a steerable ablation catheter to deflect the EV away from the interatrial septum during the procedure[16].

Complications related to the presence of EV may occur such as obstruction of the inferior vena cava, thrombosis and possibly subsequent pulmonary embolism.

Occasionally, the EV crosses the floor of the right atrium from the orifice of the IVC and inserts into the lower portion of the interatrial septum adjacent to the atrioventricular valves. Higher insertion of a very prominent EV mimicking the echocardiographic appearance of divided right atrium is very rare[17]. Such a config-

uration of a large EV may also mimic a right atrial cystic tumor[18].

A SUMMARY OF ARGUMENTS SUPPORTING THE GUILTINESS OF EUSTACHIAN VALVE AS A SERIAL PARTNER IN CRIME

EV redirects flow from the IVC to the interatrial septum through a right-to-left shunt into the LA thus explaining the left circulation paradoxical thromboembolism event

Indeed, a multivariate analysis showed that the presence of prominent EV or Chiari's network was independently related to CS and have been included in risk prediction models to identify patients at the highest risk of paradoxical embolism[19]. In particular, the OR for EV or Chiari's network as factors related to CS was 4.47 in univariate analysis (P = 0.002) and 4.71 in multivariate analysis (P = 0.009).

EV predicts the prognosis and outcomes following percutaneous PFO closure

Large EV can predict the occurrence of residual shunt in patients who underwent PFO closure for cryptogenic cerebral ischemia[20]. Inglessis *et al*[21] found that the detection of EV on transthoracic echocardiography (hazard ratio: 9.04; 95% confidence interval: 2.07 to 39.44; P < 0.0034) was significantly associated with the occurrence of cerebrovascular events after PFO closure. Interestingly, the 3 patients with a prominent EV who suffered a recurrent event had persistent residual shunt after PFO closure.

EV may be nidus for thrombus formation

In situ or from adhesion of embolic material from another distant source (lower extremity deep vein thrombosis). In this setting, PFO patients with hypercoagulable states are at very high risk.

EV may be nidus for tumors

Rare (myxomas, cystic tumors, fibroelastic papillomas).

EV may interfere with the device placement

Presence of either EV or Chiari's network may hinder the passage of wires, reduce the available space in the right atrium or even interfere with device placement[22].

EV may interfere to IVC cannulation

A detailed echocardiographic right atrial anatomy inspection can help suggesting an alternative plan and prevent complications during surgery[23].

EV may mimic ASD rim

EV may potentially complicate a simple percutaneous ASD device closure: the free end can be confused in fact with superior rim on TEE bicaval view[24,25]. During surgery, EV could be mistaken for the true septum and inadvertently incorporated into the patch. This causes iatrogenic right to left shunt due to diversion of the IVC blood flow into the LA[26].

CONCLUSION

Echocardiography plays a key role in the identification and understanding of the eustachian valve and the other right atrial structural abnormalities, in order to avoid misdiagnosis and to prevent complications during interventional patent foramen ovale and before atrial septal defect closure procedures.

Large prominent eustachian valve has been found guilty at all the degrees of judgment and represents an important risk factor fostering paradoxical thromboembolism in patients with right-to-left shunting *via* patent foramen ovale. Bartolomeo Eustachio, the papal anatomist, would never have thought that his valve could have been identified as a serial partner in crime.

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ORIGINAL ARTICLE

Retrospective Study

Effect of trabeculated myocardial mass on left ventricle global and regional functions in noncompaction cardiomyopathy

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Abstract

BACKGROUND

Left ventricular (LV) noncompaction cardiomyopathy is a rare cardiomyopathic subtype that has been recognized in recent years and is being diagnosed at an increased rate. There is no consensus regarding the diagnosis of the disease, and increased trabeculation rates that meet the existing diagnostic criteria may even be present in healthy asymptomatic people. This indicates that differentiating criteria for diagnosis are needed.

AIM

To examine the increase in myocardial trabeculation and the change in left ventricular global and regional functions.

METHODS

This retrospective study included 65 patients (28 females, 37 males) diagnosed with LV noncompaction cardiomyopathy who underwent cardiac magnetic resonance imaging between January 2011 and August 2016 and had a noncompacted/compacted myocardial thickness ratio of over 2.3 in more than one segment in the left ventricle. The distribution and ratios of trabeculations in apical, midventricular, and basal regions were examined in short-axis images obtained from cardiac magnetic resonance. In addition, by using short-axis cine images, regional ejection fraction (EF) and global EF were calculated using the Simpson method in the left ventricle at apical, basal, and midventricular levels.

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RESULTS
While the number of trabeculated segments were similar at the apical (3.2 ± 1.0) and midventricular levels, a statistically significant level of involvement was not observed at the basal level (0.4 ± 0.9) ($P > 0.05$). The highest noncompacted/compacted (trabeculation) ratio was observed at the apical level (3.9 ± 1.4), while this ratio was higher at the anterior (59%-89.4%) and lateral (62%-84.8%) segments ($P > 0.05$). Global EF was positively correlated with apical, midventricular, and basal regional EF ($P < 0.05$). However, there was no significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in all three regions; nor was there a significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in the entire LV ($P > 0.05$).

CONCLUSION
No global or regional relationship was observed between LV dysfunction and trabeculation rate or the number of trabeculated segments. This limits the usefulness of change in LV functions in the differentiation between normal and pathological trabeculation.

Key Words: Isolated noncompaction of the ventricular myocardium; Cardiomyopathies; Magnetic resonance imaging; Stroke volume; Magnetic resonance imaging; Ventricular function

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Core Tip: With the advancements in cardiac magnetic resonance, there is increased frequency of left ventricular noncompaction cardiomyopathy diagnosis; meanwhile, increased trabeculation that meet diagnostic criteria may also be observed in healthy asymptomatic individuals. This suggests the need for new diagnostic criteria of the disease. In this regard, our retrospective study investigates the impact of the number of trabeculated segments and the trabeculation ratio on regional and global left ventricular functions.

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INTRODUCTION

Left ventricular noncompaction cardiomyopathy (LVNC) is a form of cardiomyopathy that has been classified as primary genetic cardiomyopathy by the World Health Organization since 2006[1,2]. It is characterized by phenotypically prominent trabeculations, deep intertrabecular recesses, and thick noncompacted endocardium *vs* thin compacted epicardium. Etiologic factors of the disease are not fully clear. Genetic transmission may occur in sporadic or familial forms[3,4]. Several hypotheses have been prepared to explain the development mechanism of LVNC. However, there is a consensus of ideas that the left ventricle is the result of abnormal morphogenesis. In the 8th wk of gestation, myocardial trabeculations begin to be compacted starting from the basal region of the heart (compaction: Compacting of the trabeculations)[5]. Ventricular compaction advances from the epicardium towards the endocardium, from the base of the heart towards the apex and from the septum towards the free wall [6]. In the fetal heart, ventricular myocardial compaction is completed in the 4th mo. If the compaction process is interrupted, non-compaction cardiomyopathy occurs and the clinical manifestation varies depending on the stage of interruption. In addition, autopsy studies have shown that prominent trabeculations arising from the embryonal development process can also be found in high rates in the hearts of normal people and can be observed in the apex[7-9].

The actual prevalence of non-compaction cardiomyopathy is not fully known; however, one single-study in the literature reported that it varies between 0.014%-1.3% [10]. The most important diagnostic parameter is the ratio of non-compacted layer in relation to compacted layers of myocardium; this ratio should be over 2 in echocardiography and over 2.3 in cardiac magnetic resonance (CMR) imaging[11,12]. Different criteria have been proposed for diagnosis, the most important of which is to decide whether the trabeculations observed in imaging are normal, a normal variant, or pathological. The existing diagnostic criteria based on echocardiographic and CMR findings have certain limitations[13]. Recent studies have shown that increased trabeculation ratios may also be present in healthy asymptomatic individuals, leading to increased rates of LVNC diagnosis and indicating that new diagnostic criteria are needed. In addition, LVNC may be complicated by heart failure and result in cardiac transplantation, while the existing diagnostic criteria cannot determine or predict this process[6,14].

In this retrospective study, we aimed to investigate the effect of increased myocardial trabeculation on left ventricular global and ejection fraction (EF). In this regard, changes in EF can be included among the diagnostic criteria of the disease, preventing misdiagnosis, and can be used in the follow-up of the disease.

MATERIALS AND METHODS

Patient population

A total of 65 patients between ages 18-65 who were diagnosed with LVNC and referred to our department between January 2011 and August 2016 were included in our study. Patients were diagnosed by experienced cardiologists according to Jenni echocardiographic criteria. In the retrospective evaluations, the most important inclusion criteria independent from age and gender was CMR noncompacted/compacted myocardium ratio (NC/C) of 2.3 or higher. Exclusion criteria were as follows: Presence of contraindications for CMR, presence of other cardiomyopathies and congenital or non-congenital heart disease, and history of neuromuscular disease.

CMR protocol

The cardiac magnetic resonance imaging (MRI) protocol for LVNC in our clinic was applied to the patient group. Imaging was conducted in supine position with a 1.5 Tesla (Philips Achieva; Philips Medical Systems, Amsterdam, Netherlands) MRI device. The SENSE-XL-Torso cardiac coil was placed on the anterior chest wall, and a signal acquisition system using electrocardiogram and respiratory trigger was applied. Initially, cardiac survey imaging was performed for the coronal, axial, and sagittal planes with Single Shot Balanced transcription factor E sequence. From the survey images, the plane formed between the mitral valve and apex in the axial plane and long axis two-chamber cine images from the Balanced transcription factor E sequence were obtained. Long axis four-chamber cine and short-axis (SA) cine images were obtained from these images. Since equal breath-hold is important for image quality, patients were asked to hold their breath at the end of expiration.

Imaging analysis

Cardiac MRI images were retrospectively evaluated by two radiologist who were experienced with cardiac images together using the standard approach on a Philips workstation. In the analyses, first the segment's non-trabeculated segment ratio was measured according to the American Heart Association's 16-segment model based on the ratio of trabeculated segment to non-trabeculated segment in the left ventricle (LV) at end-diastole[15]. Segments above the 2.3 cutoff value in all three SA planes (apical, mid, and basal), and the segment with the highest ratio in each axis was determined when making measurements. When distinguishing segmentation, the papillary muscle level was specified for the midventricular segment, the superior of the papillary muscles for the basal segment, and inferior of the papillary muscles as the apical segment. When determining the basal regions, the short axis section where more than half of the lumen was surrounded by myocardium was chosen. According to the current protocol, trabeculations were determined as regions with muscular structure moving together with the inner myocardium border, extending towards the cardiac region, and not accompanying the papillary muscles at the end of systole. The border between compacted and trabeculated myocardium in each segment was chosen outside of the line where trabeculation was not prominent (Figure 1). In the second step, systolic function analysis was performed separately for all three axes and

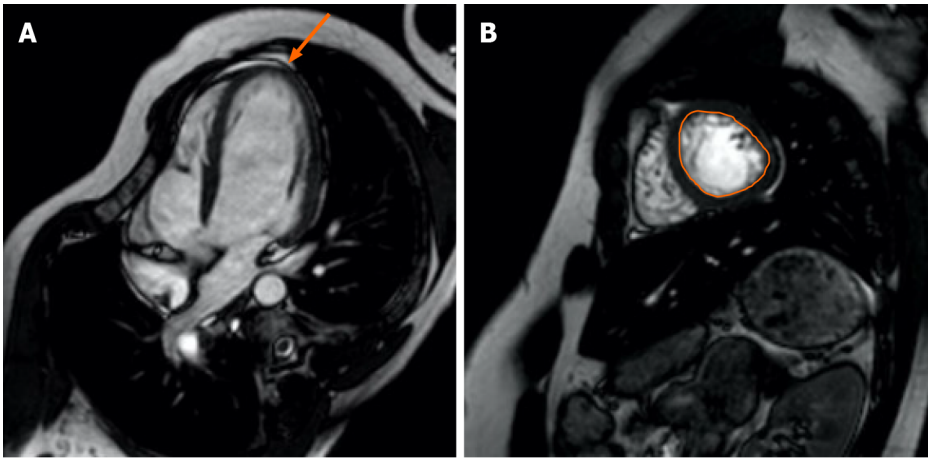


Figure 1 Cardiac magnetic resonance imaging appearance of left ventricular non-compaction. Cardiac magnetic resonance of a 21-year-old male patient with left ventricular noncompaction cardiomyopathy. The end-diastolic appearance of compacted and noncompacted myocardium in the left ventricle of a patient with left ventricular noncompaction cardiomyopathy. A: In four-chamber cine images, trabeculated myocardium and deep intertrabecular recesses are more prominent in the apical and mid-ventricular regions (arrow); B: In short-axis cine, the boundaries between the trabeculated myocardial mass and the non-trabeculated myocardial mass are seen at the midventricular region.

globally for the entire LV. Simpson method was used for analysis. In the calculation of EF values, diastole and end-systolic endocardial boundaries were drawn manually for all three axes in short axis images, and finally, global EF values were calculated by drawing systole and end-diastolic endocardial boundaries in all sections from the apex to the base. The narrowest and widest ventricular cavity size was used at the mid-ventricular region to determine the systole and end-diastolic phases, respectively. Endocardial boundaries were drawn using the difference between the hyperintensity of the blood-filled cavity and the moderate intensity of the myocardium[16]. Papillary muscles were included in the ventricular cavity since they did not affect mass and cavity volume change in EF measurements.

Statistical analysis

Statistical analyses were performed using the SPSS 22.0 package program (Armonk, NY, United States). Mean, standard deviation, median, lowest-highest frequency, and percentage values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Mann-Whitney *U* test was used in the analysis of quantitative independent data. Chi-square test was used to analyze qualitative independent data, and Fischer's exact test was used when Chi-square test conditions were not met. Spearman's rank correlation coefficient was used for correlation analysis.

RESULTS

We reviewed the electronic medical records and the baseline clinical characteristics, and cardiovascular compliments (congestive heart failure, syncope, embolic events, and any arrhythmias) of the patient population are summarized in Table 1. Also, in the study group none of the patients had diabetes mellitus and dyslipidemia. However, 5 patients had hypertension.

All patients who were included in the study met echocardiographic and CMR diagnostic criteria. All 65 patients had trabeculation ratio over 2.3 in at least three segments and at least two regions (apical, midventricular, basal). The number of trabeculated segments were high and similar at apical (3 ± 1) and midventricular (3 ± 1.4) regions, while there was no statistically significant involvement in basal regions. According to segmental distribution, trabeculation was most frequently observed in the apical-lateral (93.9%) and apical-anterior (89.4%) segments ($P < 0.001$). The highest trabeculation ratio was seen in the apical region (3.6 ± 1.4) (Tables 2 and 3).

There was a positive correlation between global EF and apical, midventricular, and basal EFs ($P < 0.05$). In addition, there was a positive correlation between the EFs of all three regions ($P < 0.05$) (Figure 2).

Table 1 Clinical characteristics of the study population

Clinical characteristics	mean ± SD, *n* (%)
Age in yr	31.09 ± 10.22
Male gender, *n* (%)	37 (56.9)
Syncope	5 (7.7)
Arrhytmia	2 (3.1)
Embolic events	1 (1.5)
CHF	0
Asymptomatic	57 (87.7)

CHF: Chronic heart failure; SD: Standard deviation.

Table 2 The highest values of the trabeculation ratio for apical, midventricular, basal regions, and global left ventricle and the distribution of the total number of trabeculated segments

	Min-Max	Media	mean ± SD
Highest ratio			
Apical, global	0.4-9.0	3.6	3.9 ± 1.4
Midventricular	1.7-6.5	3.2	3.3 ± 0.9
Basal	2.0-4.0	2.6	2.7 ± 0.6
Number of segments			
Total	0.0-11.0	7.0	6.3 ± 2.2
Apical total	0.0-4.0	3.0	3.2 ± 1.0
Mid total	0.0-5.0	3.0	2.8 ± 1.4
Basal total	0.0-3.0	0.0	0.4 ± 0.9

In cardiac magnetic resonance short axis images, the highest trabeculation ratio was observed in the apical region in the measurements made according to Simpson method. Similarly, the number of trabeculated segments s observed more prominently in the apical and midventricular regions. SD: Standard deviation.

There was no correlation between global EF and total number of segments involved and highest trabeculation rates for all three apical, midventricular, and basal regions ($P > 0.05$). No correlation was found between the regional EF values of the apical, midventricular, and basal regions and the number of trabeculated segments and the highest trabeculation ratio in these regions ($P > 0.05$) (Tables 4 and 5).

DISCUSSION

Noncompaction cardiomyopathy is a form of cardiomyopathy characterized by a bilayered compacted and noncompacted myocardium model with prominent myocardial trabeculations and intertrabecular recesses[17]. While it may be isolated, it may also be accompanied by multiple cardiac malformations[18]. Although there is no consensus regarding the etiopathogenesis of the disease, genetic studies have identified certain sarcomeric and non-sarcomeric cardiomyopathy genes[19,20]. Usually, the LV is affected alone[21]. While clinical presentation may occur at all ages, it usually manifests in childhood[19]. The disease may be asymptomatic, or symptoms may vary depending on the severity of involvement, symptoms of the accompanying syndrome, and congenital heart diseases[18]. In the literature, the most common clinical findings related to LVNC include heart failure, arrhythmias, and systemic embolic events[18]. The compaction process in the fetal heart occurs from the epicardium towards the endocardium, from the base of the heart towards the apex, and from the septum towards the lateral, and severity of the phenotype varies

Table 3 Segmental distribution of trabeculations in the apical, midventricular, and basal regions of the left ventricle

	n	%
Apical		
Septal	31	47.0
Anterior	56	84.8
Lateral	62	93.9
Inferior	59	89.4
Midventricular		
Anterior	42	63.6
Anterolateral	52	78.8
Inferolateral	49	74.2
Inferior	30	45.5
Inferoseptal	7	10.6
Anteroseptal	3	4.5
Basal		
Anterior	7	10.6
Anterolateral	10	15.2
Inferolateral	7	10.6
Inferior	2	3.0
Inferoseptal	0	0.0
Anteroseptal	1	1.5

$P < 0.01$ Mc Nemar test. Trabeculations were commonly observed in the apical-lateral segment, and there were no patients with a noncompacted/compacted myocardial ratio above 2.3 in the basal-inferoseptal segment.

Table 4 Comparison of highest trabeculation ratio and ejection fraction in global and regional left ventricular function

		Highest trabeculation ratio		
		Apical	**Midventricular**	**Basal**
Global EF	r	0.072	-0.054	-0.128
	P value	0.573	0.687	0.707
Apical EF	r	0.028		
	P value	0.825		
Midventricular EF	r		-0.022	
	P value		0.873	
Basal EF	r			-0.91
	P value			0.789

There was no correlation between global ejection fraction (EF) and highest trabeculation ratios of apical, midventricular, and basal regions ($P > 0.05$). There was no correlation between apical EF and apical highest ratio, between midventricular EF and midventricular highest ratio, or between basal EF and basal highest ratio ($P > 0.05$).

depending on the time of interruption[21]. In our study, trabeculations were observed more commonly in the apical and midventricular regions, consistent with the fetal compaction process.

In order to diagnose LVNC, the main defined structural features must be revealed with imaging. The most important parameter in diagnosis is the ratio of the noncompacted layer to the compacted layers. This ratio must be more than 2 in echocardi-

Table 5 Comparison of global and regional (apical, midventricular, and basal) number of trabeculated segments and ejection fraction in left ventricular function

		Number of segments			
		Total	Apical	Midventricular	Basal
Global EF	r	0.075	-0.034	0.146	-0.169
	P value	0.555		0.246	0.179
Apical EF	r	0.120	0.048		
	P value	0.340	0.704		
Midventricular EF	r	0.173		0.225	
	P value	0.168		0.072	
Basal EF	r	0.083			-0.229
	P value	0.510			0.066

It was observed that the number of trabeculated segments had no significant effect on regional and global left ventricular functions. There was no correlation between global ejection fraction (EF) and total number of trabeculated segments at apical, midventricular, and basal regions ($P > 0.05$). There was no correlation between apical EF and apical segment number, midventricular EF and midventricular segment number, or basal EF and basal segment number ($P > 0.05$).

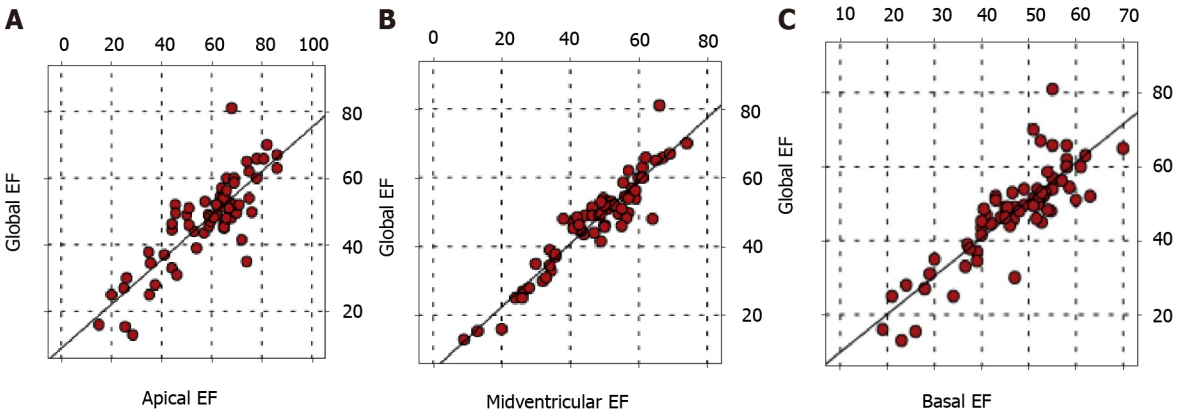


Figure 2 Comparison of left ventricular global function and regional (apical, midventricular, basal) functions. (Spearman correlation) A positive correlation was found between left ventricular global ejection fraction (EF) and EF at apical, midventricular, and basal regions ($P < 0.05$). A: Apical EF; B: Midventricular EF; C: Basal EF.

ography, and more than 2.3 in CMR. Echocardiography and CMR are the main imaging modalities used to diagnose the disease. Echocardiography is widely used due to its availability, common use, low cost, and absence of radiation exposure[22]. Chin *et al*[11] initially proposed evaluating the ratio of X to Y for echocardiographic diagnosis, in which X refers to the distance from the epicardial surface to the deepest part of the trabecular recess, and Y is the distance from the epicardial surface to the peak of the trabeculation. An X/Y ratio up to 0.5 at end-diastole is enough for diagnosis. Chin *et al*[11] also acknowledged the relationship between the clinical presentation of the disease and genetically transmitted cardiac diseases[11].

Jenni *et al*[23] specified diagnostic criteria as NC/C > 2 measured at end-systole and recommended additional morphological criteria including visualization of deep perfused intertrabecular recesses on color flow Doppler, involvement predominately in the lateral, apical, or inferior walls of the LV, and absence of additional cardiac anomaly[23]. The contribution of Stöllberger *et al*[12] to echocardiographic diagnostic criteria was > 3 trabeculations apically to the LV papillary muscles, apart from aberrant bands and false tendons[12]. However, there are many studies on the pitfalls of echocardiographic diagnostic criteria. One such was a study by Ottaviani *et al*[24], who measured trabeculations in the explanted hearts of 105 patients diagnosed as LVNC by echocardiography and who underwent orthotopic heart transplant. NC/C ratio was found as 1.7/1 ± 0.2, demonstrating the discordance between echocardiography and pathology[24]. Echocardiography has several limitations, such as such as

being operator dependent, inadequate apex evaluation, difficulty in distinguishing the bilayer appearance, and inadequate short axis imaging. Therefore, the weak correlation between the existing echocardiographic diagnostic criteria has led to the increased use of CMR in diagnosis[25]. CMR is a highly sensitive method in the diagnosis of LVNC and stands out with its ability to provide three-dimensional data, functional imaging, and tissue characterization with late gadolinium enhancement imaging[26,27]. However, its diagnostic criteria for the disease are not fully established [28].

Regarding CMR based diagnostic criteria, Petersen *et al*[27] conducted a study evaluating trabeculation distribution and NC/C ratios in different patient groups, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, as well as 7 patients with LVNC; they concluded that trabeculation ratio > 2.3 (NC/C > 2.3) measured in end-diastole SA supported non-compaction cardiomyopathy diagnosis with 86% sensitivity and 99% sensitivity[27]. Fazio *et al*[29] performed end-diastole measurements in 8 patients diagnosed with LVNC and reported that it would be more appropriate to increase NC/C ratio to 2.5[29]. Other CMR-based criteria are more quantitative measurements, based on the measurement of trabeculated mass developed by Jacquier *et al*[30] and Grothoff *et al*[31]. Jacquier *et al*[30] conducted a CMR imaging study on trabeculation mass and reported that the trabeculated LV mass should be more than 25% of the total LV mass, and the noncompacted myocardial mass should be > 15 g/m^2[30,31].

Ventricular myocardium in LVNC has varying morphology ranging from increased spongiosis to dysplastic appearance. Changes in coronary microcirculation together with myocardial abnormalities are thought to play a role in the development of fibrosis. Late gadolinium enhancement may reveal findings of subendocardial and trabecular fibrosis. Although fibrosis may emerge as a follow-up parameter due to increased fibrosis occurrence in adult patients and advanced disease, recent studies have shown that late contrast enhancement may also occur in normally compacted myocardium[32,33]. Similar to a study by Nucifora *et al*[34], the presence and prevalence of myocardial fibrosis may be associated with EF but is insufficient for diagnosis and follow-up[34]. Thanks to advances in high resolution imaging, the sensitive imaging techniques can be used to detect even the slight variations in myocardial morphology within normal limits. Dawson *et al*[35] conducted a study to determine the anatomic norm of trabeculation and evaluated normal hearts of 120 healthy volunteers using CMR. Similar to LVNC, they demonstrated the highest volume of trabeculated myocardium was at a young age and in the apical anterior segments end-diastolic, however, the study needs to be supported by large cohort studies to determine normal limits[35]. The increasing prevalence of the disease indicates the need for strict diagnostic guidelines that can distinguish between normal and pathological trabeculation. LVNC is associated with systolic dysfunction and may clinically progress to heart failure. However, the factors affecting global and regional systolic left ventricular functions and their relationship with the LV noncompacted myocardial mass are not clearly known. Therefore, studies have been conducted to examine the relationship between the change in LV systolic function and the distribution and extent of trabeculation.

In our study, we investigated the relationship between and global and regional EF of apical, midventricular, and basal regions and the trabeculation ratio and number of trabeculated segments of these regions in 65 patients diagnosed with LVNC. We did not find any concordance between EF and trabeculated segment number and ratio for all three regions or global LV. Choudhary *et al*[36] investigated the relationship between LV systolic function and global and regional LVNC mass. Contrary to our study, a significant inverse correlation was found between global EF and NC/C ratios in basal, apical, and midventricular regions in end-systolic measurements, and a significant inverse correlation was observed between end-systolic NC/C ratio and regional EF[36]. Dellegrottaglie *et al*[37] used qualitative and quantitative methods such as wall motion score and fractional wall thickening to measure regional systolic function in 16 adult patients. In measurements of regional systolic functions, an inverse relationship was found between NC/C ratio and fractional wall thickening, and a direct relationship with wall motion score. In other words, a positive correlation was found between regional function and NC/C myocardial ratio. While no significant correlation could be found between the number of noncompacted segments and left ventricular EF, it was considered an indicator of global left ventricular dysfunction[37].

Choi *et al*[38] conducted a study on 145 people [24 isolated LVNC, 33 non-isolated LVNC, 30 dilated cardiomyopathy with noncompaction, 27 dilated cardiomyopathy, and 31 healthy controls] and, similar to our study, did not find a significant correlation

between left ventricular trabeculation volumes and EF in isolated LVNC patients compared to the control group[38].

Fazio *et al*[29] evaluated the relationship between ventricular dysfunction and the number of noncompacted segments in noncompaction cardiomyopathy and found that 122 of 238 patients (mean EF 44.39%) diagnosed with isolated LVNC had ventricular dysfunction with mean EF as 34.6%. However, they did not find a correlation between the number of affected segments and systolic dysfunction[29].

The severity and extent of myocardial involvement in patients with LVNC varies according to the stage of the disease and is heterogeneous. While some studies have found a significant relationship between trabeculation ratio and change in global ventricular function, other studies did not find a significant correlation between ventricular function and the ratio and frequency of trabeculation, as in our study. In addition, most of the studies conducted to date have focused on the relationship between trabeculation volume and global LV systolic function (EF). The limited number of studies on the impact to segmental function report varying results. In our study, we did not find a significant relationship between segmental function and the number of trabeculated segments or trabeculation ratio ($P > 0.05$).

The main limitations of this study are the lack of control group and its retrospective design. In addition, cardiac biopsies and genetic factors were not available for the included patients. Histopathological findings and genetic factors could help to provide more accurate diagnoses for LVNC.

CONCLUSION

In conclusion, there is a need for large cohort studies that include healthy subjects in order to utilize changes in left ventricular function as a criterion in the diagnosis of LVNC. There is not enough evidence yet for the use of segmental and global functions in the diagnosis and follow-up of the disease.

ARTICLE HIGHLIGHTS

Research background

The frequency of left ventricular noncompaction cardiomyopathy (LVNC) diagnosis is increasing day by day due to inadequate diagnostic criteria. In addition, the criteria used cannot determine the prognosis and stage of the disease.

Research motivation

New cardiac magnetic resonance (CMR) criteria that can be used in the diagnosis of LVNC can explain when the increased trabeculation rate in healthy individuals can be called disease. In this context, left ventricular function changes due to increased trabeculation may be a parameter.

Research objectives

In our study, it was aimed to evaluate the relationship between LV global and regional function and trabeculation increase. A new parameter that can be used in diagnosis and follow-up will increase the diagnostic specificity of LVNC.

Research methods

The distribution and ratios of trabeculations in apical, midventricular, and basal regions were examined in CMR. In addition, by using short-axis cine images, regional ejection fraction (EF) and global EF were calculated with the Simpson method in the left ventricle (LV) at apical, basal, and midventricular levels.

Research results

Global EF was correlated with apical, midventricular, and basal regional EF, but there was no significant correlation between global EF and the number of trabeculated segments or trabeculation ratio in the global LV. Also, there was no significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in all three regions.

Research conclusions

Global and regional EF changes may be new diagnostic criteria in the diagnosis of LVNC and in the follow-up of the disease.

Research perspectives

Studies on the relation of LV segmental functions with trabeculation are limited. Studies with larger cohorts and control groups should be conducted.

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ORIGINAL ARTICLE

Retrospective Study

Modes of failure with fractional flow reserve guidewires: Insights from the manufacturer and user facility device experience database

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Institutional review board statement: This study was conducted from a publicly available database, therefore, an approval from the institutional review board was not required.

Informed consent statement: Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained from a freely accessible database.

Conflict-of-interest statement: We

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Abstract

BACKGROUND

Fractional flow reserve (FFR) measurement is commonly used in the cardiac catheterization laboratory to assess the functional significance of coronary arterial plaques. Robust real-world data on complications and modes of failure of FFR guidewires are limited.

AIM

To characterize these outcomes by analyzing the post-marketing surveillance data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database for commonly used FFR guidewires.

METHODS

The MAUDE database was queried from January 2010 through April 2020 for 3

have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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FFR guidewires [PressureWire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". This yielded 544 reports. After excluding incomplete reports, 486 reports were analyzed.

RESULTS

Guidewire tip fracture was the most commonly reported mode of failure, in 174 (35.8%) cases followed by guidewire kinking (n = 152, 31.3%), communication failure (n = 141, 29.0%), and shaft fracture (n = 67, 13.8%). In total, 133 (27.4%) device failures resulted in patient adverse events. The most common adverse event was retained guidewire tip, in 71 (53.4%) cases, followed by freshly deployed stent dislodgment (n = 26, 19.6%) and coronary artery dissection (n = 23, 17.3%). Seven deaths were reported.

CONCLUSION

FFR guidewire failures can occur because of various mechanisms and cause patient adverse events. The MAUDE database serves as an important platform for improved collaboration among clinicians, device manufacturers, and regulators to improve device performance and optimize patient outcomes. Our analysis provides mechanistic insights of FFR guidewire failure and associated adverse events but cannot verify causality or provide a comparison among different guidewires.

Key Words: Fractional flow reserve; Coronary guidewire; Adverse events; Modes of failure; Food and Drug Administration; Manufacturer and user facility device experience

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Core Tip: We analyzed post-marketing surveillance data from the Food and Drug Administration Manufacturer and User Facility Device Experience database to outline the most common adverse events and modes of failure encountered with Fractional Flow Reserve (FFR) coronary guidewires. Guidewire tip fracture was the most commonly reported mode of failure, in 35.8% of cases; retained guidewire tip was the most common patient complication (53.4% of cases). FFR is an important frontline measurement in the cardiac catheterization laboratory to assess intracoronary physiology. Our analysis demonstrates that in real-world practice, FFR guidewire failures can occur because of myriad mechanisms and result in patient complications.

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INTRODUCTION

Fractional flow reserve (FFR) is an essential measurement in the cardiac catheterization laboratory to assess intracoronary physiology. It is obtained by using a pressure sensing guidewire to calculate flow in the epicardial coronary arteries and determine the functional significance of stenosis. The benefits of an FFR-based revascularization strategy in coronary artery disease are well-established. Landmark clinical trials[1-5] have demonstrated that an FFR-guided decision to perform percutaneous coronary intervention reduces major adverse cardiovascular events and decreases the rate of urgent interventions. Likewise, physicians can safely defer revascularization for FFR-negative lesions[6], sparing patients the risk of invasive procedures and long-term antiplatelet therapy. FFR has considerable clinical advantages and is widely utilized.

Performing FFR requires the insertion of an additional guidewire into the patient's arterial system, which increases the risk of procedural complications. However, robust real-world data on the complications and modes of failure of commonly used FFR guidewires are limited. We aim to characterize these outcomes by analyzing the post-marketing surveillance data from the United States Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database for commonly used FFR guidewires.

MATERIALS AND METHODS

The MAUDE database is an electronic repository created by the FDA to capture major adverse events involving medical devices[7]. Reporting is either mandatory (manufacturers and device-user facilities) or voluntary (medical personnel, patients, and consumers). Developed in the 1990s, the database is updated monthly, with each report containing information on the device, event date, and event description by the provider and the manufacturer. The MAUDE database was queried from January 1, 2010, through April 1, 2020, for three commonly utilized FFR guidewires [Pressurewire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". This yielded 544 reports. Each report included a narrative description of the failure event and the results of a standardized inspection of the device if it was returned to the manufacturer. After excluding incomplete reports, duplicate reports, and older devices not in current use, 486 reports were included in the final analysis. This study was conducted from a publicly available database; therefore, an approval from the institutional review board was not required. Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained from a freely accessible database. Although the MAUDE database is a passive monitoring framework, it can provide important insight into the most commonly reported complications associated with interventional devices. Reports on safety and monitoring of approved interventional devices based on this database have been previously reported[8].

RESULTS

Tables 1 and 2 show a complete list of reported modes of failure and adverse patient events, respectively, categorized by each FFR coronary guidewire. Percentages represent the proportion of total submitted MAUDE reports and do not reflect the incidence rates. Guidewire tip fracture occurred in 174 (35.8%) cases and was the most commonly reported mode of failure. Guidewire kinking was reported in 152 (31.3%) cases, communication failure in 141 (29.0%) cases, and shaft fracture in 67 (13.8%) cases. In total, 133 (27.4%) device failures resulted in adverse patient events. The most common adverse patient events were a retained guidewire tip, in 71 (53.4%) cases, followed by freshly deployed stent dislodgment in 26 (19.6%) cases and coronary artery dissection in 23 (17.3%) cases. Seven patient deaths were reported. The device-related adverse events were most commonly reported during physiologic evaluation of the left anterior descending (LAD) artery, accounting for 54.8% of the reported adverse events. The relative involvement of other target coronary arteries is demonstrated in Figure 1.

DISCUSSION

This study demonstrates the modes of failure of commonly used FFR guidewires and highlights the potential for adverse patient outcomes. Two general categories of guidewire failure can occur: structural failure and errors in signal communication. The most common structural failures reported in this study were distal tip fractures (35.8%), kinking (31.3%), peeled coating (18.3%), and shaft fractures (13.8%). A majority of devices in this study failed from more than one of the above mechanisms. Most structural failures were attributed to operator handling issues, defined as having occurred at any point after the device was removed from packaging. Structural failures add complexity for the operator, as demonstrated by 23% of reports noting the inability to advance the guidewire. Structural failures are also directly associated with patient harm: 53% of adverse patient events were related to fractured guidewire tips

Table 1 Summary of device modes of failure for fractional flow reserve coronary guidewires

Device mode of failure	Verrata™ (Philips), *n* = 199	Comet™ (Boston Scientific), *n* = 180	PressureWire™ X (Abbott), *n* = 107	Total, *n* = 486
Guidewire distal tip fracture	55 (27.6)	68 (37.8)	51 (47.7)	174 (35.8)
Guidewire kinking	37 (18.6)	103 (57.2)	12 (11.2)	152 (31.3)
Communication failure	64 (32.2)	59 (32.8)	18 (16.8)	141 (29.0)
Failure to advance guidewire	62 (31.2)	36 (20.0)	14 (13.1)	112 (23.0)
Peeled guidewire coating	6 (3.0)	83 (46.1)	0 (0)	89 (18.3)
Guidewire shaft fracture	25 (12.6)	22 (12.2)	10 (9.3)	67 (13.8)

Percentages represent proportion of reported events and do not reflect the incidence rates. Results reported as *n* (%).

Table 2 Summary of patient adverse events for fractional flow reserve coronary guidewires

Adverse patient events	Verrata™ (Philips), *n* = 58	Comet™ (Boston Scientific), *n* = 29	PressureWire™ X (Abbott), *n* = 46	Total, *n* = 133
Retained guidewire tip	27 (46.6)	22 (75.9)	22 (47.8)	71 (53.4)
Stent dislodgement	18 (31.0)	0 (0)	8 (17.4)	26 (19.6)
Vessel dissection	8 (13.0)	4 (13.8)	11 (23.9)	23 (17.3)
Death	2 (3.4)	2 (6.9)	3 (6.5)	7 (5.3)
Vessel perforation	3 (5.2)	1 (3.5)	2 (4.4)	6 (4.5)

Percentages represent proportion of reported events and do not reflect the incidence rates. Results reported as *n* (%).

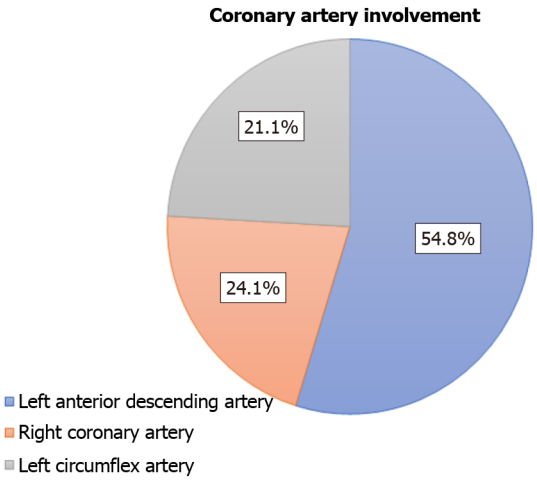


Figure 1 Adverse events stratified by target vessels for fractional flow reserve coronary guidewires.

that remained in the coronary arteries. Retained guidewire fragments increase the risk of dissection, embolization, and thrombus formation and necessitate further interventions[9]. All options, including percutaneous retrieval with a snare, surgical retrieval combined with coronary bypass, or stenting with antiplatelet therapy, increase the risk of further procedural complications and morbidity. Given the high incidence of guidewire fractures, operators should assess the integrity of the device upon removal and ensure that there are no retained pieces in the patient.

The other category of guidewire failure is an error in signal communication, which contributed to 29% of guidewire failures in this study. Pressure sensors at the tip of FFR guidewires transmit data to an external hub that processes information for clinician interpretation. In all three FFR guidewires assessed in this study, commu-

nication between the tip and hub occurs *via* internal cables threaded through the shaft of the guidewire. Errors in signal communication can manifest as the inability to zero the sensor, significant drift, or no signal detected by the hub. The currently available pressure wire sensors are either piezo-electric or optical; these pressure wires differ from routine workhorse wire, as they require integration of thin wires or optical fibers that transmit the pressure signals[10]. While the exact etiologies of communication errors of FFR guidewires were not captured in our data, they can occur after any structural failure that causes sensor or cable damage, or from manufacturing defects. Communication errors are important to detect, as they can result in inaccurate measurements, prolonged procedures, and the need for additional instrumentation.

FFR guidewires can cause patient adverse events. This study demonstrates that vessel dissection, vessel perforation, and stent dislodgement can occur with FFR guidewire use. These are clinically significant complications that must be recognized early and managed carefully to avoid further patient harm. The age of dislodged stents was not documented in the reports; however, operators should exercise caution when advancing or withdrawing an FFR guidewire across any freshly deployed stents. Seven deaths were reported among the cases reviewed. While this is noteworthy, there is not enough information to link the use of FFR guidewires with these deaths.

A majority of all reported events (54.8%) occurred in the LAD, followed by 24.1% in the right coronary artery and 21.1% in the left circumflex artery. A higher rate of reported failures in the LAD may be attributed to generally higher rates of FFR procedures performed in this vessel; however, this information was not captured in our data. Additionally, coronary characteristics such as tortuosity, calcification, and disease severity can also impact individual coronary outcomes. Without this information, the clinical significance of higher reported failures in the LAD is uncertain. Further studies that include data on coronary characteristics and operator technique would be useful to better determine whether FFR guidewires have higher failure rates in any one coronary artery.

Limitations

The MAUDE database has several inherent limitations that impact the interpretation of our study. Notably, only cases with adverse events are reported in the database, and reporting is partially voluntary. Successful cases are not reported, and there is no information on the overall frequency of the device use. Without this information, we cannot derive the incidence of failure rates associated with the use of these guidewires or compare outcomes among different devices. Adverse events may be reported both by users and manufacturers, leading to duplicate reports and difficulty in discriminating. Another notable limitation of the database is that data are provided in a non-standardized narrative form. Not all failed devices were returned to the manufacturer for standard inspections. Without standardized information on the clinical context of failure events, these data cannot be used to imply causality or comparison between procedures or devices.

CONCLUSION

The landmark clinical trials that support the routine frontline use of FFR did not specifically address adverse events related to the use of FFR guidewires. Consequently, the present study is important in understanding the common pitfalls of this widely used procedure. Our analysis demonstrates that real-world use of FFR is associated with complications and adverse patient outcomes. Knowledge of the methods of FFR guidewire failure is critical for operators to develop situational awareness, anticipate difficult situations, assess for common complications, and mitigate adverse patient events. Interpretation of MAUDE data also provides critical feedback to manufacturers and allows for collaboration among clinicians, device manufacturers, and regulators to improve devices and patient outcomes.

ARTICLE HIGHLIGHTS

Research background

Fractional flow reserve (FFR) measurement is an essential tool in the cardiac catheterization laboratory to assess the functional significance of coronary artery lesions. Robust real-world data on the commonly reported complications and modes of failure

associated with the FFR guidewires are scarce.

Research motivation

The landmark clinical trials that support routine physiologic lesion assessment with FFR did not specifically address adverse events associated with the use of FFR guidewires. Accordingly, this provided us the impetus to explore common shortcomings with one of the most common applied technology in the cardiac catheterization laboratory. With broadened global utilization of the FFR and newer iterations, standard reporting of adverse events and failure modes may improve patient selection, operator expertise and device technology.

Research objectives

The objective of our study was to investigate the most commonly reported adverse events and failure modes associated with commonly used FFR guidewires by analyzing the post-marketing surveillance data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database.

Research methods

We queried the MAUDE database from January 2010 through April 2020 for 3 FFR guidewires [PressureWire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". The search yielded 544 reports. After excluding incomplete and duplicate reports, 486 reports were included in the final analysis.

Research results

The most commonly reported mode of failure was guidewire tip fracture described in 174 (35.8%) cases followed by guidewire kinking (n = 152, 31.3%), communication failure (n = 141, 29.0%), and shaft fracture (n = 67, 13.8%). One hundred thirty-three (27.4%) device failures caused patient adverse events. The most commonly reported adverse event was retained guidewire tip described in 71 (53.4%) cases, followed by freshly deployed stent dislodgment (n = 26, 19.6%) and coronary artery dissection (n = 23, 17.3%). Seven deaths were reported.

Research conclusions

FFR guidewire failures can occur because of myriad mechanisms and cause patient adverse events. Understanding the methods of FFR guidewire failure is critical for interventionalists to develop operational awareness, forebode challenging situations, evaluate common complications, and assuage adverse patient events. The MAUDE database serves as an important pulpit for improved collaboration among physicians, device manufacturers, and regulators to improve device performance and optimize patient outcomes.

Research perspectives

Intermediate coronary lesions are commonly encountered during cardiac catheterization and present a diagnostic dilemma. Physiologic testing using a pressure wire-based system is appropriate for these lesions. The introduction of newer nonhyperemic pressure-based indices of stenosis severity such as instant wave-Free Ratio (iFR) and coregistered iFR pressure mapping may augur a paradigm shift for functional lesion assessment. It is pivotal for interventionalists to familiarize themselves with the common pitfalls associated not only with the standard FFR system but also with the newer iterations.

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CASE REPORT

Sliding with the sines − fatal hyperkalemia: A case report

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Abstract

BACKGROUND

Classic electrocardiographic manifestations of hyperkalemia starting with peaked symmetrical T-waves are widely recognized in daily clinical practice but little evidence is documented how quickly it can evolve in real-time.

CASE SUMMARY

An elderly diabetic and hypertensive male presented with acute renal failure and rhabdomyolysis. He experienced cardiac arrest with moderate hyperkalemia despite medical treatment and hemodialysis. Telemetry changes were retrospectively studied and found to have significant rhythm changes that occurred just less than 10 minutes prior to the cardiac arrest.

CONCLUSION

In hyperkalemia, telemetry rhythm can change instantaneously in a significant way. Rapidly rising potassium could be life threatening and may require more than medical treatment.

Key Words: Electrocardiogram; Arrhythmia; Hyperkalemia; Electrolyte imbalance; Cardiac arrest; Case report

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Core Tip: We present a case of acute rhabdomyolysis and renal failure where the patient experienced cardiac arrest with moderate hyperkalemia despite medical treatment and hemodialysis. This case illustrates how quickly the telemetry rhythm can change in a short period of time (9 min).

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INTRODUCTION

In rhabdomyolysis where massive tissue destruction could produce significant hyperkalemia, potassium levels are closely monitored and electrocardiographic changes would trigger immediate action even before the laboratory confirmation[1]. Rapidly rising potassium levels are more likely to present with cardiac rhythm changes but the pace of those changes is rarely reported in the literature.

CASE PRESENTATION

Chief complaints

A 76-year old male presented to emergency department with generalized weakness and encephalopathy.

History of present illness

His generalized weakness gradually started over a few months and recently he was getting weaker and also confused for a few days.

History of past illness

His past medical history was significant for hypertension, diabetes and old ischemic stroke with residual right sided weakness.

Personal and family history

He was a non-smoker and non-drinker, and he lived in a house.

Physical examination

He was somnolent but arousable. He had dry mucous membranes and mild right hemiparesis which was his baseline.

Laboratory examinations

Laboratory results were significant for serum potassium 6.7 mmol/L, serum creatinine 10.76 mg/dL, and serum creatine kinase 40673 U/L.

Imaging examinations

Computed tomography of the brain without contrast showed no acute changes. Electrocardiography (Figure 1) did not show any classic changes associated with hyperkalemia.

FINAL DIAGNOSIS

Patient was diagnosed as hyperkalemia with acute renal failure possibly due to rhabdomyolysis.

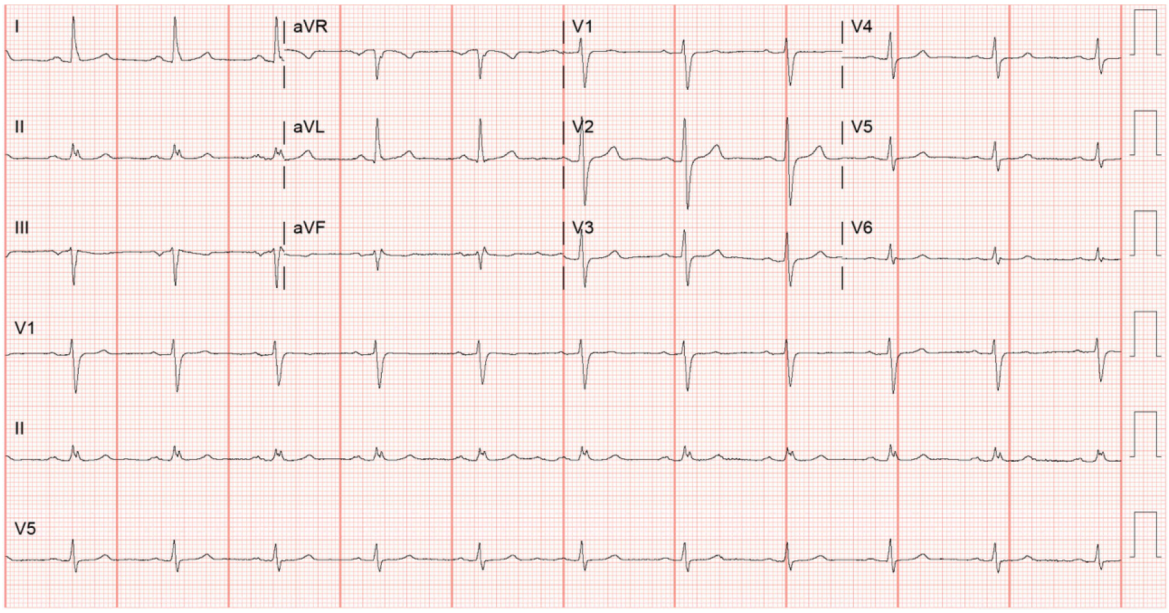


Figure 1 Electrocardiogram on admission. Twelve lead electrocardiogram without any hyperkalemic manifestations.

TREATMENT

Initial treatment

The patient received intravenous calcium gluconate, furosemide, dextrose, insulin, and sodium bicarbonate, and albuterol by nebulizer. Emergent hemodialysis was arranged and performed in the intensive care unit uneventfully, resulting in potassium decreasing to 4.0 mmol/L. CK also trended down to 37586 U/L the following day. Further daily hemodialysis sessions were provided for oliguria.

Progress during hospital stay

On the third hospital day, CK increased to 206297 U/L but the potassium level remained stable at 4.7 mmol/L. Six hours after the hemodialysis session of the day, the repeat potassium was 6.9 mmol/L. The telemetry rhythm strip (Figure 2A) showed no hyperkalemic manifestations. The patient was again administered calcium gluconate, dextrose, insulin and sodium polystyrene. Despite these efforts, two hours later the patient suffered a cardiac arrest with pulseless electrical activity. The patient was resuscitated and the repeat potassium level which was taken just before the cardiac arrest was 7.4 mmol/L. On review of the telemetry, significant changes associated with hyperkalemia were noted just 9 min before the cardiac arrest (Figure 2B-G). The potassium levels, creatine kinase levels and the treatments patient received are summarized in Table 1.

Electrocardiography following the resuscitation still showed the typical sine waves of hyperkalemia (Figure 3) with a repeat potassium level of 7.9 mmol/L.

OUTCOME AND FOLLOW-UP

The patient was intubated and continuous renal replacement therapy (CRRT) was initiated. Despite these interventions, the hyperkalemia and metabolic acidosis continued to worsen and he eventually expired from ventricular fibrillation refractory to multiple defibrillation attempts. Repeat 12 Lead electrocardiography before the last cardiac arrest showed more pronounced sine waves from hyperkalemia with corresponding potassium level of 7.1 mmol/L (Figure 4).

DISCUSSION

Traditionally, the electrocardiographic manifestations of hyperkalemia are sufficient to make emergent interventions indicated even prior to laboratory confirmation[1-4].

Table 1 Potassium levels, creatine kinase levels and treatments received

Timeline	Potassium levels (mmol/L)	CK levels (U/L)	Treatments received
Day 0	6.7	40673	IV calcium gluconate 1 g once
			Albuterol nebulization 10 mg once
			IV furosemide 40 mg once
			IV dextrose 50% 50 g once
			IV regular insulin 5 units once
			IV sodium bicarbonate 50 mEq once
			IV sodium bicarbonate 8.4% continuous infusion was started
Day 0 (2 h)	6.2	-	Hemodialysis initiated
Day 1	4.0, 4.2	37586	Daily intermittent hemodialysis continued
Day 2	4.2, 4.7	206297	Daily intermittent hemodialysis continued
Day 3, 4 AM	6.9	198294	IV calcium gluconate 1 g once
			IV dextrose 50% 25 g once
			IV regular insulin 5 units once
			PO sodium polystyrene 30 g once
Day 3, 6 AM	7.4	-	Cardiac arrest before result was out
			IV epinephrine 1mg × 3
			IV calcium chloride 1g × 2
			IV sodium bicarbonate 50 mEq × 3
			IV dextrose 50% 25 g once
			IV regular insulin 10 units once
			CRRT initiated after resuscitation

CK: Creatine kinase; IV: Intravenous; CRRT: Continuous renal replacement therapy.

Continuous electrocardiographic telemetry is typically sufficient for monitoring cardiac rhythm. However, this patient did not demonstrate the classic peaked, symmetrical T waves on telemetry despite significant hyperkalemia. The amplitudes of T waves in lead II (Figure 2A) were less than half the height of QRS complexes and it had similar morphology on telemetry for the first three days. If a 12-lead electrocardiogram had been recorded prior to cardiac arrest, it might have shown some peaked T waves in the other non-monitoring leads.

Hyperkalemia is also associated with atrioventricular conduction disturbances[5,6] and we observed the left bundle branch block morphology just 3 minutes prior to cardiac arrest (Figure 2F).

Hyperkalemia is generally classified as moderate for the level between 6.5 mmol/L to 8.0 mmol/L and severe for the level above 8.0 mmol/L. Rapidly progressive hyperkalemia is more likely to present with cardiac rhythm changes[7]. This patient only experienced moderate hyperkalemia but suffered cardiac arrest likely because of a rapidly rising potassium. Moreover, it is also notable that the sine waves were more dramatic with potassium level of 7.1 mmol/L (Figure 4) when he eventually demised than with potassium level of 7.9 mmol/L (Figure 3) from his first cardiac arrest.

Intravenous regular insulin 5 units with dextrose can reduce the potassium level by 0.54-1.04 mmol/L at one hour[3] and a systematic review showed regular insulin 10 units could reduce the potassium by average of 0.78 ± 0.25 mmol/L in an hour[8]. The beta-2 agonist, salbutamol 10 mg nebulization, is also another potent agent that can reduce the potassium by 0.62 ± 0.09 mmol/L after 120 min of administration[9] but with the possible side effect of severe tachycardia and is limited in patients with heart failure or coronary artery disease. However, all of these treatments influence the potassium level by intracellular transfer without actually reducing total body potassium. Intravenous loop diuretics are largely ineffective in relieving hyperkalemia in oliguric patients. Oral agents that increase gastrointestinal potassium excretion, in-

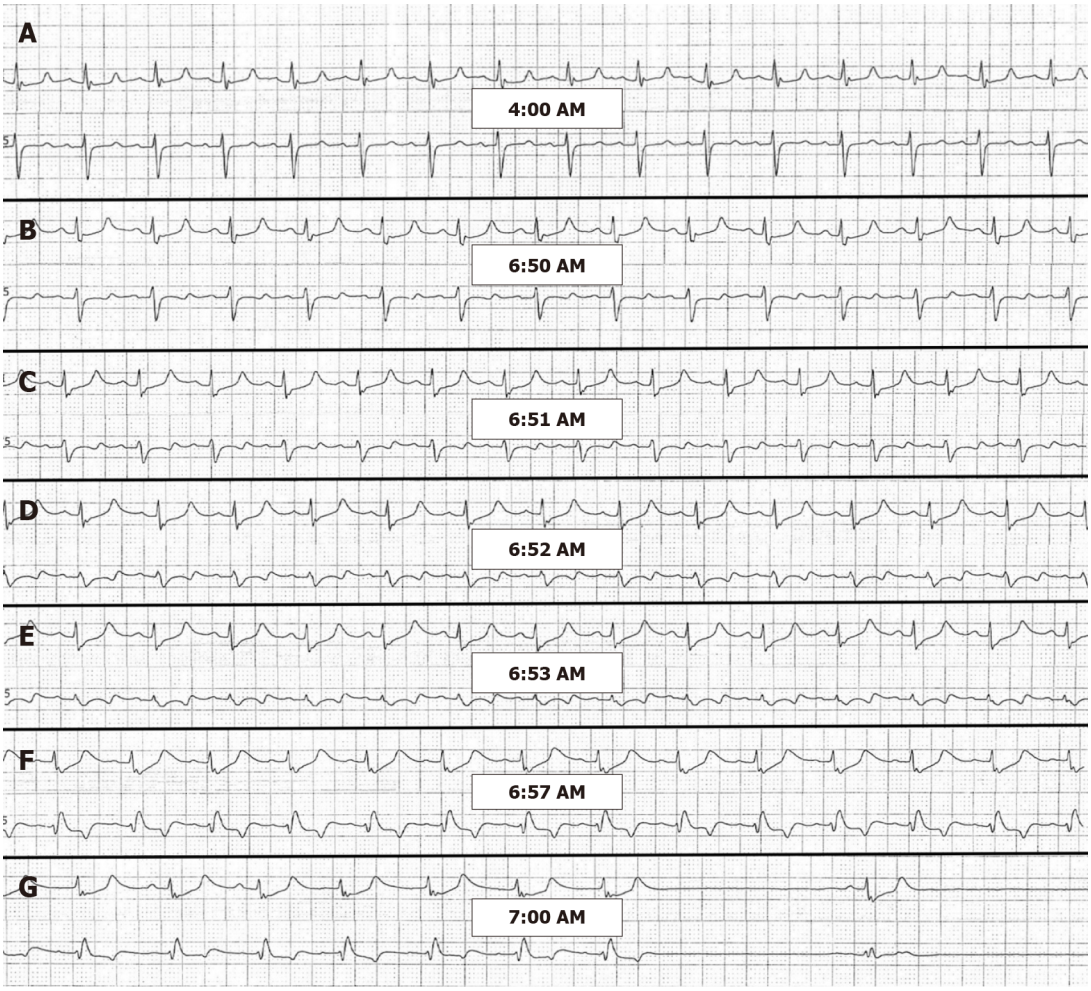


Figure 2 Telemetry strips (rate 25 mm/s). The upper rhythm is lead II and lower rhythm is lead V5. A: At 4:00 AM. when potassium level started rising. T wave amplitude measuring 2-2.5 mm in lead II. PR interval 0.16-0.20 s. QRS 0.1-0.12 s. QT prolongation from hypocalcemia; B: At 6:50 AM. T waves in lead II seems to be slightly taller, maybe about 0.5 mm (half small square) than Figure 2. Similar measurements for PR interval and QRS. Non-specific T waves changes in V5; C: At 6:51 AM. ST and T waves changes more pronounced in V5. ST depression by 0.5-1 mm in V5. QRS slightly widened beyond 0.12 s in both lead II and V5; D: At 6:52 AM. QRS widened more with further ST depression. Transitioning into sine wave, more obvious in lead V5; E: At 6:53 AM. Complete loss of original QRS morphology in lead V5 and transforming into sine waves. P waves still visible with PR interval 0.16 s in lead II; F: At 6:57 AM. QRS morphology in lead II deformed with marked ST depression, transitioning into sine waves. QRS in V5 is showing left bundle branch block morphology at the similar heart rate; G: At 7:00 AM. Sinus pause over 2 s and pulseless electrical activity cardiac arrest.

cluding sodium polystyrene, patiromer and sodium zirconium, have a slow onset of action. Sodium zirconium could potentially have incremental effect in treatment of hyperkalemia with potassium reduction of 0.41 mmol/L as early as 4 h after administration[10].

In addition to the above medical intervention, it is warranted to initiate renal replacement therapy in the setting of hyperkalemic emergency with rhabdomyolysis. Our patient, however, was already on daily hemodialysis with potassium level under control for two days. Nevertheless, his rebound hyperkalemia should have been managed aggressively with immediate hemodialysis rather than medical management and wait for another two hours for response.

After the medical management, potassium level should be repeated one to two hour after treatment. In our patient, it was scheduled to be repeated two hour after treatment which was reasonable. More aggressive approach to repeat the potassium at one hour or earlier might have shown worsening hyperkalemia which would have prompted more intervention.

Hemodialysis is the mainstay for the emergency management of hyperkalemia but daily intermittent hemodialysis may be inadequate as shown in this case. There is not enough evidence to suggest that continuous renal replacement therapy (CRRT) is superior to intermittent hemodialysis in management of rhabdomyolysis but CRRT has been found to remove myoglobin more effectively and is more practical in the setting of hypotension[11]. Early initiation of continuous veno-venous hemodialysis

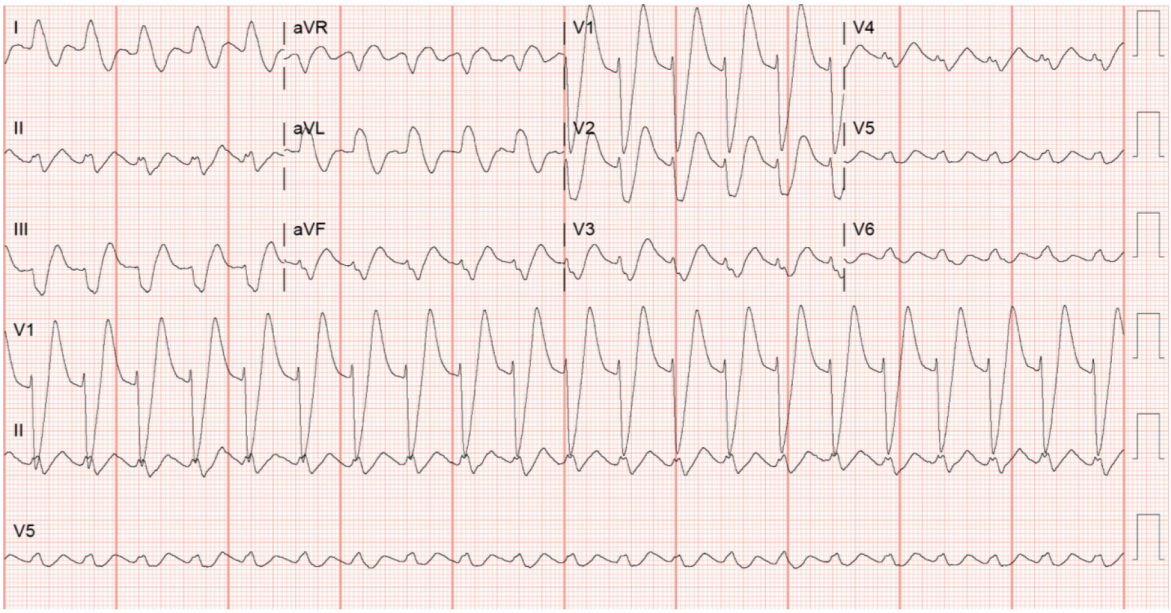


Figure 3 Electrocardiogram after resuscitation. Twelve lead electrocardiogram showing classic description of hyperkalemic manifestations, peaked T waves in V1, V2, widened QRS complexes, P waves not seen and sine waves in V4, V5, V6.

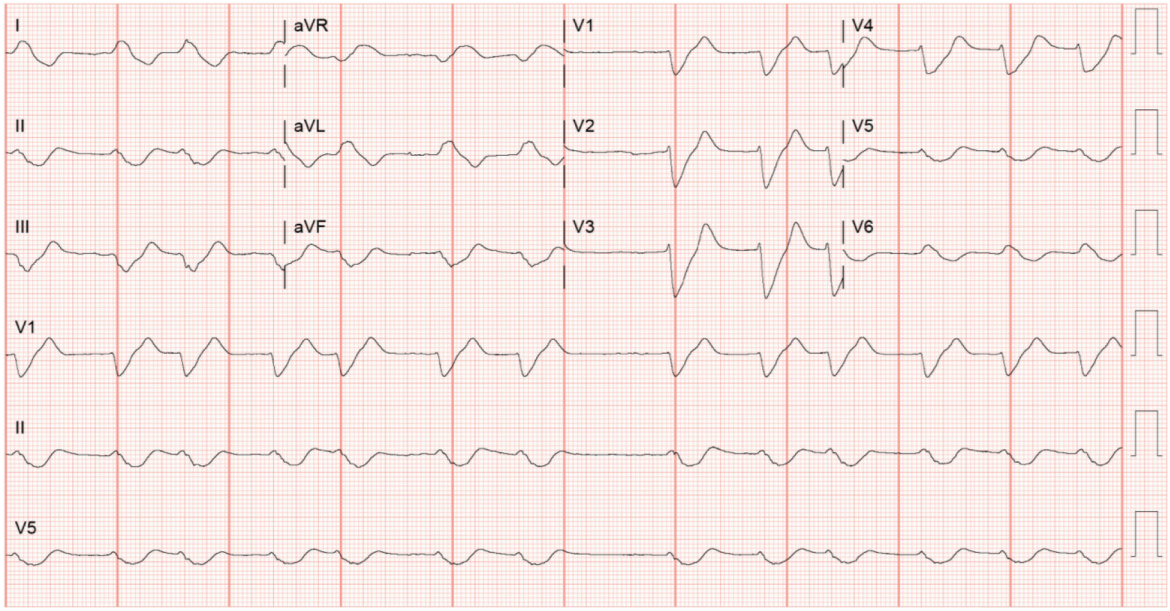


Figure 4 Electrocardiogram showing typical sine waves of hyperkalemia. Findings include loss of P waves, severe widening of QRS complexes resulting in fusion of QRS complexes and T waves, decrease in amplitudes of QRS complexes and T waves.

along with aggressive potassium monitoring may be necessary for severe cases of rhabdomyolysis.

CONCLUSION

Frequent 12-lead electrocardiograms in addition to the close attention to continuous telemetry monitoring are necessary for patient with hyperkalemia from rhabdomyolysis. Despite appropriate support with daily hemodialysis, this case demonstrates how rapidly acute hyperkalemia can worsen and cause an evolution of the cardiac rhythm. Timely intervention and reassessment for clinical response are critical in the management of hyperkalemia.

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EDITORIAL

ISCHEMIA trial: How to apply the results to clinical practice

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Abstract

During the last years two questions have been continuously asked in chronic coronary syndromes: (1) Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? Therefore, there was a need for a large definitive trial. This study was the ISCHEMIA trial, a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and optimal medical treatment (OMT) *vs* OMT alone in 5179 patients enrolled after a stress test. During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio for the invasive strategy as compared with the conservative strategy was 0.93 (95% confidence interval 0.80-1.08, P = 0.34). The ISCHEMIA trial deeply disrupted many of our prior attitudes regarding management strategies for patients with stable coronary artery disease. The findings underscore the benefits of disease-modifying OMT for stable coronary artery disease patients. The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to decision-making processes. Obviously, this changed after the trial results. The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

Key Words: Stable angina; Chronic coronary syndrome; ISCHEMIA; Stress testing; Therapy; Diagnosis

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Core Tip: During the last years two questions have been continuously asked in chronic coronary syndromes: Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

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INTRODUCTION

Since the first definition of angina by the English physician William Heberden in 1772 [1] many aspects have been discussed about this entity. Heberden described with a lot of detail a symptom, but he did not comprehend the disease. Later, in 1793, Edward Jenner detected thickened coronary arteries at an autopsy of his colleague John Hunter after sudden cardiac death due to an angina attack[2]. It took decades to get a first treatment (amyl nitrite)[3] for angina pectoris, and it was an even greater time for a valid understanding of the underlying disorder.

In 1967, Favaloro[4] used a saphenous vein and sewed it to the narrowing diseased coronary artery, making this the first coronary artery bypass grafting (CABG). Certainly, CABG showed a marked improvement of symptoms in patients with coronary artery disease (CAD). In 1979, Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty[5]; later this technique has been known as percutaneous coronary intervention (PCI) with the use of stents.

During the last years two questions have been continuously asked: (1) Do revascularization procedures (CABG or PCI) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death?

The initial enthusiasm for PCI was diminished after COURAGE trial[6], which showed no benefit of revascularization over optimal medical treatment (OMT). Nevertheless, the study was criticized due to a small proportion of the recruited patients treated in the participating centers and the use of bare metal stents. Then came the ORBITA trial[7] comparing OMT with PCI, this time using drug-eluting stents in a sham-controlled design, and the final result again was neutral. Once more, the same criticisms about small sample size were raised, and while symptoms and exercise tolerance only showed a tendency, regional wall motion was improved substantially in the stress echocardiograms[8].

Therefore, because of this uncertainly, there was a need for a large definitive trial. This study was the ISCHEMIA trial, which was presented at the American Heart Association Scientific Sessions in November 2019, and some months later it was published in the New England Journal of Medicine[9].

ISCHEMIA TRIAL

ISCHEMIA trial is a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and OMT *vs* OMT alone in 5179 patients enrolled after a stress test[9]. Related to this trial was the ISCHEMIA-CKD in patients with chronic kidney disease (CKD), which had a similar design to the ISCHEMIA trial except that the use of a computed tomography (CT) scan

was not necessary[10], and the CIAO-ISCHEMIA (Changes in Ischaemia and Angina over One year), which was a registry of patients excluded from the ISCHEMIA trial because of a negative CT scan. These latter patients represented around 14% of those initially considered for the ISCHEMIA trial and ultimately considered as ischemia with normal coronary arteries (INOCA)[11]. Moreover there was a quality of life study in the main ISCHEMIA trial, which included 4617 patients[12] that brought interesting results.

The rationale of the trial was clearly stated by the authors in the study abstract, "among patients with stable coronary disease and moderate or severe ischemia, whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain"[9].

One key element of the trial was the performance of a blinded coronary computed tomography angiography (CCTA) prior to enrolment to exclude the presence of left main CAD and the absence of obstructive CAD.

We could consider this trial as the largest comparative effectiveness trial of an invasive *vs* conservative strategy in patients with stable coronary disease. It is important to highlight a recent terminology change; these stable patients are now known as patients with chronic coronary syndromes due to a new definition of the European Society of Cardiology[13].

The ISCHEMIA study has tried to address the key limitations of previous trials, namely: Recruiting high-risk patients with at least moderate inducible ischemia at baseline, randomizing patients prior to the diagnostic coronary angiogram to reduce both selection and referral bias, incorporating the current state-of the-art revascularization techniques that include the fractional flow reserve-guided PCI and the last generation drug-eluting stents at high-volume interventional sites who were selected for their proficiency and skill in revascularization, and employing an algorithm-based OMT and guidance for intensifying therapies in both arms of the trial.

The primary outcome of the trial was a five-component composite endpoint comprising cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, and resuscitated cardiac arrest, whereas the major secondary endpoints were time to cardiovascular death or non-fatal MI, anginal symptoms, and quality of life.

During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio (HR) for the invasive strategy as compared with the conservative strategy was 0.93 [95% confidence interval (CI) 0.80-1.08, P = 0.34]. There was no heterogeneity of treatment effect based on a broad range of pre-specified subgroups, including the presence of diabetes mellitus, high rate of OMT attainment, new or more frequent angina, degree of baseline ischemia, CAD severity based on 50% stenosis (*i.e.* one, two, or three vessel disease) or the presence of proximal left anterior descending coronary stenosis > 50%

There was no significant difference in total death for the invasive strategy (n = 145) group *vs* the conservative strategy (n = 144) group (HR = 1.05, 95%CI: 0.83-1.32) or in cardiovascular death (HR = 0.87, 95%CI: 0.66-1.15). There was also no significant difference in the rate of overall MI between the two treatment strategies (adjusted HR = 0.92, 95%CI: 0.76-1.11), although there were more procedural infarctions in the invasive strategy arm in early follow-up and more spontaneous myocardial infarctions in the conservative strategy arm in the late follow-up period[9].

There were significant and lasting improvements in angina control and quality of life metrics with an invasive approach in those patients who had significant angina [consider as daily/weekly (20% of ISCHEMIA patients)], but more modest improvements in patients with monthly angina (44%), while there was no improvement in patients with less frequent or no angina (35%)[12].

In the companion ISCHEMIA trial study (ISCHEMIA-CKD) of patients with CKD (defined as estimated glomerular filtration rate < 30 mL/min/body surface area)[10], with the same entry criteria and randomized treatment strategies, there was similarly no significant difference in outcome results between invasive *vs* conservative arms for the primary or secondary endpoints, however the invasive arm was associated with a higher incidence of stroke than the conservative arm (HR = 3.76, 95%CI: 1.52-9.32, P = 0.004) and higher incidence of death or initiation of dialysis (HR = 1.48, 95%CI: 1.04-2.11, P =0.03). There were no significant or sustained benefits in relation with angina-related health status between the two arms.

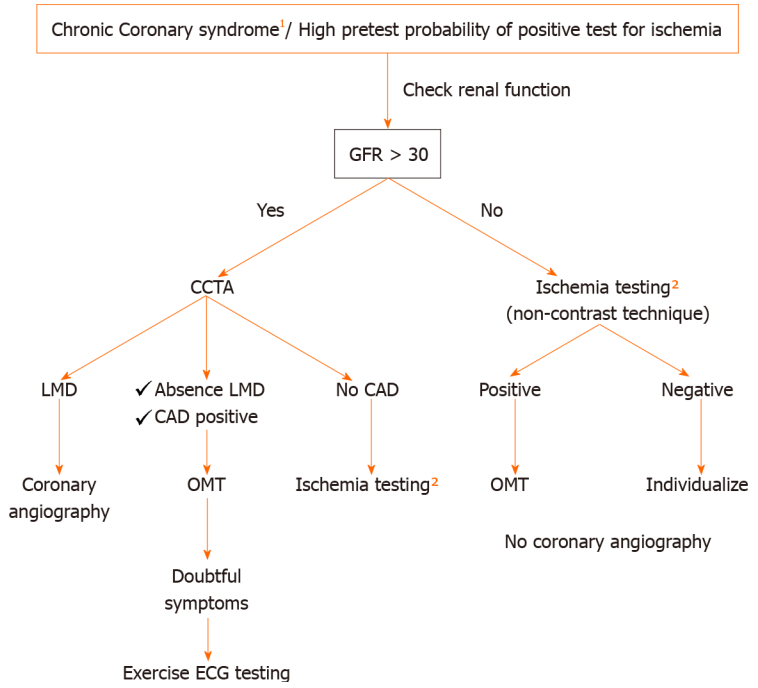


Figure 1 Algorithm for chronic coronary syndrome with high pretest probability of positive test for ischemia. [1]Previously known as stable angina. [2]Stress echocardiography (non-contrast technique), single photon emission computed tomography (non-contrast technique), or magnetic resonance imaging (contrast technique). CAD: Coronary artery disease; CCTA: Coronary computed tomography angiography; GFR: Estimated Glomerular filtration rate (mL/min/1.73 m^2); LMD: Left main disease; OMT: Optimal medical therapy.

HOW TO APPLY THE RESULTS TO CLINICAL PRACTICE

The ISCHEMIA trial deeply disrupts many of our prior attitudes regarding management strategies for patients with stable CAD. The findings underscore the benefits of disease-modifying OMT for stable CAD patients, and this must be our most important focus. While revascularization will always have a crucial role in symptom relief and improving quality of life, our primary goal should be to reduce incident cardiovascular events by utilizing proven therapies that stabilize vulnerable coronary plaques and improve event-free survival.

The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to the decision-making processes. Obviously, this has changed after the trial results.

The results of this study cannot be applied to patients with a known higher risk, such as those with very severe symptoms, left ventricular dysfunction (left ventricular ejection fraction < 35%), or left main disease, since these patients were excluded from the ISCHEMIA study. The authors of the study point out, however, that the selection was near to our daily practice patients; more than half of those included were patients with severe ischemia, and also almost half of them had multivessel disease and/or CAD that included the proximal left anterior descending artery, in whom before we went to invasive management without even considering another option.

The results of ISCHEMIA and ISCHEMIA CKD might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease[13] that were based on studies published before the ISCHEMIA trial. In the next two figures we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes. Figure 1 shows our approach for high pretest probability patients where renal function needs to be known in advance, and Figure 2 can be applied for the low to moderate pretest probability patients. It should be pointed out that starting the work-out diagnosis by CCTA in every patient would miss a considerable number of patients with INOCA according to the combined ISCHEMIA and CIAO results (data not yet published)[11]. In addition, an initial CCTA approach would significantly increase the number of further functional tests due to unconclusive/positive CCTAs and spurious revascularizations[14]. Another important remark for a better comprehension of our approach is that according to the ISCHEMIA-CKD results, starting ischemia testing and trying to avoid coronary intervention seems desirable for patients with kidney dysfunction.

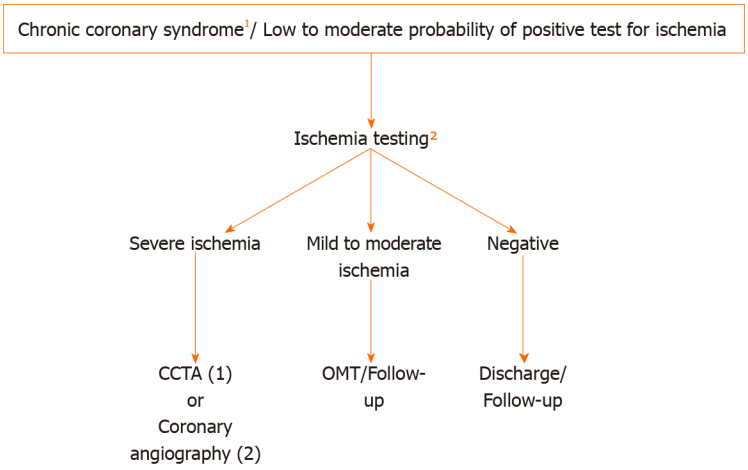


Figure 2 Algorithm for chronic coronary syndrome with low to moderate pretest probability of positive test for ischemia. [1]Previously known as stable angina. [2]Stress echocardiography [any glomerular filtration rate (GFR) (mL/min/1.73 m²)], single photon emission computed tomography (any GFR), or magnetic resonance imaging (only if GFR > 30). CCTA: Coronary computed tomography angiography; LMD: Left main disease; OMT: Optimal medical therapy.

CONCLUSION

To summarize our view on stable coronary disease patients after the ISCHEMIA trial, the assessment of ischemia loses priority in this scenario, symptoms evaluation gains importance, and ischemia (and not anatomy) should be the focus in certain entities like CKD or INOCA[15].

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ACADEMIC ACTIVITY REPORT

Shortened dual antiplatelet therapy in contemporary percutaneous coronary intervention era

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Abstract

Percutaneous coronary intervention with stenting is followed by a duration of dual antiplatelet therapy (DAPT) to reduce stent thrombosis and avoid target lesion failure. The period of DAPT recommended in international guidelines following drug-eluting stent implantation is 12 mo for most patients with acute coronary syndrome, and 6 mo for patients with chronic coronary syndrome or high bleeding risk. The new generation of drug-eluting stents have metallic platforms with thinner struts, associated with significantly less stent thrombosis. Shortened DAPT has been investigated with these stents, with evidence from randomised clinical trials for some individual stents showing non-inferior safety and efficacy outcomes. This has to be balanced by the effect of DAPT on secondary prevention of systemic cardiovascular disease especially in high-risk populations. This review will outline the current evidence for individual stents with regards to DAPT duration for both acute coronary syndrome and chronic coronary syndrome and discuss further directions for research and personalised medicine in this contemporary percutaneous coronary intervention era.

Key Words: Coronary artery disease; Drug-eluting stent; Percutaneous coronary intervention; Dual antiplatelet therapy; Stent thrombosis; Target lesion revascularization

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Core Tip: The new generation of drug-eluting stents have different properties such as reduced strut thickness allowing lower level of local stent thrombosis, which may be feasible with shortened dual antiplatelet therapy (DAPT). Only a small number of

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individual stents have been validated for reduced DAPT, such as 1 mo for the BioFreedom stainless steel biolimus-eluting stent and the Onyx Resolute cobalt-chromium zotarolimus-eluting stent but in only certain populations. Future trials will compare DAPT durations within the same stent. Future research should also examine risk stratification and the parameters for patients to benefit the most from shortened DAPT.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is an interventional procedure which generally involves coronary angioplasty and stenting for individuals with coronary artery disease. Stent implantation is associated with greater lumen diameter increase in the acute period. The dimensions and the material of a stent are associated with different degrees of re-epithelialisation and risk of thrombosis. Intimal hyperplasia may cause restenosis of a vessel in bare metal stents (BMS), and metallic drug-eluting stents (DES) coated with anti-proliferative agents were developed to prevent this. However, delayed re-endothelialisation lengthens the duration of increased thrombosis risk. (Figure 1).

Dual antiplatelet therapy (DAPT), which is a combination of aspirin and an oral inhibitor of the platelet P2Y12 inhibitor, is therefore recommended for a duration of time post stent implantation. Bare metal stents may only need 1 mo of DAPT, but the traditional duration for DAPT is at least 12 mo following drug-eluting stent insertion for low bleeding risk patients with acute coronary syndrome (ACS), which is Class I and Level I evidence in European Society of Cardiology and American College of Cardiology/American Heart Association Guidelines, and at least 6 mo for patients with stable coronary disease or with high bleeding risk[1,2]. High bleeding risk is defined as an increase of spontaneous bleeding during DAPT, which can be objectively calculated through risk scores such as PRECISE-DAPT[3,4].

However, the duration of this period has constantly been a subject of research, which has been influenced by the development of different P2Y12 inhibitors, and evolution of drug eluting stents with different materials and anti-proliferative agent. The newer generation of stents have reduced the risk of late and very late stent thrombosis. This yields the question of whether the full period for DAPT is required and/or could it be shortened. Shortening DAPT will reduce the risk of bleeding, reduce patient noncompliance, and will be more cost effective.

This clinical review will examine the current generation of stents, and evidence for the shortened length of DAPT post stent implantation for acute coronary syndrome and stable coronary disease in the contemporary PCI era.

NEW GENERATION DES

A DES comprises 3 main components: the metallic platform, the polymer, and the anti-proliferative agent (Table 1)[5-19].

The metallic platform has a direct relationship with the dimensions of the stent. First-generation stents were constructed from stainless steel, but alloys such as cobalt-chromium, nickel-titanium, and platinum-chromium allow greater tensile strength with similar or reduced elasticity, allowing thinner struts[20]. Stainless steel stents normally have a strut of > 100 μm, but some of the newer second-generation stents such as the Orsino stent (60 μm), MiStent (64 μm), and BioMime (65 μm) are associated with 16% reduction in target lesion failure, and lower rates of any stent thrombosis in a meta-analysis of 10 trials[19]. Another meta-analysis of 69 trials comparing ultrathin (60-80 μm), thin (81-100 μm), intermediate (101-120 μm), and thick (≥ 120 μm) strut-thickness DES found that ultrathin devices had significantly less stent thrombosis (OR = 0.43, 95%CI: 0.27-0.68)[21].

Table 1 Current stents categorised by stent material, polymer, eluted drug, and shortened dual antiplatelet therapy duration validated for followed by aspirin or P2Y12 inhibitor monotherapy

Stent	Metallic platform	Polymer	Anti-proliferative agent	DAPT duration validated for	Ref.
Onyx Resolute	Cobalt-chromium (has a platinum iridium core)	Permanent	Zotarolimus	1 mo	[5,6]
BioFreedom	Stainless steel	Polymer-free	Biolimus	1 mo[1]	[7,8]
Biomatrix; Biomatrix Flex	Cobalt-chromium	Bioresorbable	Biolimus	Standard/no short DAPT	[9,10]
Nobori	Cobalt-chromium	Bioresorbable	Biolimus	6 mo	[11]
Xience	Cobalt-chromium	Permanent	Everolimus	1-3 mo[2]	[12,13]
EluNIR	Cobalt-chromium	Permanent	Ridaforolimus	Standard/no short DAPT	[14]
Ultimaster; Orsino	Cobalt-chromium	Permanent	Sirolimus	Standard/no short DAPT	[15,16]
Cre8	Cobalt-chromium	Polymer-free	Amphilimus	Standard/no short DAPT	[17]
Xposition S (self-apposing)	Nickel-titanium	Permanent	Silolimus	Standard/no short DAPT	[18]
Promus	Platinium-chromium	Bioresorbable	Everolimus	6 mo	[12]
Synergy	Platinium-chromium	Bioresorbable	Everolimus	3 mo[1]	[19]

If there was no randomised control trial or prospective trial with a paired control investigating dual antiplatelet therapy (DAPT) duration, DAPT duration validated for is put down as 'standard/no short DAPT.

[1]All trials examined both acute coronary syndrome and chronic coronary syndromes, though the EVOLVE Short DAPT study and the One-Month DAPT trial did not include patients with myocardial infarction.

[2]The STOPDAPT-2 trial examined 1-mo DAPT followed by P2Y12 inhibitor therapy. DAPT: Dual antiplatelet therapy.

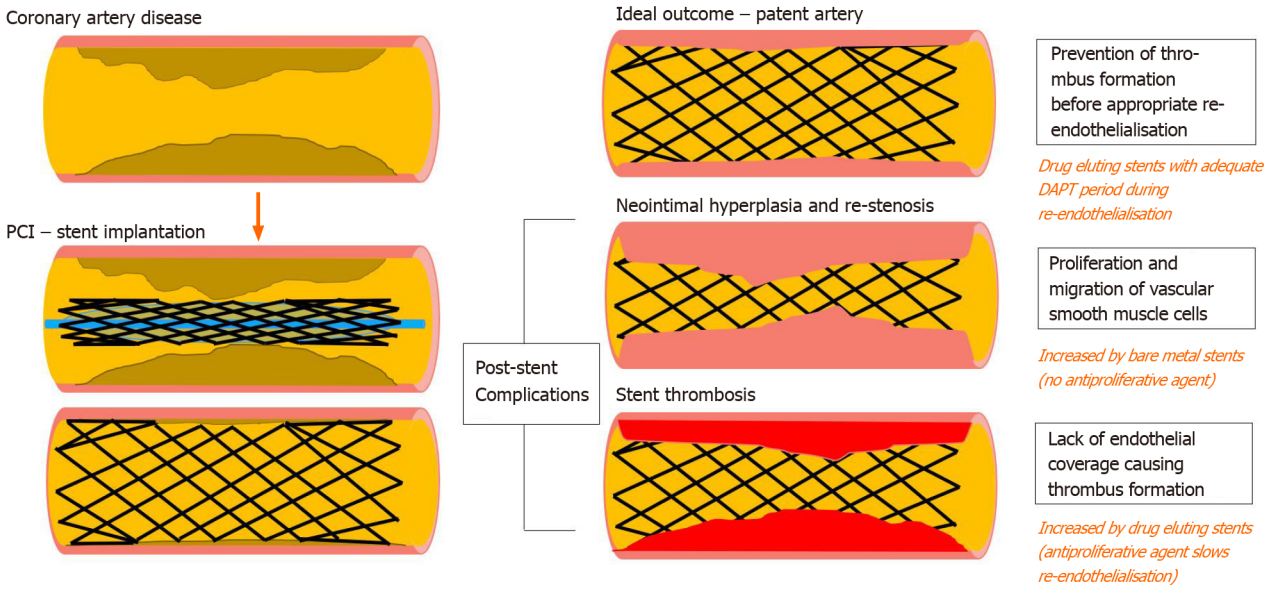


Figure 1 Percutaneous coronary intervention with stent implantation for coronary artery disease, and complications associated. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy.

Some stents have permanent or bioresorbable polymers which incorporate the anti-proliferative drug. Permanent polymers are non-biodegradable and allow continuous release of the drug. Bioresorbable polymers allow the effect of the drug to occur in the early phase of stent deployment and reverts to a bare metal stent once the polymer has become degraded, aiming to reduce very late stent thrombosis. The polymers used in first-generation stents were historically associated with delayed vascular healing and more very late stent thrombosis, but newer polymers are biocompatible. To avoid polymers entirely, some stents have the drug applied over the metallic platform of the

DES in micropores. Many network meta-analyses have found no significant difference in stent thrombosis, target lesion revascularisation, very-late stent thrombosis (defined as ≥ 1 year after implantation), or clinical outcomes between the use of different polymers independent of struct thickness and metallic platform[22,23].

The anti-proliferative drugs tend to be immunosuppressive agents, and the majority comprise sirolimus, everolimus, biolimus, and zotarolimus. Other drugs also used include amphilimus and ridaforolimus. A meta-analysis showed no difference in stent thrombosis between zotarolimus and everolimus stent[24]. However, the cobalt-chromium sirolimus stent Orsino appeared to have less stent thrombosis than the stainless-steel biolimus stent Nobori, though this may have been due to other confounding factors such as metallic platform and strut thickness, which has been previously shown to affect thrombosis[25].

Bioresorbable vascular scaffolds (BVS) are an alternative option which fully resorbs over time. However, they are less favoured in PCI currently due to association with increased risk of stent thrombosis and target lesion failure during the first 3 years after implantation and would therefore be less suitable for consideration for shortened DAPT duration[26].

As reducing strut thickness appears to be associated with less stent thrombosis, the development of the current generation of ultrathin DES with smaller strut thickness raises the question of whether shortened DAPT may be suitable in these patients.

DECREASING DAPT DURATION

The success of a PCI, stent and DAPT regimen is measured by outcomes including target lesion failure, target lesion revascularisation, major adverse cardiovascular events including stroke, myocardial infarction (MI) and cardiac death, stent thrombosis, and bleeding events measured through Thrombolysis in Myocardial Infarction (TIMI) or Bleeding Academic Research Consortium (BARC).

SHORTENED DAPT WITH NEWER GENERATION DES

A systematic review and network meta-analysis analysed 17 randomised control trials comparing at least 2 of the 3 durations of DAPT (short term < 6 mo, standard term 12 mo, and long term > 12 mo) post PCI for both ACS and chronic coronary syndrome with DES deployment, and determined that there were higher rates of major bleeding (OR = 1.78, 95%CI: 1.27-2.49) and non-cardiac death (OR = 1.63, 95%CI: 1.03-2.59) in those on long-term treatment, and higher rates of any bleeding (OR = 1.39, 95%CI: 1.01-1,92), and no significant difference in other primary endpoints[27]. Additionally, assessing the subgroup of patients with newer-second generation DES found longer term DAPT had higher bleeding events and all-cause mortality compared to short-term DAPT (OR = 1.99, 95%CI: 1.04-3.81), but had similar efficacy and safety[27].

EVIDENCE FOR SHORTENED DAPT DURATION FOR SPECIFIC STENTS

Single-arm prospective studies with paired control

It appears that shortened DAPT may be suitable for some of the new second-generation DES. The STOPDAPT single-arm study was the first prospective study to examine DAPT shorter than 6 mo for the everolimus-eluting cobalt-chromium stent (CoCr-EES). The study enrolled 1525 patients to 3 mo of DAPT followed by aspirin monotherapy after the XIENCE CoCr-EES and compared this to the CoCr-EES group in the RESET trial as a historical control, where 90% had DAPT at 12 mo. At 1 year, the primary endpoint of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and TIMI major/minor bleeding was less in the STOPDAPT than the RESET group (2.8% *vs* 4.0%, $P = 0.06$), and the incidence of stent thrombosis was lower in the STOPDAPT than in the RESET group (0% *vs* 0.3%, $P = 0.03$), suggesting that 3 mo was non-inferior to the historical control group[28].

The EVOLVE Short DAPT trial prospectively assessed the safety of 3-mo DAPT followed by aspirin monotherapy in high bleeding risk patients with the SYNERGY stent and compared this to a historical 12-mo DAPT control[19]. The primary results showed adjusted rate of death or MI in the following 3 to 15 mo was 5.6% in the 3-mo DAPT group, and 5.7% in the 12-mo control[19]. Unlike the other studies, this trial

excluded acute myocardial infarction and complex lesions.

Randomised control trials

The STOPDAPT-2 randomised clinical trial examined patients undergoing PCI with the Xience CoCr-EES and randomised them to 1-mo DAPT followed by clopidogrel against 12 mo of DAPT for 3045 patients. 1-mo DAPT was superior to 12-mo DAPT (2.36% *vs* 3.70%, hazard ratio 0.64, $P = 0.04$ for superiority), for the primary endpoint, which was a composite of cardiovascular death, myocardial infarction, stroke, definite stent thrombosis, or TIMI major/minor bleeding at 12 mo[29]. There was slightly increased stent thrombosis for 1-mo DAPT compared to 12-mo DAPT (0.3% *vs* 0.07%, $P = 0.21$ for superiority), but this was not statistically significant. 1-mo DAPT was shown to be superior with statistical significance in secondary outcomes such as TIMI major/minor bleeding and BARC 3 or 5 bleeding at 1 year.

Further studies have examined reducing this time further and using aspirin as monotherapy. The two DES with most evidence for 1-mo DAPT are the BioFreedom DES and the Resolute Onyx DES.

The LEADERS FREE I double-blinded randomised control trial examined 2466 patients with a high risk of bleeding and randomised them to the BioFreedom Biolimus polymer-free stent or the Gazelle uncoated BMS with only one month of DAPT. The BioFreedom DES was shown to be superior for the primary safety endpoint of cardiac death, myocardial infarction, or stent thrombosis, and superior for the efficacy endpoint, defined as clinically driven target-lesion revascularization[7]. This was the first time 1-mo DAPT was shown to be feasible in a DES and favourably compared to a BMS, though limitations are that BMS only has a small indication possibly in patients who need urgent surgery in < 1 mo after stenting[30].

A randomised control trial of 3020 patients compared the BioFreedom DES with short 1-mo DAPT followed by aspirin monotherapy against other DES (BioMatrix and Ultimaster) with 6-12 mo DAPT was presented at the American Heart Association Scientific Sessions 2020[8]. They examined a composite primary outcome of cardiac death, nonfatal MI, target vessel revascularisation, cerebrovascular attack, or major bleeding. There was no difference in the BioFreedom short DAPT arm compared to the contemporary DES treatment arm (5.9% *vs* 6.5%, p for noninferiority < 0.001, P for superiority 0.475). There was no statistical difference in the individual components of the composite. This included patients with and without a high bleeding risk, but did not include patients with myocardial infarction. However, an intention-to-treat analysis was used for this study, and 17% of patient remained on DAPT at 1.5 mo. Additionally, the DES that BioFreedom was compared to had not been given FDA approval for use, so the comparison group was not the current best available therapy.

The ONYX ONE Global trial randomised 1996 patients to the BioFreedom DES and the Resolute zotarolimus-eluting Onyx DES, both with 1-mo DAPT followed by single antiplatelet therapy with aspirin or P2Y12 inhibitor. Inclusion criteria were those with high bleeding risk (adjunctive oral anticoagulation to continue after PCI, age ≥ 75, baseline haemoglobin < 110 g/L, previous intracerebral bleed, stroke in the last 12 mo, hospital admission for bleeding during the last 12 mo, nonskin cancer diagnosed or treated ≤ 3 years, planned daily NSAID or steroids for ≥ 30 d after PCI, planned surgery that would require interruption of DAPT within the next 12 mo, renal failure CrCl < 40 mL/min, thrombocytopenia < 100000/mm^3, severe chronic liver disease, expected noncompliance to prolonged DAPT). 51% of these had acute coronary syndrome, and 32% had atrial fibrillation. They found no significant difference between Resolute and BioFreedom in primary outcomes of composite cardiac death/myocardial infarction/stent thrombosis (17.1% *vs* 16.9% $P = 0.011$ noninferiority, $P = 0.84$ superiority). The myocardial infarction rate was very high in both Resolute and BioFreedom (13.4% *vs* 14.7%), which may represent the high-risk population, but the lack of a comparison with a 3 to 6-mo DAPT regimen means this cannot be completely separated from the use of 1-mo DAPT. Additionally, BARC 2-5 bleeding was high in both groups, reflecting the high bleeding risk inclusion criteria, being slightly higher in the Resolute group but not statistically significant (15.1% *vs* 13.7%, $P = 0.4$)[5]. The Onyx One Clear Study complemented this by examining 1506 patients who had DAPT adherence and without major adverse events during the first month and found the primary endpoint of cardiac death or myocardial infarction at 1 year at be 7.0%. The Resolute Onyx DES therefore became the first 1-mo DAPT indication for high bleeding risk patients in Europe, and was FDA approved for use in the United States[6].

Observational studies

There appear to be some observational studies with evidence for shortened DAPT. The Ultimaster stent had similar rates of a composite measure of target lesion vascularisation, cardiac death, and MI for 6-mo and 12-mo DAPT in an observational study [15]. Similarly, for the Cre8 stent, an observational study showed no significant difference between patients discharged with ≤ 3-mo DAPT due to high bleeding risk or urgent non-cardiac surgery and regular DAPT duration ≥ 6 mo for a composite endpoint of target vessel revascularisation, cardiac death, and MI[17]. Although this does show the real-world feasibility of shortened DAPT for this population of patients, the lack of a randomised control means that there is limited information for the direct comparison of DAPT duration.

Planned studies and future directions

EXCELLENT was a randomised control trial examining 6-mo DAPT compared to standard 12-mo DAPT in 1443 patients with the XIENCE/Promus everolimus stent which demonstrated non-inferiority for target vessel failure[11]. However, stent thrombosis appeared to occur more, and the study appeared underpowered for death and myocardial infarction. The XIENCE Short DAPT Program was announced in 2020, consisting of a series of 3 single-arm trials investigating 3-mo and 1-mo duration in patients undergoing PCI with XIENCE compared with historical controls[12].

Similarly, the prospective multicentre REIWA registry was announced in 2020 to investigate very short DAPT for patients with biodegradable polymer DES, such as the Synergy, Ultimaster, or Orsino. It will investigate the safety and feasibility of 1-mo DAPT followed by P2Y12 inhibitor monotherapy, much like the STOPDAPT-2 trial, but this time on bioresorbable-polymer DES rather than permanent-polymer DES[31].

Further focus could examine the use of P2Y12 inhibitor monotherapy for these stents, as this has been proved useful in the STOPDAPT-2 randomised clinical trial, or trials focusing on purely aspirin, unlike the ONYX ONE global trial. As well as clopidogrel monotherapy, ticagrelor monotherapy has also been investigated, where high-risk patients with PCI and 3-mo of DAPT continued with ticagrelor and were randomised to aspirin or placebo for one year. This showed death from any cause, MI, or stroke was 3.9% in both groups, but the 3-mo group had a lower incidence of clinically significant bleeding, warrant this as an area for further research[32]. A direct comparison of DAPT lengths between groups of 1-mo *vs* 3-mo and 6-mo DAPT can be carried out and keeping the stent type constant. Very short DAPT can be assessed in specific non-high bleeding risk patient groups to broaden the population validated for (Table 2).

DAPT DURATION DETERMINED BY SECONDARY PREVENTION OF SYSTEMIC CARDIOVASCULAR DISEASE

Although the characteristics of the newer generation of stents may be associated with the feasibility of shortened DAPT to reduce local stent thrombosis, it may be balanced out by the effect of DAPT on secondary prevention of systemic thrombosis and major adverse cardiovascular events. The PEGASUS-TIMI 54 randomised control trial examined patients ≥ 50 years old with at least one additional high-risk feature and spontaneous MI 1-3 years before enrolment. These included ≥ 65 years, diabetes mellitus, second myocardial infarction, multivessel disease, or chronic renal dysfunction. 60mg ticagrelor twice a day had marginally higher absolute benefit in terms of the primary efficacy endpoint than the absolute harm in the primary safety endpoint[33]. The DAPT trial compared 12 mo of DAPT with 30 mo of DAPT and showed an absolute risk reduction in the primary efficacy end point of the composite of death, MI, and stroke by 1.6%, and stent thrombosis by 1%[34].

A meta-analysis which included PEGASUS along with other studies with clopidogrel and prasugrel found prolonged DAPT decreased major adverse cardiac events and cardiovascular deaths compared with aspirin, but it was associated with a significant risk of bleeding, and no difference in all-cause mortality[35]. However, the efficacy may have been underestimated by PEGASUS, which allowed patients who had been off DAPT for several years to restart therapy. European and American guidelines therefore recommend consideration of prolonged DAPT in patients at low risk of bleeding with class IIb evidence[1-3].

Table 2 Summary of evidence of shortened dual antiplatelet therapy duration for specific stents from randomised control trials and single-arm prospective studies with a historical control

	Population	Study	Intervention	Control	Primary endpoint
Single-arm study	ACS (32%) and CCS (68%)	STOPDAPT [28]	1525 patients, XIENCE CoCr-EES with 3-mo DAPT followed by aspirin monotherapy	1559 patients, Endeavor CoCr-EES approximately 90% with 1-yr DAPT followed by aspirin monotherapy (RESET trial)	12-mo cardiovascular death, MI, stroke, thrombosis, bleeding; 2.8% *vs* 4.0% (P = 0.06)
	No acute myocardial infarction, High bleeding risk	EVOLVE Short DAPT[19]	1487 patients, SYNERGY stent with 3-mo DAPT followed by aspirin monotherapy	1493 patients, 1-year DAPT	3-15 mo death or MI; 5.6% *vs* 5.7% (P = 0.0016 non-inferiority)
RCT	ACS (38%) and CCS (62%)	STOPDAPT-2 [29]	1523 patients, XIENCE CoCr-EES with 1-mo DAPT followed by clopidogrel monotherapy	1522 patients, XIENCE CoCr-EES with 12-mo DAPT	12-mo Cardiovascular death, MI, stroke, thrombosis, bleeding; 2.36% *vs* 3.70% (superiority P = 0.04)
	ACS (42%) and CCS (58%); High bleeding risk	LEADERS FREE I[7]	1196 patients, BioFreedom DES with 1-month DAPT followed by one antiplatelet	1189 patients, Gazelle uncoated BMS with 1-month DAPT followed by one antiplatelet	390 d cardiovascular death, MI, stent thrombosis 9.4% *vs* 12.9% (P = 0.005 superiority)
	No acute myocardial infarction	One-month DAPT trial[8]	1507 patients, BioFreedom DES with 1-mo DAPT followed by aspirin monotherapy	1513 patients, BioMatrix and Ultimaster DES with 6-12 mo DAPT	12-mo cardiovascular death, MI, target vessel revascularization, stroke, major bleeding; 5.9% *vs* 6.5% (noninferority P < 0.001)
	ACS (62%) and CCS (38%)High bleeding risk	ONXY ONE Global[5]	1003 patients, Resolute Onyx DES with 1-mo DAPT followed by one antiplatelet	993 patients, BioFreedom DES with 1-mo DAPT followed by one antiplatelet	Cardiac death, MI, thrombosis 17.1% *vs* 16.9% (P = 0.011 noninferiority)

ACS: Acute coronary syndrome; DAPT: Dual antiplatelet therapy; CoCr-EES: Everolimus-eluting cobalt-chromium stent; DES: Drug-eluting stents; MI: Myocardial infarction.

PERSONALIZED ASSESSMENT OF DAPT DURATION

With the development of risk stratification and personalised medicine, DAPT duration will also be influenced by patient factors. The PRECISE-DAPT score is used at the time of stenting to determine whether the patient may benefit from 3-6 mo short DAPT or 12-24 mo standard/DAPT, and the DAPT score is used after 12 mo of DAPT to determine whether DAPT can be stopped, or if the patient should continue it to 30 mo. The PRECISE-DAPT score uses factors such as Hb, WBC, age, creatinine clearance, and prior bleeding[4]. The DAPT score uses patient factors such as age, smoking, diabetes mellitus, previous stenting or myocardial infarction, but also disease factors such as stent characteristics (diameter, paclitaxel, vein graft stent), left ventricular ejection faction, myocardial infarction at presentation[36]. A further risk scoring model was generated from the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) registry, which calculates a risk score for both ischaemia and major bleeding at 24 mo post PCI to inform decision-making[37]. The coronary thrombotic events score used the factors of diabetes mellitus, ACS, smoking, renal function, previous PCI, and previous CABG. The bleeding events score used the factors of age, body mass index, smoking, anaemia, renal function, and triple therapy on discharge [37]. However, these have not been prospectively validated in a randomised control trial. The approval of the Onyx DES indicated for high bleeding risk patients is a step towards the personalised assessment of DAPT duration, and future research will focus on further parameters and patient stratification to identify individuals which may benefit from very short DAPT.

CONCLUSION

The period of DAPT following PCI is an area of research which has been increasingly focused on with the current cohort of contemporary DES. New stents such as the Orsino, MiStent, and BioMime are associated with thinner struts which are generally associated with less late thrombosis and may be suitable for shortened DAPT. This has been supported by a network meta-analysis which demonstrated less all-cause mortality for shortened DAPT duration (3-6 mo) compared to standard DAPT duration in the subgroup of patients with newer second-generation DES.

The STOPDAPT and STOPDAPT-2 trials directly examined the feasibility of shortened DAPT duration of less than 6 mo with CoCr-EES. STOPDAPT showed no significant difference in primary outcomes of bleeding, stent thrombosis, cardiovascular death or myocardial infarction between 3-mo DAPT followed by aspirin monotherapy against 6-12 mo DAPT, and STOPDAPT-2 showed superiority of 1-mo DAPT followed by clopidogrel monotherapy against 6-12 mo DAPT for the same composite outcome but including stroke. These are two studies which have allowed a direct comparison of DAPT timings within the same type of DES.

Some patients may benefit from shortened DAPT more due to their high bleeding risk or need to be on monotherapy by a certain point. These are patients who may have coagulation abnormalities, previous significant bleeding, recent malignancy, severe kidney or liver dysfunction, or are due to undergo timely surgical procedures. Assessing this patient subgroup for shortened DAPT trials may show greater benefit in terms of composite outcome of stent thrombosis, bleeding, cardiovascular death or myocardial infarction. The Resolute Onyx DES was tested in this population and has subsequently received a 1-mo DAPT indication in Europe and the United States. The BioFreedom DES was tested in patients both with and without a high bleeding risk. However, the limitation of these trials was the comparison against DES which were not currently licensed or standard management. Future research should focus on comparison against contemporary DES representative of current therapy, and direct comparison of DAPT duration for the same stent. There are currently registries and trials undergoing for the XIENCE, Synergy, Orsino, and Ultimaster stent, allowing direct comparison of DAPT duration in the same stent.

In addition to local effects to prevent stent thrombosis, recent evidence suggests that DAPT is useful for secondary prevention of systemic thrombosis and preventing future major adverse cardiovascular events, especially in patients with high-risk features such as diabetes mellitus, a second myocardial infarction, or multivessel disease. European Society of Cardiology and American College of Cardiology/American Heart Association guidelines support the consideration of extended DAPT for these patients.

Therefore, we are gradually moving from a "one size fits all approach" towards an era of personalised medicine where different parameters are identified to guide DAPT duration, which is reflected in current international guidelines. The development of risk scores to guide DAPT duration reflects this shift, but these remain to be clinically validated.

The contemporary PCI era brings a new generation of stents which may be beneficial, some of which are validated for shortened DAPT especially in patients with high bleeding risk. Further research is required to assess which other patient groups may benefit from this shortened DAPT approach, and balance this against the patient groups which may benefit from systemic antiplatelet therapy.

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EVIDENCE REVIEW

Multimodality imaging in the diagnosis and management of prosthetic valve endocarditis: A contemporary narrative review

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Abstract

Infective endocarditis is one of the leading life-threatening infections around the world. With the exponential growth in the field of transcatheter interventions and advances in specialized surgical techniques, the number of prosthetic valves and cardiac implantable devices has significantly increased. This has led to a steep rise in the number of cases of prosthetic valve endocarditis (PVE) comprising up to 30% of all cases. Clinical guidelines rely on the use of the modified Duke criteria; however, the diagnostic sensitivity of the modified Duke criteria is reduced in the context of PVE. This is in part attributed to prosthesis related artifact which greatly affects the ability of echocardiography to detect early infective changes related to PVE in certain cases. There has been increasing recognition of the roles of complementary imaging modalities and updates in international society recommendations. Prompt diagnosis and treatment can prevent the devastating consequences of this condition. Imaging modalities such as cardiac computed tomography and ^{18}-fluorodeoxyglucose positron emission tomography/computed tomography are diagnostic tools that provide a complementary role to echocardiography in aiding diagnosis, pre-operative planning, and treatment decision-making process in these challenging cases. Understanding the strengths and limitations of these adjuvant imaging modalities is crucial for the implementation

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of appropriate imaging modalities in clinical practice.

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Core Tip: Prosthetic valve endocarditis comprises up to 30% of all cases of infective endocarditis with a reported in-hospital mortality of 14%-22% and 1-year mortality as high as 40%. Its prompt diagnosis, although often challenging, is of critical importance to prevent deleterious consequences for patients. Advances in the field of 3-dimensional-echocardiography and the increased applications of adjuvant, complementary imaging modalities, including ^{18}-fluorodeoxyglucose positron emission tomography/computed tomography, have enhanced the diagnostic accuracy. In the present narrative review, we discuss the epidemiology, clinical manifestations, management principles, and advantages and limitations of various imaging modalities available for the diagnosis and management of prosthetic valve endocarditis.

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INTRODUCTION

Infective endocarditis (IE) is the third most common life-threatening infection in the world with a reported in-hospital mortality as high as 14%-22% and 1-year mortality of up to 40%[1]. The volume of prosthetic valve replacement procedures has dramatically increased over the last decades[2]. This has led to an increase in the incidence of prosthetic valve endocarditis (PVE), accounting for 20% to 30% of all cases of IE[2-4]. Traditionally, the diagnosis of IE is based on the modified Duke Criteria which relies on echocardiography[5]. Initially, transthoracic echocardiography (TTE) is utilized to assess for PVE; however, due to technical limitations and acoustic shadowing, transesophageal echocardiogram (TEE) is generally mandated when it is difficult to evaluate the prosthetic structures or the clinical suspicious remains high despite an apparently unremarkable TTE, according to the contemporary guidelines from the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology guidelines (AHA/ACC)[3,5,6]. In cases where TEE yields a negative result and clinical concern persists, guidelines recommend to either repeat the study in 3-7 days or to complement the evaluation with an alternative imaging modality such as 18-fluorodeoxyglucose photon emission tomography/computed tomography (PET/CT ^{18}F-FDG) or cardiac computed tomography (CCT)[3,5,6]. Although TEE has generally good diagnostic performance, it is limited by prosthetic material-related artifacts, and certain complications of PVE, such as abscesses and pseudoaneurysms may be missed in some cases by TEE[7].

Patients with PVE are at a higher risk of developing complications and worse outcomes when compared with native valve endocarditis (NVE) patients, even when the causative organism are similar[3,8]. Therefore, it is of uttermost importance to accurately diagnose this condition and institute prompt treatment to ameliorate its deleterious consequences. There has been increased recognition of the pivotal role of multimodality imaging in the diagnosis and treatment of PVE[9,10]. The purpose of this narrative review is to focus on the diagnosis of PVE with a special emphasis on the emerging complementary use of multimodality imaging modalities.

EPIDEMIOLOGY

The incidence of PVE ranges between 1% to 4% in the first year after surgery followed by approximately 1% per year thereafter[11]. The risk of developing PVE is higher within the first 5-years post-surgery (1.4% to 5.7%), and half of the patients with PVE develop a prosthetic valve abscess and pseudoaneurysm, which are associated with increased mortality of 30%-54%[7,12,13]. The reported incidence of PVE is heterogeneous, reflecting valve-related, patient, and geographical factors.

Valve-related factors

In a study from the Danish national registry of 18041 patients, the overall incidence of PVE was 69.8/10000 person years in patients undergoing surgical valve replacement [14]. When examined based on the anatomical location, the incidence was 65/10000 person years for mitral valve replacement (MVR), 70/10000 person years for aortic valve replacement (AVR), which increased to 89.4/10000 person years when both mitral and aortic valves were replaced[14]. Despite this difference, the cumulative incidence of PVE at 10-years was similar for both MVR and AVR (5.2%)[14].

PVE comprises 11% of all cases of tricuspid valve endocarditis and 43% of all cases of pulmonary valve endocarditis (Figure 1)[15]. In a cohort of congenital heart disease patients, 924 surgical pulmonic valve replacement were performed with 19 (2%) cases attributed to PVE, corresponding to an incidence of 333/100000 person years[16]. A large single-center cohort of 2124 adult patients (median age 41.5 years) with IE reported 24 cases of pulmonary valve endocarditis, of which 54.2% of cases occurred in the context of prosthetic valves[17].

PVE is also a feared complication in transcatheter aortic valve replacement (TAVR) [18]. In a meta-analysis by Ando *et al*[19] in 3761 patients undergoing percutaneous or surgical AVR (SAVR), the overall incidence of PVE was not significantly different between TAVR and SAVR at 1, 2 and 3.4 years follow-up[19]. Over this period of time, there was a trend towards a higher incidence of PVE in the TAVR group (0.86% to 2%) compared to the SAVR group (0.73% to 1.3%), and this was enhanced in patients with intermediate surgical risk [2.3% *vs* 1.2%; odds ratio (OR) = 1.92, 95% confidence intervals (CI): 0.99 to 3.72, P = 0.05]. In the Nordic Aortic Valve Intervention (NOTION) trial, 280 Low-surgical risk patients with severe aortic stenosis were randomized to TAVR (self-expanding CoreValve) or SAVR (stented bioprosthesis) [20]. This trial showed a non-significant difference in the 5 year-cumulative incidence of PVE between these two approaches (6.2% for TAVR *vs* 4.4% SAVR)[20]. Similar results were reported by Summer *et al*[21], in a pooled cohort of all patients from PARTNER I and PARTNER II trials (8530 patients, 107 cases of PVE), where the incidence over time of PVE was similar for TAVR [5.21 PVE per 1000 person-years (95%CI: 4.26–6.38)] and for SAVR [4.10 per 1000 person-years (95%CI: 2.33–7.22); incident rate ratio, 1.27 (95%CI: 0.70–2.32); P = 0.44][21]. Ando *et al*[19] also reported a subgroup analysis in TAVR patients which demonstrated comparable risk between balloon-expandable valves (BEV) and self-expandable valves (SEV)[19]. Similar findings were described by Regueiro *et al*[22] in a cohort of 6363 patients undergoing TAVR, where the incidence of PVE at 1-year did not significantly differ (0.95% SEV *vs* 1.25% BEV; P = 0.33)[22]. When other complications were analyzed, the rate of systemic stroke and embolism was higher in patients with BEV (8.7% *vs* 20.0% adjusted OR = 2.46, 95%CI: 1.04–5.82, P = 0.04)[22].

Furthermore, percutaneous edge to edge mitral valve repair is an increasingly relevant transcatheter intervention, where post clip implantation endocarditis has been described only in case reports, remaining an extremely rare presentation[23].

In terms of the type of valve prosthesis, the Danish National Registry demonstrated in 18041 patients undergoing left-sided valve replacement that the use of bioprosthetic valves was associated with an increased risk for prosthetic infection in patient undergoing either MVR (HR = 1.91, 95%CI: 1.08–3.37) or AVR (HR = 1.70, 95%CI: 1.35–2.15) over 10 years follow-up[14]. These results were similar to those reported by Brennan *et al*[24] in a large cohort of patients undergoing SAVR (bioprosthetic = 24410; and mechanical = 14789) followed up for 12 years where the risk of PVE was higher in those patients undergoing bioprosthetic valve replacement (HR = 1.60; 95%CI: 1.31–1.94). However, a limitation of these studies was their retrospective nature [14, 24]. Conflicting evidence arises from 3 randomized clinical trials, comprising a total of 40207 patients that underwent left sided valve replacement, which showed no significant difference between bioprosthetic and mechanical prosthesis [22-24]. A major limitation of these trials is the lack of power to detect meaningful differences since IE was not specified as a major endpoint[25-27].

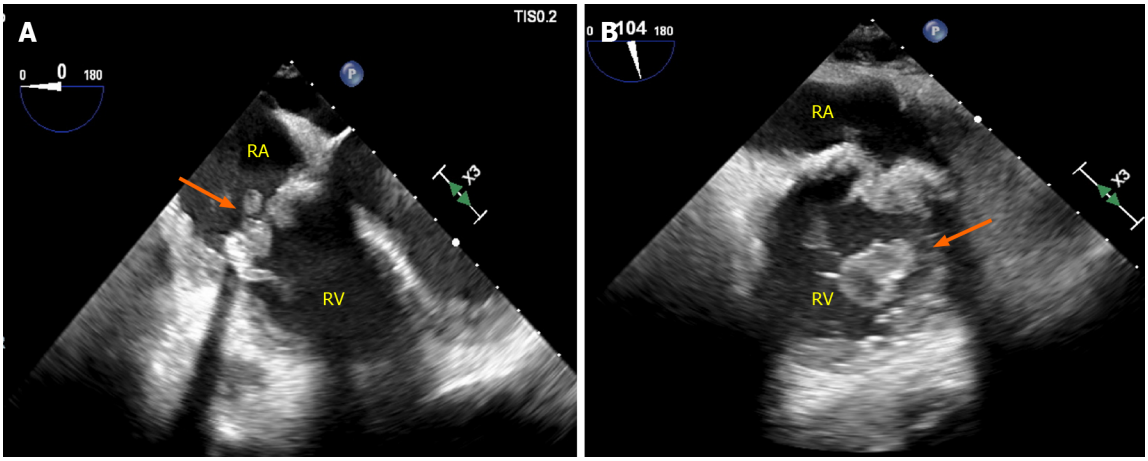


Figure 1 Prosthetic valve endocarditis complicating prior bioprosthetic tricuspid valve replacement secondary to intravenous drug abuse relapse. Thirty-two year-old male with a history of intravenous drug abuse status post bioprosthetic tricuspid valve replacement presenting with methicillin-sensitive Staphylococcus Aureus prosthetic valve endocarditis due to relapsed drug abuse. Images from Panel A and B demonstrate a tricuspid valve prosthesis at mid esophageal 4 chamber right ventricular focused (A) and modified bicaval views (B) with severe thickening and attached vegetations on both sides of the valve. RA: Right atrium; RV: Right ventricle.

Patient factors

There is conflicting data regarding the age group most susceptible to develop PVE. In the Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES) Database registry, which included 3120 patients with IE, patients 65-79 years old (elderly) had a significantly higher incidence of PVE compared with those < 65 years (young) and ≥ 80 years old (octogenarian) (37.3% *vs* 24.4% and 26.3%, respectively, $P < 0.001$)[28]. This observation was also demonstrated by López *et al*[29], studying a cohort of 600 Left-sided IE patients 40% of whom had PVE, showing a similar age distribution[29]. In contrast, a smaller observational study of 72 patients with IE by Menchi-Elanzi *et al*[30] demonstrated that elderly patients (65-79 years old) had a significantly lower prevalence of PVE compared to the young and octogenarians[30].

In patients with PVE, there is male predominance with 3:1 ratio across various studies[14,28-30]. This ratio changes towards 1:1 in the octogenarian group[28-30]. Interestingly, in an observational study of 621 patients with left-sided IE, mitral mechanical valve PVE was more common in women than in men[31]. The mechanism behind these findings remain unclear, and further studies are required to examine the age and gender influence on PVE.

Geographical factors

In an observational, prospective multicenter cohort of 2670 patients from 28 countries with IE, 556 patients (20.1%) had PVE[1].The highest percentage of PVE cases was in Southern Europe, Middle East and South Africa (26.10%), and it was the lowest in South America (11.9%)[2]. In the United States, the incidence of PVE was 20.9%, with the highest source corresponding to health care associated infections (44.8%), followed by intravascular device-related infection (27.6%), non-nosocomial heath care-associated PVE (21.1%), and hemodialysis (12.9%)[2].

CAUSATIVE AGENTS

The prevalence of the most common causative organisms causing PVE according to the timing and technique of valve surgery are shown in Figure 2. Within 60 days from surgical valve replacement, the most common causative organism of PVE is Staphylococcus Aureus (30%) followed by Streptococcus species (28%). Between 2 to 12 months after surgery, coagulase-negative Staphylococci are the most common organism (36%), and after one year, Streptococci predominantly viridians group, are the leading cause [2,32-35]. After TAVR, Enterococci and Staphylococcus Aureus (25% and 16%-24%, respectively) are the predominant organisms (Figure 2)[36,37].

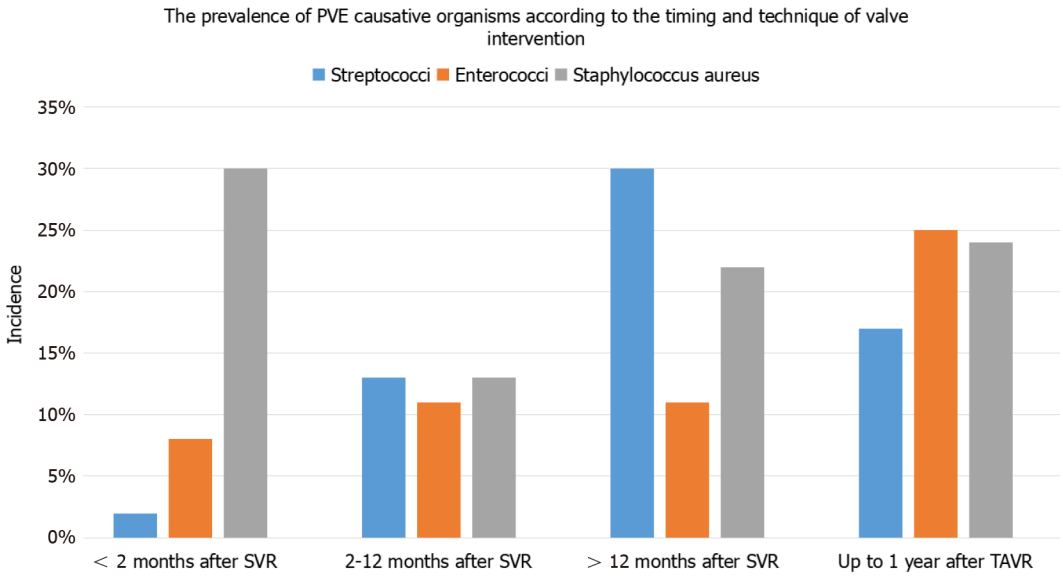


Figure 2 Prevalence of causative organisms according to timing and technique of valve intervention. The prevalence of causative organisms of prosthetic valve endocaridits in surgical left-sided valve replacement among 579 patients pooled from 5 studies[2,32-34,79] and transcatheter aortic valve replacement among 275 patients from 2 studies[35,36], categorized according to time since the index procedure. PVE: Prosthetic valve endocarditis; SVR: Surgical valve replacement; TAVR: transcatheter aortic valve replacement.

CLINICAL FEATURES

The clinical diagnosis of PVE is challenging as patients often manifest non-specific symptoms, such as fever, weakness and poor appetite in the early post-operative period[38]. Therefore, the presence of a new murmur, new or worsening congestive heart failure (CHF), conduction abnormalities and stroke should all raise suspicion for PVE[38]. Data from the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (PCS) reported the occurrence of CHF in 32.9%, intra-cardiac abscess in 29.7%, stroke in 18.2% and other systemic embolization in 14.9%, among 556 patients with PVE[2]. When comparing NVE and PVE, both had a similar incidence of CHF, stroke and persistent bacteremia; however, the incidence of systemic embolization was lower in PVE[2].

From the TAVR international registry consisting of 245 patients who developed PVE after TAVR (BEV and SEV), the most common initial symptom was fever (approximately 80%), followed by CHF (approximately 40%), and cutaneous manifestations (approximately 3%) with a median time to onset after TAVR of 5.3-5.5 months[22]. In this study, stroke was significantly higher with BEV compared to SEV (24.6% *vs* 7.8%, $P < 0.01$)[22]. The lower rate of cutaneous manifestations in PVE, such as Osler's nodes, Janeway lesions and Roth's spots could be attributed to a more acute course of the disease in PVE, compared to a more protracted course commonly seen in NVE[38]. In Reguiero's cohort, patients with PVE following TAVR had no significant difference in mortality between BEV and SEV (37% *vs* 36%, respectively)[22].

In terms of mortality, Wang *et al*[2], described in-hospital mortality was significantly higher in the PVE group (127/556 patients) compared to NVE (310/1895 patients) (23% *vs* 16%, $P < 0.001$). After multivariate analysis, the key drivers of increased mortality were CHF (OR = 2.33, 95%CI: 1.62-3.34), intracardiac abscess (OR = 1.86, 95%CI: 1.10-3.15), and stroke (OR = 2.25, 95%CI: 1.25-4.03). Østergaard *et al*[14] in a cohort of 18,041 undergoing left sided valve replacement (AVR 88.8%, MVR 9.7%, and both 1.5%) demonstrated that PVE in AVR patients was associated with higher mortality than in MVR at 10 years (44% *vs* 39%, $P < 0.01$)[14]. Moreover, they also divided these results according to the prosthesis type showing a significantly higher mortality with bioprosthetic compared to mechanical valve in both AVR and MVR at 10-years. However, when both groups were matched, there was no significant difference in mortality[14].

DIAGNOSTIC IMAGING MODALITIES

Transthoracic and transesophageal echocardiography

Although acoustic shadowing and reverberation artifacts from prosthetic material hamper the imaging resolution, echocardiography remains the forefront diagnostic modality in suspected PVE[5]. Wide availability, low cost, rapid acquisition and interpretation, and a lack of radiation are some of the important qualities that make echocardiography the first-line imaging modality[6]. The echocardiographic examination should focus on identifying infection-related changes, such as vegetations, perivalvular abscess, prosthesis dysfunction or dehiscence, fistulas, or unexpected and premature structural degeneration of the valves[3] (Figure 3).

The sensitivity of TTE in PVE ranges from 17% to 36%; in comparison, it increases to 82% to 96% with TEE, suggesting the importance of TEE for better assessment of all cases of suspected PVE[39,40]. Despite the enhanced temporal and spatial resolution of multiplanar TEE, its ability to identify prosthetic valve abnormalities can be challenging[41]. Another commonly encountered limitation is an inability of echocardiography to differentiate between active and healed vegetations following antibiotic treatment. To overcome this limitation, serial studies are required to assess for size progression of the vegetation[41].

Three-dimensional (3D) echocardiography is a complementary modality which provides valuable information regarding the anatomy of the prosthetic valves and adjacent structures from different angles. Novel 3D-rendering software aid in the characterization of the vegetation size and location, destructive changes, perforations, abscess characterization, prosthetic dehiscence and associated regurgitant jets[42-44]. Chahine *et al*[45] described in 242 patients, an improved sensitivity over the recent decade for the detection of PVE (70.8% *vs* 93.7%, $P = 0.009$) with contemporary TEE technology including an increased use of 3D imaging (Figure 4)[45].

Echocardiography has been shown to predict outcomes in PVE. Wang *et al*[46] studied 115 patients with surgically proven IE (52% with bioprosthetic valves; 15.5% with metallic valves) and recognized that abscess or pseudoaneurysm detected by TEE were independently associated with increased in-hospital mortality and morbidity [OR: 3.66 (95%CI: 1.76–7.59); $P = 0.001$][46].

In cases where the clinical suspicion remains high despite an initial negative result, short-term interval follow-up is a strategy that can enhance imaging sensitivity at the expense of prolonging the time to diagnosis. This can usually be performed 3-7 days following the initial evaluation[3]. In contrast to this "watch and wait approach", adjuvant imaging modalities play a complementary role in the diagnosis of PVE, potentially expediting patient care[7].

CCT

CCT has become an increasingly important imaging tool for the diagnosis and preoperative planning of patients with PVE. CCT offers a number of technical advantages over echocardiography including higher spatial resolution and imaging window independence[47]. CCT has demonstrated similar diagnostic yield for the detection of perivalvular complication[7]. Feutcher *et al*[47] compared CCT with TEE in 37 patients with IE, 6 of whom had PVE. The study showed that CCT had an excellent correlation with TEE in determining vegetation size (vegetation size by TEE 7.6 ± 5.6 mm) ($r = 0.95$; $P < 0.001$). In addition, vegetation mobility was accurately diagnosed by CCT in 96% of the patients, and both modalities had similar detection rates for abscesses and pseudoaneurysms with the caveat that CCT provided more detailed anatomical location and extension[47]. Fagman *et al*[48] compared ECG-gated CT and TEE with surgical findings including abscess, vegetation, and dehiscence in 27 patients with aortic PVE. The agreement was good between surgical findings and ECG-gated CCT (kappa 0.66, 95%CI: 0.49–0.87) and TEE [0.79 (0.62–0.96)], but the combination of both TEE and ECG Gated CCT provided even better diagnostic performance [0.88 (0.74–1.0)][48]. In a more recent study by Koneru *et al*[49] in 122 patients with PVE undergoing pre-operative evaluation, the performance of high-resolution ECG synchronized 4D-CT was similar to TEE for the detection of abscess/pseudoaneurysm in prosthetic valves, independent of the type of prosthesis (70 *vs* 68 %; $P = 0.82$) and anatomical location with a synergistic effect seen when both modalities were combined (sensitivity: CT alone, 70%; TEE alone, 68%; CT + TEE, 86%)[49]. This incremental benefit of combining both modalities for PVE assessment was also described in a metanalysis by Habets *et al*[40] who reported a pooled sensitivity/specificity of 36/93% for TEE, 86/98% for CCT, and 100/94% for both modalities together. The authors also described improved detection of peri-annular PVE complic-

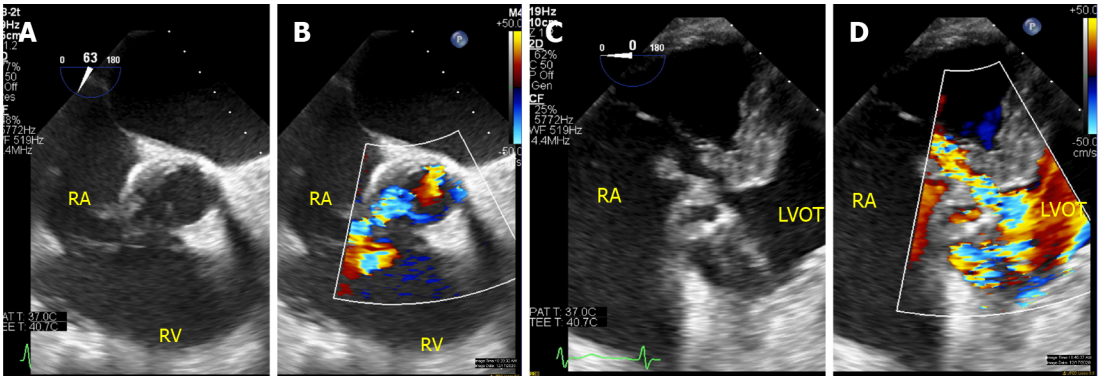


Figure 3 Para-valvular fistula in a patient with complicated endocarditis involving prior stentless aortic valve. Eighty-two year-old male with a history of coronary artery bypass grafts and stentless aortic valve replacement presenting with Streptococcus Gallolyticus prosthetic valve endocarditis complicated by aortic root abscess and fistulous tract treated with homograft aortic root replacement (25 mm Cryo-Life aortic allograft root), bovine pericardial closure of aortic root to right atrium fistula, right atrium reconstruction with bovine patch and bypass revision. A and B: TEE interrogating the aortic valve replacement with color compare demonstrated thickening of the leaflets and abnormal color flow into the right atrium; C and D: Additional imaging from deep transgastric views with color compare in the left ventricular outflow tract demonstrated a complex fistulous tract (Gerbode-type defect) communicating the left ventricular outflow track, right atrium and aortic root. RA: Right atrium; RV: Right ventricle; LVOT: Left ventricular outflow tract.

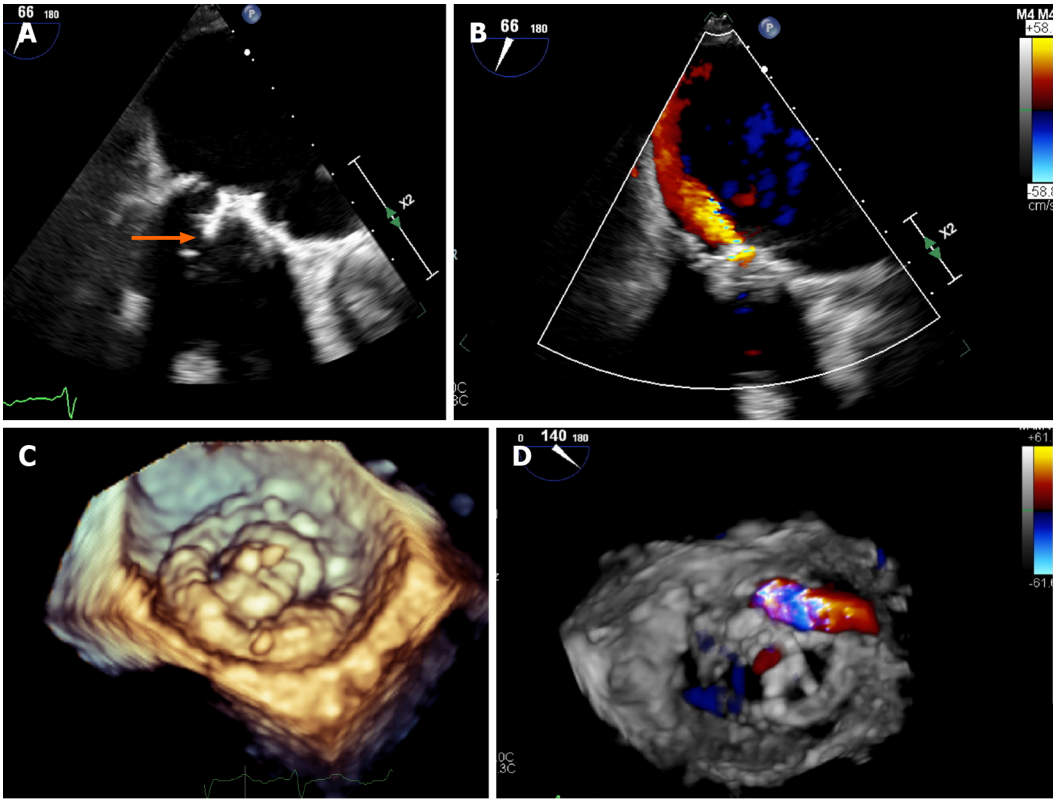


Figure 4 Transesophageal echocardiogram in a patient with mitral valve replacement endocarditis with 3D-reconstruction. Sixty-six year-old male with a history of coronary artery bypass graft and mitral valve replacement three years before presenting with Enterococcus Faecalis endocarditis. Transesophageal echocardiogram demonstrated severe structural degeneration of the mitral valve replacement with attached vegetation (A: Arrow). Color Doppler analysis demonstrated a large jet arising from the leaflet body consistent with prosthetic leaflet perforation confirmed by 3D-reconstruction (B-D).

ations with CT scan, especially when occurring towards the anterior aspect of the aortic root where acoustic artifacts affect visualization with TEE[40]. In a contemporary metanalysis of 872 patients with definite endocarditis, the subgroup analysis for PVE showed that TEE demonstrated a higher sensitivity when compared with CCT for the detection of vegetations (89% *vs* 78%) at the expense of lower specificity (74% *vs* 94%, $P < 0.05$)[50]. Although CCT showed a trend towards improved detection of periannular complications (% *vs* 89%; $P = 0.06$), TEE was more sensitive for the detection of leaflet perforation (79% *vs* 48%; $P < 0.05$)[50].

CCT has also proven to be useful in surgical planning by providing additional diagnostic information regarding the anatomy of coronary arteries and aorta, and degree of calcification[3,51]. The major advantage of CCT over coronary angiography, is the ability to demonstrate coronaries and bypass graft patency non-invasively, avoiding risk of vegetation embolization during catheter manipulation[47]. It may also be valuable in the urgent evaluation of hemodynamically unstable patients who are unable to undergo TEE (Figures 5 and 6)[52].

A potential weakness of CCT is its relatively low temporal resolution, resulting in decreased sensitivity for the detection of small vegetations (< 4 mm) and leaflet perforation (< 2 mm); however, it has a comparable diagnostic performance to TEE for detecting fistulas, paravalvular leaks and prosthetic valve dehiscence[47,50] (Figure 5). Therefore, TEE remains a superior technique for the detection of small vegetations that are < 5 mm (Table 1)[53]. Some inherent technical challenges include the need for use of contrast which may exclude patients with iodine allergy or advanced kidney disease; the presence of arrhythmia that impairs the quality of image acquisition and the non-negligible amount of radiation exposure[54]. Similar to echocardiography, CCT has prognostic value in PVE. In a cohort of 155 patients with surgically proven IE, 112 (72.3%) corresponding to patients with previous valve replacement (metallic and bioprosthesis) or repair, the presence of pseudoaneurysm, abscess, and fistulas detected on CCT independently predicted mortality (HR = 3.82, 95%CI: 1.25–11.7, P < 0.001; and 9.84, 95%CI: 1.89–51.0, P = 0.007 respectively)[46].

Cardiac magnetic resonance imaging

The roles of cardiac magnetic resonance imaging (MRI) in IE, and more specifically in PVE, are currently limited, and less well defined. In general, this imaging modality offers several unique advantages such as improved 3D-visualization of cardiac structures compared to TEE, the ability to identify inflammatory changes in the myocardium and pericardium *via* delayed enhancement imaging, differentiation of vegetations from intracardiac masses, ability to diagnose infiltrative cardiomyopathies, accurate quantification of regurgitant valvular lesions and the ability to be used in patients unable to receive iodine-based contrast[54,55]. However, the role of MRI for evaluation of infective changes, especially in PVE is limited. Some of the factors that account for its limitations include incompatibility with some implantable cardiac devices, reduced availability and significant artifacts caused by metallic leaflets[53,54].

As part of the pre-operative work up, MRI does not provide as accurate information regarding the anatomy of the chest wall and its proximity to cardiac structures as does CCT, and thus is not usually favored for this purpose[56]. Nevertheless, MRI of the brain is recommended in pre-operative patients who have neurologic deficits and may also be reasonable in high-risk left-sided IE to screen for subclinical embolic events[3,56]. The ability of brain MRI to detect subclinical cerebral lesions, which may be found in up to 70% of patients who are neurologically intact clinically, has substantial clinical implications, as presence of systemic embolization represents one minor Duke criterion[5]. This in turn may allow earlier diagnosis and the implementation of therapeutics[57,58].

PET/CT

Hybrid modalities such as leucocyte scintigraphy and ^{18}F-FDG PET/CT have also been recognized as important complementary diagnostic imaging modalities. ^{18}F-FDG PET/CT relies on the administration ^{18}F-FDG radioisotope, which is taken up by active inflammatory cells at the site of the infection. On the other hand, leucocyte scintigraphy isolates and labels granulocytes with ^{99m}Tc that can be localized and quantified at a specific acquisition point in time[3,59]. The steps in preparation of leucocyte scintigraphy involving the drawing and reinjection of leucocytes, makes the utilization of ^{18}F-FDG radioisotope more favorable in clinical practice[1].

The modified Duke criteria only considers echocardiography as the diagnostic imaging modality for IE. The AHA guidelines, despite acknowledging the usefulness of PET/CT for the detection of extracardiac complications, have not yet recommended its routine use for diagnosis[5]. In contrast, in the latest iteration of the ESC guidelines for the management of IE, the presence of abnormal activity of ^{18}F-FDG PET/CT or leucocyte scintigraphy SPECT/CT (> 3 months after implant) around the perivalvular region of a prosthetic valve was upgraded as a major imaging criterion for diagnosis of IE[3]. As a result, Saby *et al*[60] reported an improvement of the modified Duke criteria sensitivity from 70% to 97% without trading-off its specificity, with the use of PET/CT [60]. Although similar findings in terms of sensitivity were found by Philip *et al*[61] in 115 patients with PVE (91 definite cases and 24 rejected cases) where the sensitivity increased from 57.1% to 83.5%; there was a decrease in specificity from 95.8% to 70.8%,

Table 1 Comparison between different imaging modalities in the evaluation of prosthetic valve endocarditis

Modality	Strengths	Weaknesses	Sensitivity	Specificity
Echocardiography	Available, convenient, no radiation exposure, hemodynamic data, high temporal resolution.	Operator- and imaging window-dependent, affected by prosthesis-related artifacts.	TTE: 17%–36%; TEE: 82%–96%	TTE: 86%[39,40]; TEE: 94%[39,40,45]
Cardiac CT	Spatial resolution, defining paravalvular complications, delineating coronary-aorta anatomy, preoperative planning.	Radiation exposure, contrast exposure limits use in advanced CKD.	88%–97%	95%[47,48,50]
Cardiac MRI	Characterizing paravalvular complications, depicts inflammatory changes, assess the degree of intra-cardiac shunting.	Limited data, lower spatial resolution, incompatibility with some cardiac devices. Limited clinical applicability.	Limited data	Limited data
^{18}F-FDG PET/CT	Excellent diagnostic role in PVE, detection of metastatic infection foci.	Availability, cost, requires special pre-test preparation, expertise, radiation exposure.	73%–97%	80%–94%[60-62]

TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; CTA: Computed tomographic angiography; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computer tomography.

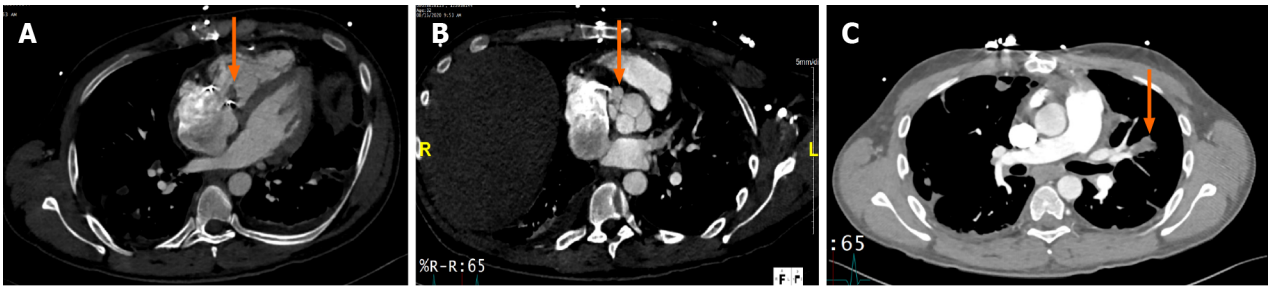


Figure 5 Cardiac computed tomography in a patient with tricuspid valve replacement endocarditis with peri-valvular extension. Thirty-two year-old male with a history of intravenous drug abuse status post bioprosthetic tricuspid valve replacement presenting with methicillin-sensitive Staphylococcus Aureus due to relapsed drug abuse. Cardiac computed tomography demonstrated thickening of the valve leaflets (A: Arrow) and a 2.7 cm × 1.9 cm × 1.4 cm lobulated pocket of free-flowing blood/contrast interposed between the tricuspid annulus and the aortic annulus consistent with abscess/fistula (B: Arrow). Prominent pulmonary septic embolism was also detected (C: Arrow).

with an overall improvement in accuracy from 65.2% to 80.9%. Wang *et al*[62] also reported in 333 patients with PVE an enhanced sensitivity of 86%, however, the sensitivity of the test decreased to 72% in the presence of cardiac implantable electronic devices (CIED)[62].

^{18}F-FDG PET/CT can be utilized early in the evaluation of suspected PVE, especially if microbiologic cultures and echocardiographic imaging are unrevealing[63]. ^{18}F-FDG PET/CT is a useful complimentary imaging modality for the diagnosis of IE that has demonstrated improving performance over time, especially in challenging cases of PVE and CIED related infections[62,64]. It has also been suggested to have a potential role in monitoring the response to antibiotic therapy[63,65]. The enhanced diagnosis of PVE with PET/CT has important clinical implications, helping to re-classify up to 90% of the "possible IE" cases by modified Duke Criteria, and providing a conclusive diagnosis (definite/rejected) in 95% of the cases[66]. It has also significantly altered the treatment plan in up to 35% of the cases by virtue of antibiotic treatment prolongation (27.5%), surgical referral (15%) and prevention of unnecessary device extraction (17.7%)[67]. This is attributed in part to its ability to detect extracardiac foci of infection, either septic emboli or other sources of infection, in around 17% of the cases with whole body PET/CT (Figure 7)[68].

Cautious interpretation of ^{18}F-FDG PET/CT results must be entertained, especially in the early postsurgical period during the first 3 months. Following the implantation of a prosthetic valve, an inflammatory response to the foreign body occurs, which is reactive in nature without necessarily implying the presence of infection[69]. Other causes of false positive results include: soft atherosclerotic plaques and active thrombi, cardiac tumors (whether primary or metastatic), and inflammatory conditions such as vasculitis and myocarditis[70,71]. Rouzet *et al*[59] described in a cohort of 39 patients with prosthetic valves and absence of clinical infection that approximately half of these patients will continue to have a homogenous uptake on ^{18}F-FDG PET/CT in the perivalvular area that may persist years after surgery, and therefore should not be confused with infective changes[59]. On the other hand, false negative may still occur

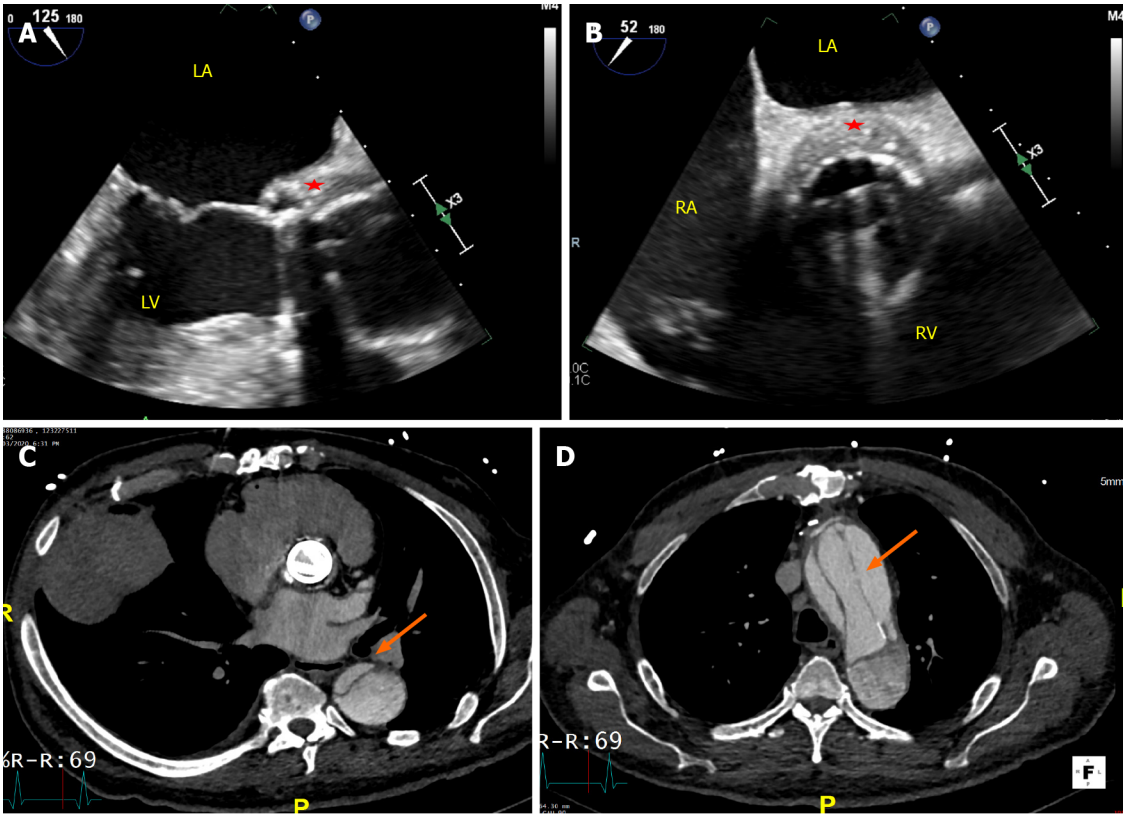


Figure 6 Transesophageal echocardiogram and cardiac computed tomography in a patient with metallic aortic valve replacement endocarditis, complicated by aortic dissection. Sixty-two year-old male with a history of type A aortic dissection status post repair with #27 CarboMedics valve conduit with reimplantation of the coronary arteries, #28 mm Hemashield bridge graft to the distal ascending aorta, presenting with PVE and extension of dissection from the distal ascending aorta to the femoral arteries. His transesophageal echocardiogram demonstrated the presence of a metallic AVR with pathological thickening of the aorto-mitral curtain and aortic root posteriorly (A and B: Star). Cardiac computed tomography axial view of the metallic aortic valve demonstrated widely open occluders and further inspection of the aorta at the level of the arch demonstrated the aortic dissection extending into the descending thoracic aorta (C and D: Arrow). RA: Right atrium; RV: Right ventricle; LA: Left atrium.

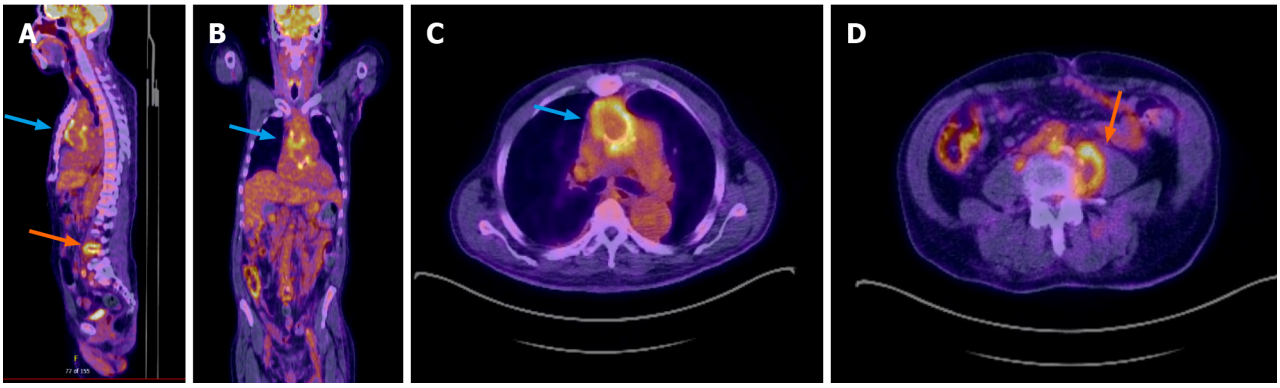


Figure 7 18-fluorodeoxyglucose photon emission tomography/computed tomography in a patient with prosthetic aortic valve endocarditis complicated by septic emboli. For details of clinical presentation, refer to Figure 6. Noted increased ^{18}F-FDG-uptake along the aortic root graft (A-C: Blue arrow) and distant septic foci at the level of L3-L4 with extension of abnormal hypermetabolism into the left psoas muscle consistent with L3-L4 discitis and left psoas muscle abscess (A and D: Orange arrow).

in the presence of small vegetations (< 5 mm), recent antibiotic administration, metastatic brain lesions and high glucose states[3,72]. Although contemporary data reported equipment availability in 70.3% of European centers and 56.3% non-ESC centers, the availability, cost, and expertise needed with this imaging modality impose additional limitations on its employment in routine clinical practice[4,73].

Real world data from the ESC-EORP EURO-ENDO (European infective endocarditis) registry in 3116 adults with IE from around the globe (2470 from Europe, 646 from non-ESC countries), identified 939 (30.1%) cases of PVE and 308 (9.9%) with

device related infection[4]. ^{18}F-FDG PET/CT was implemented in 518 cases (16.6%) and leucocyte scintigraphy in 38 (1.2%)[4]. Around 25% of the ^{18}F-FDG PET/CT were obtained in patients with PVE, and 26% in patients with device infections, which were significantly higher when compared with NVE (9.5%) ($P < 0.0001$) [4]. The test performance was superior in patients with PVE with a reported sensitivity of 66.8% (*vs* 28% for NVE and 16.3% for device infections) [4]. Extracardiac foci were observed in close to 40% of patients (34.5% in PVE, 42.3% in NVE, and 43.8% in device infections), most frequently seen in the lungs (27.1%)[4].

MANAGEMENT

In this section, a brief overview of the general management principles will be discussed; however, a detailed discussion of antimicrobial therapies and surgical techniques is beyond the scope of this article. Treatment of PVE consists of broadly surgical and/or medical management. Randomized controlled trial data comparing combined treatment to medical treatment alone are lacking. However, several large cohorts examined outcomes in surgical and medical therapy group. In a large meta-analysis by Mihos *et al*[74] of 32 studies including 2636 patients with PVE, surgical management was associated with lower 30-day mortality and higher survival at 22 months and similar rate of recurrence compared to medical therapy alone (25% *vs* 34% and 69% *vs* 58%, respectively)[74]. The limitation of this study is lack of adjustment analysis for risk factors and time from medical therapy to surgery[74]. In another large prospective study of 1025 patients with PVE, early surgery was associated with lower 1- year and in-hospital mortality compared with medical therapy alone (HR = 0.57, 95%CI: 0.49-0.67 and HR = 0.44, 95%CI: 0.38-0.52, respectively)[8]. However, this benefit with early surgery was absent after adjustment for survivor bias and clinical factors[8]. In several observational studies, the benefit of surgery was mostly seen in patients with PVE complications that carry high mortality rate such as valve regurgitation or dehiscence, paravalvular abscess or fistula, heart failure, and coagulase negative or Staphylococcus Aureus PVE[75-77]. In this context, a 2015 scientific statement from the AHA, 2015 ESC and 2016 American Association for Thoracic Surgery guidelines recommended as class I indication surgical intervention after weighing risks and benefits based on operative risk profile and overall outcome in the following scenarios: PVE with complications, such as new or worsening CHF, prosthetic valve dehiscence, hemodynamically significant valvular or paravalvular regurgitation, obstruction or intracardiac abscess[3,5,56]. It is reasonable to proceed with surgery as class II indication in cases of persistent bacteremia, infection-relapse despite appropriate antibiotics treatment, aggressive infection by Staphylococcus Aureus or fungi, non-HACEK gram negative organisms, multi-resistant organisms or in the presence of fastidious organism clustered as "culture negative" PVE[3,5,56,78]. PVE vegetations are at risk for embolization, especially when the size exceeds 10 mm, or there is increasing in size despite antibiotics[3,34,56]. In these situations, surgical intervention should be considered[3,34,56].

Antibiotic therapy should be initiated in all cases of PVE with consultation of an infectious disease specialist for guiding the antibiotic choice[3,5,38,56]. Three sets of blood cultures separated by 30-60 minutes should be obtained before antibiotic initiation and at least every 24-48 h until the blood culture is negative[3,5,38,56]. All patients should be monitored for side effects of antibiotics, clinical response and symptoms/signs that suggest PVE complications. In the latter case, an echocardiogram should be repeated. The treatment duration is generally 6 week starting from the first negative blood culture, and it can be extended for an additional 6 week if surgical specimens demonstrate a positive gram stain and culture or positive polymerase chain reaction. Antibiotic therapy should subsequently be tailored according to the culture results[3,5,38,56].

CONCLUSION

The diagnosis of PVE remains challenging due to its often non-specific clinical presentations and prosthesis-related artifacts that impair the optimal visualization of cardiac structures by echocardiography. Echocardiography continues to be the first-line imaging modality in suspected cases of PVE due to is wide availability, low cost, rapid interpretation, and safety. TEE is mandated in most PVE cases due to the reduced sensitivity of TTE in this context. The consequences of missing prosthesis-related

infections are serious, and therefore, evaluation of PVE requires the optimal complementary use of imaging modalities to achieve the best outcomes. Adjuvant imaging modalities, particularly CCT and ^{18}F-FDG PET/CT have important niche roles. These imaging modalities improve the ability to accurately and timely diagnose PVE, contribute to the pre-operative planning of appropriate patients, and guide decision-making for therapies.

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REVIEW

Potential role of an athlete-focused echocardiogram in sports eligibility

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Abstract

Sudden cardiac death (SCD) of an athlete is a rare but tragic event and sport activity might play a trigger role in athletes with underlying structural or electrical heart diseases. Preparticipation screenings (PPs) have been conceived for the potential to prevent SCD in young athletes by early identification of cardiac diseases. The European Society of Cardiology protocol for PPs includes history collection, physical examination and baseline electrocardiogram, while further examinations are reserved to individuals with abnormalities at first-line evaluation. Nevertheless, transthoracic echocardiography has been hypothesized to have a primary role in the PPs. This review aims to describe how to approach an athlete-focused echocardiogram, highlighting what is crucial to focus on for the different diseases (cardiomyopathies, valvulopathies, congenital heart disease, myocarditis and pericarditis) and when is needed to pay attention to overlap

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diagnostic zone ("grey zone") with the athlete's heart. Once properly tested, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices, potentially available during first-line evaluation.

Key Words: Echocardiogram; Athletes; Sport eligibility; Pre-participation screening; Sudden cardiac death; Sport cardiology

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Core Tip: Echocardiography is a helping tool in detecting several cardiovascular (CV) conditions afflicting athletes. As physicians become more experienced with sonography, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices. This technique could help to detect some hidden CV condition and to distinguish between physiological and pathological adaptation to physical activity, assisting in sport eligibility process. In this review we aimed at describing athlete-focused echocardiogram that could be an effective time and cost-saving first line evaluation in granting sport eligibility to athletes.

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INTRODUCTION

The advantages of sport practicing in improving cardiovascular (CV) health are evident, but a concomitant raise in CV events has been seen during exercise[1]. Physical activity therefore is a double-edge sword, with both benefits and risks mostly in predisposed subjects, even if not all people are conscious about it[2].

Sudden cardiac death (SCD) of an athlete is as uncommon as shocking event[3]. Sport practice might be a trigger event of cardiac arrest in athletes with underlying heart diseases, with syncope as a frequent first manifestation[4]. Indeed, these diseases are often clinically silent and unsuspecting[5]. Athletes have an increased risk of SCD compared with their non-active counterpart, related to pathologies theoretically identifiable through pre-participation screening (PPS)[6]. Therefore, several PPSs have been developed with the aim to uncover possible hidden and fatal CV condition in athletes. There is a significative debate about the efficacy and feasibility of different kind of PPSs proposed by national and international society worldwide. While the American Heart Association has never recommended a history collection and a physical examination, opposing the routine use of electrocardiogram (ECG)[7], the European Society of Cardiology (ESC) protocol focuses on history collection, physical examination, and ECG[8] and it has been adopted by different sport committees and international federations[9]. Controversies arise regarding the sensitivity and specificity of individual tests as well as the availability of expertise and cost effectiveness[10-13].

Nevertheless, some cardiac structural diseases can be difficult to detect on physical examination and ECG, but they may definitely be recognized with further cardiac investigations. About 10% of SCD cases have been related to cardiac diseases showing structural but no electrical manifestations[14]. While in Italy an exercise stress test is mandatory before engaging in competitive sports, transthoracic echocardiography has also been hypothesized to have a role in PPS: it might be a useful, convenient and noninvasive tool to increase diagnostic power of screening evaluation[15]. Even if echocardiography is frequently adopted as a first-line screening tool for athletes[16], also by major sporting bodies such a Federation Internationale de Football Association (FIFA) or Union of European Football Association (UEFA), and mainly as a valuable second line investigation to the diagnose malignant cardiac conditions[17,18], it has never been recommended as a first-line screening tool in athletes[19,20], nor included

in recent ESC 2020 guidelines on sport cardiology[3]. Diagnostic necessity, time constrains and cost-effectiveness are probably unfavorable reasons for its use[21], even if there are only few data[22] regarding the cost-effectiveness of including an echocardiography in the PPS.

However, the use of echocardiography is highly increasing among non-cardiologist physicians and it could represent a powerful tool in the sport eligibility process by sport medicine physicians.

Therefore, the aim of the present paper is to review athlete-related echocardiographic features in order to develop a first-line screening athlete-focused echocardiogram. How should an echocardiography of the athlete be performed? What should a sport physician know about echocardiography? What would an athlete-focused echocardiogram be like?

EPIDEMIOLOGY AND ETIOLOGY OF SCD

SCD could literally be defined as "natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of symptoms"[23]. Current epidemiology of the incidence of SCD in professional athletes varies from almost 1/1000000 to 1/5000 subjects per year[24,25]. Indeed, the definition of the precise frequency of SCD is made difficult by heterogeneous study methodologies. In literature, the incidence of SCD in young athletes is fluctuating[14,26-28], with a prevalence of CV predisposing conditions of about 0.2%–0.7%[29].

Several causes of SCD in athletes are related to the age of onset. In patients from birth to adolescence, the primary cause of SCD is a congenital abnormality[30]. The great majority of young victims (age ≤ 35 years) present a concealed structural heart disease[31]. Coronary artery disease is the most frequent cause of SCD in aged athletes (35 years or older)[32]. Main causes of SCD are summarized in Table 1.

ECHOCARDIOGRAPHY IN ATHLETE'S HEART

Even if a minimum dataset is recommended for all echocardiograms[33] (Table 2), previous knowledge of some demographics data, patient's personal history and physical examination, and ECG findings will help to focus the examination and the interpretation of findings: sex, age, body mass index, ethnicity, ECG changes, symptoms, training volume, type of sport and level, and family history of unexplained cardiac death < 40 years[34]. A focused echocardiogram with real-time interpretation can considerably cut the cost and time spent performing the study, as previously demonstrated[35]. Indeed, Niederseer *et al*[21] proposed to include a double screening echocardiography in the athlete: in adolescence to rule out structural heart disease, and over the age of 30 to evaluate pathological cardiac remodeling to exercise, cardiomyopathies and wall motion anomalies. Often coronary artery disease is missed by classing screening method, so in a master athlete (> 35 years) echocardiography detection of atherosclerotic plaque[36], could represent a valid example of a focused exam.

Moreover, prolonged physical activity causes structural, functional, and electrical heart modifications that represent the physiological responses ("adaptation") of the heart during physical effort: this series of remodeling is named as "athlete's heart"[37] and it can be appreciated both in ECG[38] and in echocardiograms. These adaptations, involving all the heart chambers[39] and strictly dependent upon on the duration, type and intensity of training, are often benign and physiological but, sometimes, may predispose to pathological conditions[40,41]. The challenges posed by athlete's heart require detailed assessment in order to distinguish between physiological adaptation and life-threatening cardiomyopathies[16,42-44], that often coexist in the so called "grey zones".

Also, novel advanced echocardiographic techniques play an emerging role in the echocardiographic investigation of athlete[41]: Exercise stress echocardiography in the differentiation between athlete's heart and dilated cardiomyopathy, coronary artery disease and pulmonary hypertension; speckle tracking [with left ventricular (LV) global longitudinal strain] in the differentiation between athlete's heart and dilated cardiomyopathy and hypertrophic cardiomyopathy, other than the characterization of wall motion abnormalities and right ventricle description; 3D echocardiography in estimation of cardiac mass.

Table 1 Common cardiovascular diseases associated with sudden cardiac deaths in athletes (adapted from[15,21])

Type of pathology	Pathology
Cardiomyopathies	HCM
	DCM
	LVNC
	ARVC
CAD	
Myocarditis	
Congenital defects	AOCA
	BAV
Valvulopathies	MVP
Aortic diseases	Aortic dissection
	Aortic rupture
	Aortic aneurism
Kawasaki disease	
Idiopathic scarring	
Conduction defects	WPW
Channelopathies	LQTs
	Brugada syndrome
	CPVT

HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; LVNC: Left ventricle non compaction; ARVC: Arrhythmogenic right ventricle cardiomyopathy; CAD: Coronary artery disease; AOCA: Anomalous origin of coronary arteries; BAV: Bicuspid aortic valve; MVP: Mitral valve prolapse; WPW: Wolff-Parkinson-White syndrome; LQTs: Long QT syndrome; CPVT: Catecholaminergic polymorphic ventricular tachycardia.

Therefore, echocardiography has a major role in sports cardiology, and it can help physicians not only to investigate structural diseases invisible both at anamnesis and ECG, but also to rule out these physio-pathological modifications.

ATHLETE-FOCUSED ECHOCARDIOGRAM

The concept of point-of-care ultrasound is increasingly emerging in literature[45], in different body systems[46,47], including heart. Even if it is crucial to consider the ultrasound scanner and the degree of competence and knowledge of the sonographer [48], a focused protocol for point-of-care echocardiography could be developed for physicians to help screen out major CV diseases afflicting athletes in granting sport eligibility. Such protocols may gain much more attention by the fact that nowadays, portable and handheld ultrasound devices are spreading and have proven to be equally reliable and accurate in evaluating cardiac features[49,50].

Several of athlete-focused echocardiography protocols have been proposed in literature[19,51,52] by different authors[53-55], and some are reported in Table 3. Some of them are direct to rule out specific diseases, while others are designed for global viewing but only last a few minutes. Moreover, several sportive federations, such as FIFA, have their own precompetition medical assessment that includes echocardiographic examination.

We want to propose our version of first-line athlete-focused echocardiography, as seen in Table 4 and Figures 1 and 2. Some measurements are intentionally missed: visually estimated left ventricular ejection fraction and wall motion has been found to be closely related to formal quantitative methods[56,57]; valvular heart diseases can be firstly screened by color doppler[58]. We also consider a visual assessment of cardiac chambers' dimensions. All these first-line measurements, if pathological, will be eventually followed by other measurements ("second-line"), as seen in Table 5.

Table 2 Minimum dataset for transthoracic echocardiography (adapted from[33])

Echo views	Structure	Measure
PLAX	LV	IVS
		End diastolic diameter
		Posterior wall
		Wall motion
	Mitral Valve	Leaflets and annulus
		Color
	Aortic Valve	Anulus
		Valsalva Sinus
		STJ
		Color
	Ascending aorta	Size
	RV	RVOT
	LA	Size
PSAX–aortic valve	Aortic Valve	Morphology
	OCA	
	RV	RVOT
	Pulmonary valve	Color
		PW
PSAX-base	Mitral Valve	Leaflets and annulus
PSAX–mid/apex	LV	Wall motion
A4C	LV	EF
		Wall motion
		Wall thickness
		End diastolic area/volume
	VSD	
	ASD	
	LA	LAVI
	Mitral valve	Color
		PW
		TDI
	RV	RVD1
		RVD2
		RVD3
		Wall motion
		TAPSE
	TV	Color
		CW
	Pulmonary veins	PW
A5C	Aortic valve	Color
		CW
A2C	LV	Wall motion

Subcostal	ASD	
	Inferior vena cava	Size
		Breath collapsibility
	Pericardium	Pericardial effusion
	Abdominal aorta	Size
Suprasternal	Aortic arch	Size
		Color
		CW

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area charge; LAVI: Left atrium ventricle index; LA: Left atrium; IVS: Inter ventricular septum; PW: Power doppler wave; CW: Continuous doppler wave; RA: Right atrium; STJ: Sinotubular junction; OCA: Origin of coronary arteries; PDA: Patent ductus arteriosus; COA: Aortic coarctation; ASD: Atria septum defect; VSD: Ventricular septal defect; RVD: Right ventricle diameter; TAPSE: Tricuspid annular plane excursion.

Table 3 Athlete-focused echo protocols

Ref.	Echo view (parameters assessed)	Estimated exam time
Feinstein *et al*[51]	PLAX (LV IVS, LV posterior wall, LVOT)	1-2 min
Wyman *et al* [53]	PLAX (aortic arch size, aortic valve characteristics, mitral valve characteristics, LV wall motion, LV mass); PSAX (aortic valve characteristics, aortic valve morphology, origin of coronary arteries, CW pulmonary valve, LV wall motion, LV wall thickness); A4C (tricuspid valve characteristics, mitral valve characteristics, RV size, RV wall motion, LV size); A5C (CW aortic valve)	Not specified
Weiner *et al* [52]	PLAX (aortic valve characteristics, mitral valve characteristics, CW tricuspid valve); PSAX (aortic valve characteristics, pulmonary valve characteristics, LV wall motion); A4C (RV size, RV wall motion, LV size, LV wall motion, PW mitral valve, TDI mitral valve, tricuspid valve characteristics); A5C (CW aortic valve); A2C (LV wall motion)	13 min
Yim *et al*[55]	PLAX (IVS, LV end diastolic diameter, PW, aortic arch size)	Not specified
Fishman *et al*[54]	LV IVS, LV posterior wall, LV end diastolic diameter, PW, EF, AVR, MVR aortic valve regurgitation, mitral valve regurgitation, aortic valve morphology, aortic root dimension	1 min

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; IVS: Inter ventricular septum; LVOT: Left ventricle outflow tract; LV: Left ventricle; CW: Continuous wave; RV: Right ventricle; PW: Power doppler wave; TDI: Tissue doppler imaging; EF: Ejection fraction; AVR: Aortic valve regurgitation; MVR: Mitral valve regurgitation.

Below we will describe main echo findings and grey zone in the more frequent CV conditions in athletes (Table 5), with cut off based on latest recommendations[42].

CARDIOMYOPATHIES

The diagnosis of these cardiomyopathies and their differentiation with athlete's heart still represent one of the biggest challenges of sport cardiology

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is one of the most common etiologies of SCD in athletes and represents one of the most frequent reason for denied sport eligibility according to both American and European guidelines[59-61].

Echocardiography is crucial for the diagnosis and monitoring of HCM. In the absence of another reason of hypertrophy, it can be diagnosed with a maximal end-diastolic wall thickness of ≥ 15 mm in any zone of the left ventricle; less marked hypertrophy (13–14 mm) can be diagnostic when present in relatives of a patient with HCM or along with a positive genetic test. For children, a threshold of $z > 2.5$ may be useful to identify early HCM in asymptomatic subject with no family history, while for

Table 4 Proposed echocardiographic protocol for athletes

Echo views	Structure	Measure
PLAX	LV	IVS
		End diastolic diameter
		Posterior wall
	Mitral valve	Leaflets
		Color
	Aortic valve	Valsalva sinus
		Color
	Ascending aorta	Size
PSAX–aortic valve	Aortic valve	Morphology
	OCA	
	RV	RVOT
	PDA	
A4C	LV	Trabeculations
		Wall motion
	VSD	
	ASD	
	Mitral valve	Color
		PW
	TV	Color
		CW
A5C	Aortic valve	Color
		CW
Subcostal	ASD	
	Inferior vena cava	Size
		Breath collapsibility
	Pericardium	Pericardial effusion
Suprasternal	Aortic arch	Size
	COA	

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area charge; LAVI: Left atrium ventricle index; LA: Left atrium; IVS: Inter ventricular septum; PW: Power doppler wave; CW: Continuous doppler wave; RA: Right atrium; STJ: Sinotubular junction; OCA: Origin of coronary arteries; PDA: Patent ductus arteriosus; COA: Aortic coarctation; ASD: Atria septum defect; VSD: Ventricular septal defect; RVD: Right ventricle diameter; TAPSE: Tricuspid annular plane excursion.

children with a positive family history or a positive genetic test, a threshold of $z > 2$ could be sufficient for early diagnosis.

Measurements of LV wall thickness should be executed at end diastole, in parasternal long axis (PLAX) or in parasternal short axis (PSAX) views[15].

Grey zone: The diagnosis of HCM in competitive athletes may be difficult when LV wall thickness ranges from 13 to 16 mm[62-64]. The overlap between athlete's heart and HCM is challenging in Afro-American individuals[65]. Indeed, the extreme value of LV hypertrophy in athletes is found in male (15 mm in white and 16 mm in Afro-American athletes[66]), while lower values are found in female (11 mm in whites and 13 mm in Afro-Americans[67]). The type and the intensity of sport practiced are also important aspects to consider.

Table 5 Main echo findings of cardiovascular pathologies in athletes

Pathology	What to assess? (echo view)	Cut-off mm (mean mm)	If pathological, what to assess? (echo view)	Cut-off mm (mean mm)
HCM	LV Max end-diastolic wall thickness	M white 15 (10); M Afro-American 16 (11.5); F white 11; F Afro-American 13 (9.5); M/F adolescent 16 (12)	LV wall thickness distribution	Asymmetric (HCM)
			LV end diastolic diameter (A4C)	M 70 (55); F 66 (49); Adolescent 60 (51)
			LV mass/BSA	M 117 mm/m^2 (83 mm/m^2); F 143 mm/m^2 (101 mm/m^2)
			LVOT obstruction	
			E/A (A4C)	1.3 (1.93)
DCM	LV end diastolic diameter (PLAX)	M 70 (50); F 66 (49); Adolescent 60 (51)	EF (A4C)	55% (64%)
LVNC	LV trabeculation	NC/C layer ratio > 2.0 in systole	EF (A4C)	55% (64%)
			Thickness of compact layer in systole	8
			E/A (A4C)	1.3 (1.93)
ARVC	RVOT/BSA (PSAX)	> 21 mm/m^2	RV inflow (A4C)/ LV end diastolic diameter (PLAX)	> 0.9
	RVOVT/BSA (PLAX)	> 19 mm/m^2	RV wall motion abnormalities	
			RV FAC	33%
Aortic dilatation	Aortic valve max dimension (PLAX)	M 40 (32); F 34 (28)	Other congenital defects (BAV)	
	Ascending aorta dimension (PLAX)		Aortic regurgitation	
Mitral prolapse	Mitral prolapse (PLAX)	Abnormal systolic bulging of leaflets > 2 mm toward LA	Mitral regurgitation	
			PAPS (A4C)	40 mmHg (24 mmHg)
			Pulmonary veins flow	Reverse
			EF (A4C)	55% (64%)
			LV mass/BSA	M 117 mm/m^2 (83 mm/m^2); F 143 mm/m^2 (101 mm/m^2)
			LAVI	M 36 mm/m^2 (28 mm/m^2); F 33 mm/m^2 (26.5 mm/m^2)
AOCA	Coronary arteries origin (PSAX)			
BAV	Aortic morphology (PSAX)		Aortic stenosis	
			Aortic regurgitation	
			Aortic root max dimension (PLAX)	M 40 (32); F 34 (28)
			Other congenital defects (coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly or hypoplastic left heart, as well as Williams or Turner syndrome)	
ASD	ASD		RV dimension (A4C)	Basal RV: M 55 (43.5), F 49 (39); Medial RV: M 47 (34), F 43 (32); Longitudinal RV: M 109 (89), F 100 (82)
			RA area/BSA (A4C)	M 28 mm/m^2 (19.5 mm/m^2); F 24 mm/m^2 (15.5 mm/m^2)
			PAPS (A4C)	40 mmHg (24 mmHg)

VSD	VSD		LV mass/BSA (PLAX)	M 117 mm/m^2 (83 mm/m^2); F 143 mm/m^2 (101 mm/m^2)
			PAPS (A4C)	40 mmHg (24 mmHg)
			Aortic regurgitation	
			Other congenital defects (aneurysm of Valsalva sinus, ToF, TGA, DCRV)	
PDA	PDA (PSAX)		LA/Aortic root ratio	≥ 1.4
			LV mass/BSA (PLAX)	M 117 mm/m^2 (83 mm/m^2); F 143 mm/m^2 (101 mm/m^2)
			PAPS (A4C)	40 mmHg (24 mmHg)
			Pulmonary artery size (PSAX)	
			RV dimension (A4C)	Basal RV: M 55 (43.5), F 49 (39); Medial RV: M 47 (34), F 43 (32); Longitudinal RV: M 109 (89), F 100 (82)
			RA area/BSA (A4C)	M 28 mm/m^2 (19.5 mm/m^2); F 24 mm/m^2 (15.5 mm/m^2)
			Other congenital defects (COA, pulmonary atresia)	
COA	COA (PSAX)		Aortic stenosis	
			Mitral stenosis	
			LV mass/BSA (PSAX)	M 117 mm/m^2 (83 mm/m^2); F 143 mm/m^2 (101 mm/m^2)
			EF (A4C)	55% (64%)
			Other congenital defects (BAV, ascending aortic aneurysm)	
Myocarditis	EF (A4C)	55% (64%)		
	LV wall motion abnormalities			
	Pericardial effusion			
	Increased LV wall thickness			
Pericarditis	Pericardial effusion			
Kawasaki disease	Coronary artery abnormalities			
	EF (A4C)	55% (64%)		
	LV wall motion abnormalities			
	Mitral regurgitation			
	Aortic regurgitation			
	Pericardial effusion			

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; LVNC: Left ventricle non compaction; ARVC: Arrhythmogenic right ventricular cardiomyopathy; BAV: Bicuspid aortic valve; AOCA: Anomalous origin of coronary arteries; ASD: Atrial septum defects; VSD: Ventricular septal defects; PDA: Patent ductus arteriosus; CoA: Aortic coarctation; M: Male; F: Female; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; LVOT: Left ventricle outflow tract; NC/C: Non-compact/compact; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area charge; PAPS: Pulmonary artery systolic pressure; LAVI: Left atrium ventricle index; RA: Right atrium; ToF: Tetralogy of fallot; TgA: Transposition of great arteries; DCRV: Double-chambered right ventricle.

Differential diagnosis features between HCM and athlete's heart in the gray-zone is seen in Table 6. The most practical morphologic criterion is the assessment of LV cavity size and geometry, enlarged (end-diastolic diameter > 54 mm) and with an eccentric pattern only in athlete's heart[62,68]. On the other side, an asymmetric and heterogeneous pattern of LV hypertrophy represents features of HCM[62]. Further-

Table 6 Differential diagnosis between hypertrophic cardiomyopathy and athlete's heart, in the grey-zone (adapted from[42])

HCM	Findings	Athlete's heart
Normal, reduced	LV cavity size	Enlarged, eccentric pattern
Asymmetric and heterogeneous	LV hypertrophy	Symmetric and homogeneous
Present	LVOT obstruction	Absent
Abnormal	LV diastolic function	Normal
Unchanged	LV wall thickness after detraining	Reduced

HCM: Hypertrophic cardiomyopathy; LV: Left ventricle; LVOT: Left ventricle outflow tract.

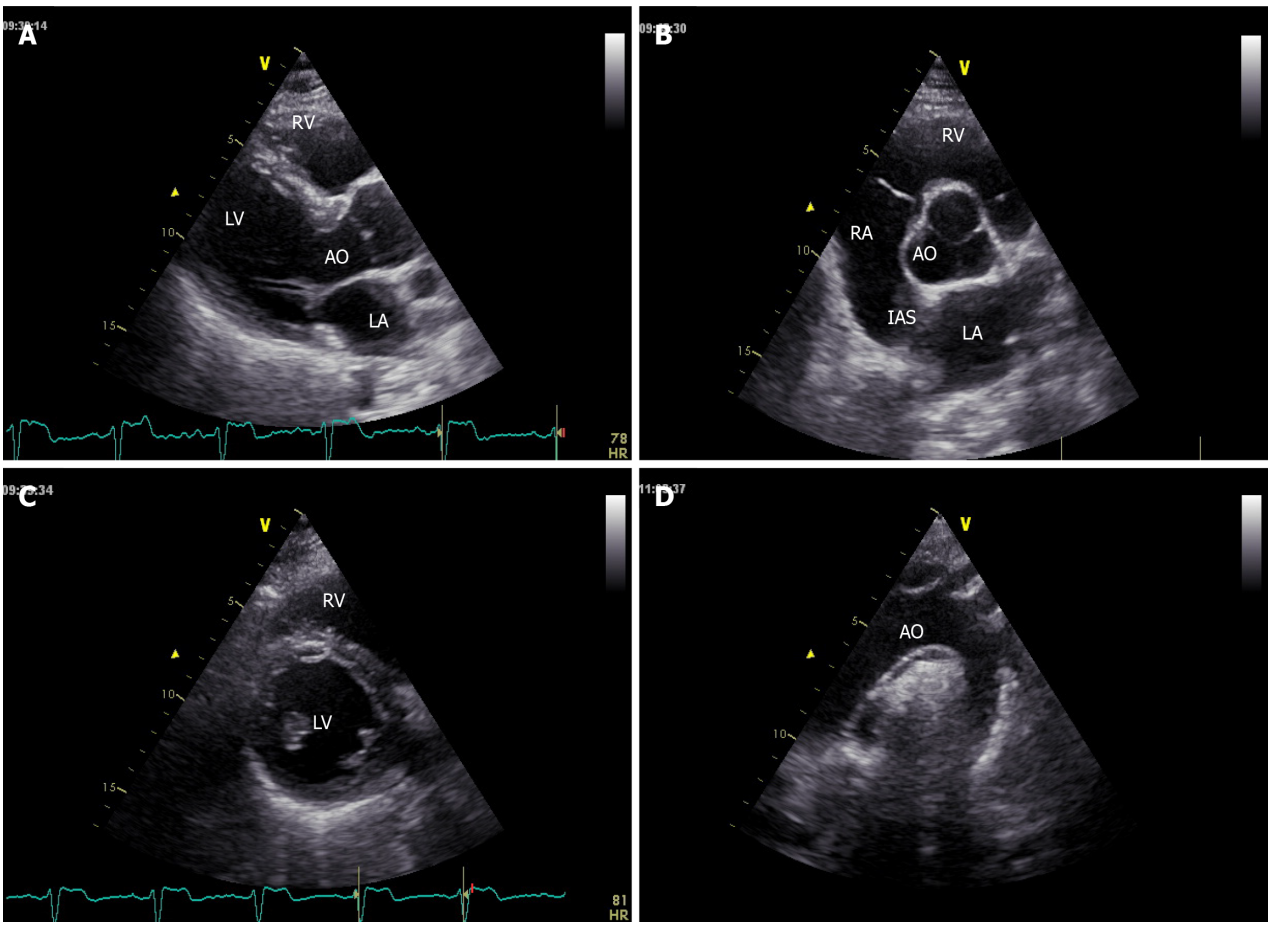


Figure 1 Parasternal long-axis, short axis and suprasternal windows showing left and right chambers and aortic valve and arch. A: Long-axis; B and C: Short axis; D: Suprasternal windows. LV: Left ventricle; LA: Left atrium: RV: Right ventricle; RA: Right atrium; AO: Aorta; IAS: Interatrial septum.

more, athletes usually show a homogeneous distribution of wall thickness and a normal diastolic function[69], besides a reduction of wall thickness after a detraining period.

What to assess? LV wall thickness. If pathological, what to assess? LV end diastolic diameter + LV mass + LV outflow tract (LVOT) obstruction + LV wall thickness distribution + LV diastolic function (E/A).

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is a not-so rare cause of SCD in athletes[70,71]. It is defined as (left) ventricular systolic dysfunction and dilatation not explained by other loading conditions. Systolic dysfunction is measured by abnormal LV ejection fraction (EF) (through biplane Simpson's rule). LV dilatation is defined by LV end-diastolic

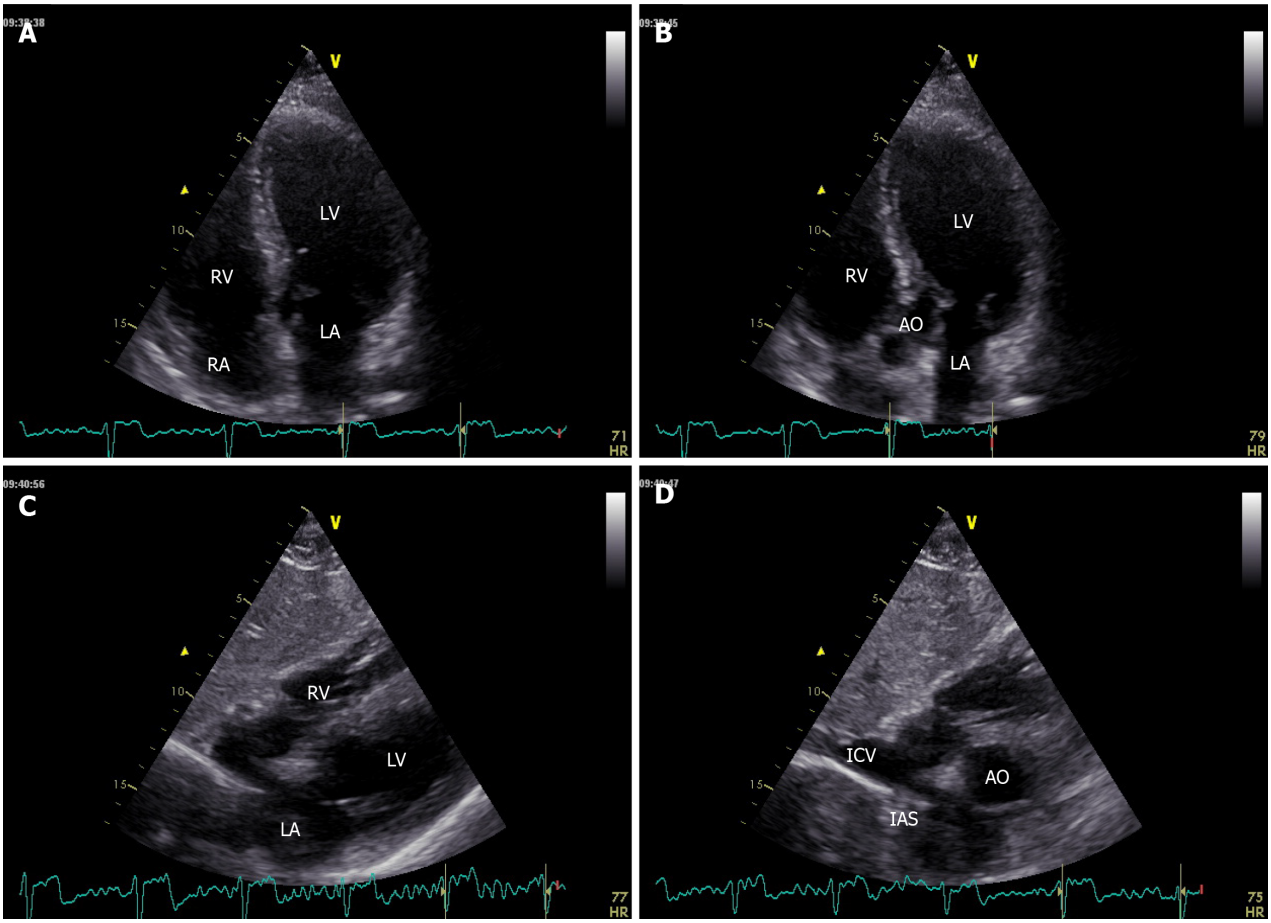


Figure 2 Apical 4-chamber, 5-chamber and subcostal windows showing left and right chambers, inferior cava vein and pericardium. A: 4-chamber; B: 5-chamber; C and D: Subcostal windows. LV: Left ventricle; LA: Left atrium: RV: Right ventricle; RA: Right atrium; AO: Aorta; IAS: Interatrial septum; ICV: Inferior cava vein.

diameters > 2 SD from normal, indexed by body surface area (BSA), age and gender. LV shape can provide additional information ("sphericity index")[72].

Grey zones: Left ventricular cavity increasing in athletes should be interpreted in the context of sport played and it is usually associated with increased wall thickness [73,74]. A significant dilation is often seen in endurance athletes. Almost 40% of athletes showed an increase of LV end diastolic diameter (> 55 mm), and almost 10% even bigger cavity (> 60 mm, with 99th percentile corresponding to 65 mm). LV dilation in athletes is frequently presented with EF > 55%. Moreover, indices of diastolic function are within normal values[75]. In case of mildly reduced ejection fraction, it may be useful to perform a stress test echocardiography, along with the measure of stroke volume.

Differential diagnosis features between DCM and athlete's heart in the grey zone is showed in Table 7.

What to assess? LV end diastolic diameter. If pathological, what to assess? EF.

LEFT VENTRICLE NON COMPACTION

Left ventricle non-compaction (LVNC) is a cardiomyopathy identified by increased myocardial trabeculations and inter-trabecular recesses[76,77], ranging clinically from asymptomatic to SCD outcomes. Diagnosis is based on three proposed echocardiographic criteria, showing high non-compacted to compacted ratio within the LV myocardium[78,79].

Grey zones: About 1 in 5 athletes has LV hypertrabeculation, with about 10% complying LVNC diagnostic criteria[80,81]. This may be due to cardiac adaptation to load training. ESC guidelines on cardiovascular imaging[42] proposed the threshold for defining an LV trabeculations on echocardiography: a non-compacted to compacted (NC/C) layer ratio > 2.0 in systole[82].

Table 7 Differential diagnosis between dilated cardiomyopathy and athlete's heart (adapted from[42])

DCM	Findings	Athlete's heart
> 60 mm	LV end diastolic diameter	< 60 mm
Reduced	EF	Normal
Abnormal	Diastolic function	Normal

DCM: Dilated cardiomyopathy; LV: Left ventricle; EF: Ejection fraction.

In athletes achieving criteria for LVNC, an history of cardiac symptoms or family SCD, are suggestive of pathology. Additional echocardiography features of LVNC include low EF not improving with exercise, altered diastolic function and a thickness of compacted layer in systole < 8 mm.

Differential diagnosis features between LVNC and athlete's heart in the gray-zone is showed in Table 8.

What to assess? LV trabeculation. If pathological, what to assess? FE (Simpson) + thickness of compact layer in systole + LV diastolic function (E/A).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiomyopathy characterized by progressive waste of myocytes that are substituted by fibrofatty tissue. It typically (but not only) involves the right ventricle (RV).

Diagnostic imaging criteria have been defined in 2010[83]: Disproportionate enlargement of the right ventricle outflow tract (RVOT) and RV motion abnormalities are essential characteristics of this disease[84].

Grey zones: Long-term physical activity could promote the expression of ARVC: exercise remodeling includes RV (basal) enlargement and mild reduction of global RV peak systolic longitudinal strain[15]. ESC guidelines on cardiovascular imaging[42] propose that only major dimensional criteria, indexed by BSA, should be used to define RV enlargement in athletes: specifically, RVOT > 19 mm/m^2 in PLAX, and/or > 21 mm/m^2 in PSAX. Other useful measures include the ratio of RV inflow dimension (in apical 4 chambers view (A4C))/LV end-diastolic dimension (PLAX) > 0.9[85], the RV fractional area change (FAC) < 33%[86], and a subclinical RV dysfunction with reduced RV global longitudinal strain[87]. About 50% of ARVC subjects could have regional akinesia, dyskinesia, or aneurysmal deformation.

Differential diagnosis features between ARVC and athlete's heart is seen in Table 9.

What to assess? RVOT PSAX + RVOT PLAX. If pathological, what to assess? RV inflow apical/LV end diastolic PLAX + RV regional wall abnormalities + RV FAC.

AORTIC DISEASES

Aortic pathologies, such as aortic dissection or aortic aneurism, are important etiologies of SCD in athletes[88,89] and could be related to Marfan disease. Practically, aortic root diameter measurements should be performed from the PLAX view using the leading edge-to-leading edge convention (except for the measurement of the annulus, in which it is used inner edge to inner edge convention) and preferring 2D measurements[90,91]. Otherwise, in children and in subjects ≤ 25 years, aortic root dimensions should be carried out using the inner-wall-to-inner-wall technique during systole[92]. Measurements should embrace the aortic valve annulus, the sinuses of Valsalva, the sinotubular junction and the proximal ascending aorta.

Grey zone: Remodeling of the aortic root in athletes is strictly related to the overload training[93-95]. Large increases in aortic size are rare in athletes and often related to an underlying potentially fatal aortic disease[96]. The American College of Cardiology and the American Heart Association have proposed the use of z-scores to identify subjects with significant aortic root dilation[97]. If dilated aortic root dimensions are found, it is recommended to exclude the presence of associated conditions such as Marfan Syndrome of bicuspid aortic valve (BAV)[98,99]. In athletes with dilated aortic root, a periodical diagnostic assessment to monitor dimension is recommended.

Table 8 Differential diagnosis between left ventricle non compaction and athlete's heart, in the grey zone (adapted from[42])

LVNC	Findings	Athlete's heart
Reduced	LV systolic function	Normal
Reduced	Thickness of compact layer	Normal
Abnormal	Diastolic function	Normal

LVNC: Left ventricle non compaction; LV: Left ventricle.

Table 9 Differential diagnosis between arrhythmogenic right ventricular cardiomyopathy and athlete's heart, in the grey-zone (adapted from[42])

ARVC	Findings	Athlete's heart
Exceeding major criteria for ARVC	RV size	Not exceeding major criteria for ARVC
Abnormal	Regional RV wall motion	Normal
Abnormal	Global RV function	Normal

ARVC: Arrhythmogenic right ventricular cardiomyopathy; RV: Right ventricle.

What to assess? aortic root dimension + ascending aortic diameter. If pathological, what to assess? BAV + aortic valve regurgitation.

VALVULOPATHIES

Mitral valve prolapse

Mitral valve prolapse (MVP) is a common valve abnormality in population that, in some case, has been associated to SCD especially in young individuals[100]. Echocardiography, ideally in PLAX view, is essential for MVP diagnosis[40]: It is literally defined by "abnormal systolic bulging of one or both leaflets toward the left atrium (LA) with displacement of coaptation point into the LA (> 2 mm beyond a line connecting the annular hinge point)". Leaflets are usually elongated and thickened: "classic" MVP is characterized by a leaflet thickness ≥ 5 mm, while "non-classic" MVP is defined by leaflet thickness < 5 mm. Furthermore, mitral annulus is usually enlarged.

Grey zone: MVP is one of the most frequent cause of mitral valve (MV) regurgitation in athletes[101]. If rare, cases of malignant arrhythmic prolapse have been reported and therefore this is a must be ruled-out condition[102-104]. Athletes usually has mild mitral regurgitation (MR), even if severe MR must be excluded (Table 10). Also pulmonary artery pressures (PAPS) and reverse flow in the pulmonary veins assessment should be performed. LV and LA dimensions must be evaluated to exclude cardiac chamber dilatation associated.

What to assess? MV prolapse. If pathological, what to assess? MR (vena contracta, CW jet area, PISA, MR flow, CW doppler, E wave) + PAPS + pulmonary vein flow + LV mass + LV function + LA dimension.

Other valvulopathies

Valvular heart disease is frequently related to degenerative processes and usually age-related[14], but may also involve younger individuals. Moreover, specific recommendations exist for athletes with valvulopathies[105]. Congenital defects are common cause of valvular heart disease in young individuals. Although cardiac magnetic resonance offers a better quality of imaging[106], these are conditions to be considered when performing an echocardiogram in athletes. Right-sided valvular pathologies and regurgitant lesions are better tolerated[107].

Valvular Stenosis

Aortic valve stenosis (AVS) counts for 5% of congenital heart defects, and is frequently caused by BAV[108]. Even if mostly asymptomatic, these subjects have a small but

Table 10 Echocardiographic criteria for the definition of severe valve regurgitation (adapted from[165])

	AVR	MVR	TVR
Vena contracta width (mm)	> 6	≥ 7	≥ 7
Other	Pressure half-time < 200 ms	TVI mitral/TVI aortic > 1.4	PISA radius > 9 mm
EROA (mm^2)	≥ 30	≥ 40	≥ 40
Regurgitant volume (mL/beat)	≥ 60	≥ 60	≥ 45

AVR: Aortic valve regurgitation; EROA: Effective regurgitant orifice area; MVR: Mitral valve regurgitation; PISA: Proximal isovelocity surface area; TVR: Tricuspid valve regurgitation; TVI: Time velocity integral.

significant risk of sudden death[109]. Echocardiography is the gold standard diagnostic tool[110] (Table 11).

Mitral valve stenosis (MVS) in young individuals can be of rheumatic origin. It results in elevated LA pressure and eventually pulmonary hypertension. An exercise-related cardiac output increase can lead to acute pulmonary edema[111]. The degree of MVS can be categorized through echocardiography (Table 8).

Tricuspid valve stenosis (TVS) can be caused by rheumatic fever and is frequently associated with MVS, rather than alone[111].

Pulmonary valve stenosis accounts for about 10% of the congenital heart syndrome [112]. It is commonly present in tetralogy of Fallot, Nooan syndrome and maternal rubella syndrome[113]. Most of these patients are asymptomatic, but rarely SCD. Evaluation of pulmonary stenosis is best evaluated with echocardiography[114,115].

Valvular regurgitation

Valvular regurgitation is a common and often harmless condition in athletes. In particular, mitral and tricuspid regurgitation are widely diffused in young subjects [116].

The more common causes of aortic valve regurgitation (AVR) include BAV, rheumatic fever, endocarditis, Marfan syndrome and aortic dissection. AVR causes LV dilatation with subsequent LV pressure and volume loading. LV dilatation should be evaluated by echocardiography. Often LV cavity dimension can be raised in healthy athletes[111]. Quantification of AVR is seen in Table 9.

There are many causes of mitral valve regurgitation (MVR), including MVP, endocarditis, rheumatic heart disease, coronary artery disease, and dilated cardiomyopathy[117]. In athletes, mitral regurgitation is mostly related to MVP. Quantification of MVR is showed in Table 9.

Tricuspid valve regurgitation (TVR) is often the result of RV dilatation. Primary TVR leads to RV volume overload and increased venous pressure. The severity of TVR can be determined by echocardiography (Table 10)[111].

CONGENITAL HEART DISEASES

A once-in-a-lifetime echocardiography allows to identify congenital heart disease in order to plan an individualized follow-up and exercise recommendation, other than screening of the athlete's family.

ANOMALOUS ORIGIN OF CORONARY ARTERIES

Anomalous origin of coronary arteries (AOCA) is a rare but recognized cause of sports related SCD[108], often missed to ECG. Identification of AOCA is not easy because these are often asymptomatic individuals and do not necessarily exhibit distinctive features on ECG stress testing. Even if echocardiography is not the gold standard for its diagnosis, this examination is the first line test recommended when there is such a suspicion also because it is the only noninvasive tool to visualize the ostia and first tracts of coronary arteries[118-120]. Each coronary artery (CA) usually originates from its respective sinus above the aortic valve leaflets, with the right CA (RCA) arising from the right sinus of Valsalva and the left main CA (LCA) arising from the left sinus of Valsalva[121]. Not all AOCA have the same prognostic impact: the most at-risk

Table 11 Echocardiographic parameters indicative of the degree of severity of different valve stenosis (adapted from[111,165])

	AVS			MVS			TVS	PVS		
	Low	Moderate	Severe	Low	Moderate	Severe	Clinically significant	Low	Moderate	Severe
V max (m/s)	2.6-2.9	3.0-3.4	≥ 4.0					< 3	3-4	≥ 4
DP mean (mmHg)	< 30	30-40	≥ 40	< 5	5-10	> 10	> 5	< 30	30-50	> 50
Valve orifice area (cm^2)	> 1.5	1.0-1.5	< 1.0	> 1.5	1.0-1.5	< 1.0				

AVS: Aortic valve stenosis; MVS: Mitral valve stenosis; TVS: Tricuspid valve stenosis; PVS: Pulmonary valve stenosis; PAP: Pulmonary artery pressure.

anomalies include an anomalous origin from a wrong aortic sinus [aortic anomalous origin of coronary arteries (AAOCA)[15]].

About the AAOCA, the ostium and proximal course of the left main and right coronary arteries can be visualized by echocardiography respectively in over 98% and 80% of subjects[122], especially from a PSAX view. The left main CA origin is approximately 4 o'clock and the RCA origin at 11 o'clock. Additional color flow mapping can help in the identification process[123]. Occasionally, clockwise rotation of the transducer in the PSAX view frequently allows the identification of the left main CA as it bifurcates into the left anterior descending branch and the left circumflex branch.

In infants and small children with good subcostal windows, the LCA origin can be seen from a coronal plane; the RCA origin is frequently best seen from a PLAX view.

What to assess? Origin of coronary arteries (PSAX). if pathological, what to assess? Additional color flow mapping of the inter-arterial space.

BICUSPID AORTIC VALVE

BAV is one of the most common congenital cardiac abnormalities[124]. Subjects with BAV may consequently have larger dimensions of the aortic sinus, ascending aorta, and aortic arch[15,89], beside possible progression to subsequent valvulopathies. The most common fusion pattern involves the right and left cusps[125]. Moreover, BAV may be associated with other diseases such as coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly, as well as Williams or Turner syndrome[126,127]. The leaflets number and fusion, and the presence of a 'raphe' can be easily evaluated in the PSAX view, while systolic doming is better seen in PLAX view. Doppler echocardiography permits assessment of valve dysfunction[110,128]

What to assess? Aortic valve morphology (PSAX). If pathological, what to assess? Aortic stenosis + aortic regurgitation + dimension of aortic root (PLAX) + other congenital defects (coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly or hypoplastic left heart, as well as Williams or Turner syndrome).

ATRIAL SEPTAL DEFECTS

Atrial septal defect (ASD), the failure to close the communication between RA and LA, afflicts 1 in 4 children[129]. There are five subtypes of atrial septal defects: patent foramen ovalis, ostium secundum defect, ostium primum defect, sinus venosus defect, and coronary sinus defect[89,130]. The atrial septum can be assessed from subcostal, apical and PSAX[131,132] views, even if subcostal is the preferred one. The four-chamber view allows hemodynamic assessment of the ASD (RA and RV dilatation) RV pressure estimation (TVR jet velocity). Associated lesions include anomalous pulmonary venous connection, pulmonary valve stenosis, and mitral valve prolapse. This condition is frequent in Ebstein anomaly[89].

What to assess? ASD (subcostal). If pathological, what to assess? ASD (A4C/PSAX) + RA dimension + RV dimension + PAPS.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSD) are the most common congenital cardiac abnormality in young individuals and the second one in adults, following only BAV[133]. Four locations of the defect within the interventricular septum are possible. Multiple windows can be used to assess the ventricular septum[131], such as PSAX and A4C views. VSD is also a common component of complex anomalies, such as Tetralogy of Fallot (ToF) and transposition of the great arteries (TGA)[89]. Key findings to provide are location, number, and size of defects, severity of LV volume overload, and estimated PAPS. Double chambered right ventricle (DCRV) and sinus of Valsalva aneurysm must be ruled out[89].

What to assess? VSD (A4C). If pathological, what to assess? LV mass + PAPS + aortic regurgitation + other congenital defects (aneurysm of Valsalva sinus, ToF, TGA, DCRV).

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus (PDA) is the lasting communication between the proximal left pulmonary artery (PA) and the descending aorta, just distal to the left subclavian artery[89]. Echocardiography is choice diagnostic tool[131]. PDA is best seen from the PSAX and suprasternal windows, where the duct can be visualized along the left border of the pulmonary artery: there is bidirectional flow across the duct, confirmed on pulsed wave doppler (PW); moreover, LA/Aortic root ratio ≥ 1.4 is suggestive of shunt[134]. A complete echocardiographic assessment should be performed to exclude pulmonary atresia or coarctation of the aorta. Furthermore, it must be assessed the degree of LV volume overload, PAPS, PA size, and right heart change.

What to assess? PDA (PSAX). If pathological, what to assess? PWPDA (PSAX) + LA/Aortic root ratio ≥ 1.4 + LV mass + PAPS + PA size + RV dimension + RA dimension.

AORTIC COARCTATION

Aortic coarctation (CoA) is considered a part of a more general arterial disease[89]: It occurs as a stenosis or as a hypoplastic aortic (arch) segment. Associated lesions include BAV ascending aortic aneurysm, aortic stenosis, mitral stenosis or complex congenital heart defects. Echocardiography provides information regarding site, structure, and extent of CoA, LV function and LVH, and aortic vessel diameters[89].

What to assess? Aortic coarctation (PSAX). If pathological, what to assess? Aortic stenosis + mitral stenosis + FE + LV mass + other congenital defects (BAV, ascending aortic aneurysm).

OTHER CONGENITAL DISEASES

Improvements in modern medicine has led to an increase in the number of adults with congenital heart disease engaging in sports activities[89,135]. Therefore, an echocardiography assessment of others various congenital heart diseases is crucial for sport eligibility.

ToF is a congenital cardiac malformation made by VSD, RVOT obstruction, override of the ventricular septum by the aortic root, and RV hypertrophy[136]. The initial presentation of ToF varies depending on the severity lung blood flow obstruction. Echocardiography has become the standard modality in its diagnosis[137]. The ventricular septal defect, the aortic override, and RV hypertrophy can be seen in PLAX view, while the pulmonary outflow tract obstruction in PSAX view[138].

Transposition of the great vessels is a group of congenital heart defects involving an abnormal spatial arrangement of any of the great vessels[139]. Congenital heart diseases involving only the primary arteries (pulmonary artery and aorta) belong to a sub-group called TGA: the aorta aligns with the RV and the pulmonary artery aligns with the LV[140]. It is the fourth most common type of major cardiac defect[141] and the second most common cyanotic lesion after ToF[140]; if not treated, it is the leading cause of SCD in neonates and infants[142]. Important echocardiographic assessments in case of TGA are position of the great arteries in PLAX or subcostal views, presence

of ASD and VSD, presence of LVOT obstruction, eventual anomalies of coronary arteries[140].

Ebstein's anomaly (EA) is a malformation of the tricuspid valve (TV) with myopathy of the RV[143]. Initial presentation of EA in adulthood is common, and natural history demonstrates decreased survival with biventricular failure[144]. Echocardiography is the imaging standard in EA and provides a platform for TV leaflet, determination of right-heart size and function and dynamic evaluation of intracardiac shunts and defects, through color doppler[143,145].

Complete atrioventricular canal, also referred to as complete atrioventricular septal defect, is characterized by an ostium primum atrial septal defect, a common atrioventricular valve and a variable deficiency of the ventricular septum inflow[146]. It is a rare congenital heart condition. Echocardiography is the key tool for its diagnosis and anatomic classification[147].

OTHER PATHOLOGIES

Even if these are acute conditions that usually manifest with other symptoms, these pathologies are often cause of sudden cardiac death in athletes and therefore need to be screened.

MYOCARDITIS

Myocarditis accounts for almost 15% of SCDs in younger populations, especially in athletes[148]. The clinical presentation varies from chest pain, exertional dyspnea and fatigue, to cardiogenic shock[148]. Some patients heal completely while other may evolve in DCM[149]. An higher incidence of sport related SCD in case of myocarditis is documented[148], for the higher rate of life-threatening ventricular arrhythmias[150]. In acute form, echocardiography may show global LV dysfunction[151], wall motion abnormalities and pericardial effusions[15,152,153], an diffuse myocardial edema (increased wall thickness)[154-157]. In healed form, echocardiographic LV systolic dysfunction is found rarely because there is often small myocardial fibrosis, with undetectable scar at echocardiography[158]: Its evaluation still represent one of the bigger challenges of sport cardiology.

What to assess? EF; LV wall motion abnormalities; pericardial effusion; increased LV wall thickness.

PERICARDITIS

In athletes presenting with chest pain, the diagnosis of pericarditis should always be taken in consideration[159], particularly in younger ones[160]. Pericarditis and myocarditis may coexist in 20%–30% of patients[135]. Specific sport recommendations exist for patients with this disease[135]. Echocardiography is the diagnostic test of choice. The presence of pericardial fluid is recorded as an echo-free space between the posterior pericardium and left ventricular epicardium (in case of small effusion) or anterior right ventricular epicardium (in case of larger effusion)[159]. It can be assessed mostly in subcostal view.

What to assess? Pericardial effusion.

KAWASAKI DISEASE

Kawasaki disease (KD) is an acute vasculitis affecting young children, resulting in coronary artery abnormalities in case of delayed diagnosis[161,162].

Echocardiography is the imaging modality of choice for its detection: LV function and wall motion, of valvar regurgitation (particularly the mitral and aortic valves), and pericardial effusion should be assessed[163,164].

What to assess? Coronary artery abnormalities (PSAX/PLAX); EF; LV wall motion abnormalities; mitral regurgitation; aortic regurgitation; pericardial effusion.

CONCLUSION

Echocardiography is a valuable tool helping in detecting several CV conditions afflicting athletes. As physicians become more experienced with sonography, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices. This technique could help to detect some hidden CV condition and to distinguish between physiological and pathological adaptation to physical activity, assisting in sport eligibility process. Even if we admit that a good manual skill, a training period and echocardiography experience should be required to perform it, our athlete-focused echocardiography could be an effective time-saving first line evaluation tool in sport eligibility process, eventually followed by a carefully exam. As such, a focused cardiac ultrasound examination may optimize cost-effectiveness: early detection of asymptomatic structural heart conditions could have important prognostic implications, with a relative less expensive cost than a complete echocardiogram. Nevertheless, further clinical trials should investigate its efficacy, accuracy, and applicability.

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In-depth review of cardiopulmonary support in COVID-19 patients with heart failure

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Abstract

Coronavirus disease 2019 infection has spread worldwide and causing massive burden to our healthcare system. Recent studies show multiorgan involvement during infection, with direct insult to the heart. Worsening of the heart function serves as a predictor of an adverse outcome. This finding raises a particular concern in high risk population, such as those with history of preexisting heart failure with or without implantable device. Lower baseline and different clinical characteristic might raise some challenge in managing either exacerbation or new onset heart failure that might occur as a consequence of the infection. A close look of the inflammatory markers gives an invaluable clue in managing this condition. Rapid deterioration might occur anytime in this setting and the need of cardiopulmonary support seems inevitable. However, the use of cardiopulmonary support in this patient is not without risk. Severe inflammatory response triggered by the infection in combination with the preexisting condition of the worsening heart and implantable device might cause a hypercoagulability state that should not be overlooked. Moreover, careful selection and consideration have to be met before selecting cardiopulmonary support as a last resort due to limited resource and personnel. By knowing the nature of the disease, the interaction between the inflammatory response and different baseline profile in heart failure patient might help clinician to salvage and preserve the remaining function of the heart.

Key Words: COVID-19; Heart failure; Cardiopulmonary support; Extracorporeal membranous oxygenation; Ventricular assist device; Coagulopathy

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Core Tip: Coronavirus disease 2019 (COVID-19) infection might cause severe respiratory distress and demonstrates an extrapulmonary involvement. Recent evidence shows direct involvement of COVID-19 and deterioration of the heart function. Severe infection is commonly found in high risk population, indicates a complex interaction between host inflammatory response and the infection itself, signifies the use of cardiopulmonary support and associated with high mortality. There are relatively scarce information regarding the use of ventricular assist device and extracorporeal membrane oxygenation and here we will be discussing the possible mechanism of how cardiopulmonary support may improve COVID-19 infection outcome.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging viral infection which has caused global pandemic with resulting both high global economic burden and mortality rate [1,2]. It also caused an alteration and restructuration in our healthcare system, especially in treating patients with infection and chronic disease[3]. Patients with both condition of COVID-19 and prior cardiovascular disease have an increased risk of cardiovascular complications which severely affect the mortality rate.

COVID-19 is also associated with higher incidence of cardiovascular complication in compare to previous coronavirus outbreaks[4,5]. Deterioration of the cardiac function is prominent in COVID-19 and those with lower baseline function are prone to further decline in cardiac function. A study demonstrate the preexistence of chronic heart failure (CHF) and high cardiac biomarkers is associated with worse outcome[6]. Recent study also shows that patient with heart failure (HF) is associated with an increased risk of mechanical ventilation and overall mortality regardless of left ventricular ejection fraction (LVEF)[7].

The use of cardiopulmonary support in COVID-19 shares the same prominent role in managing severe conditions such as severe respiratory distress and heart failure[3,8]. However, there are several distinct clinical characteristics of HF patients which may differ from non-pre-existing HF patients. These factors have to be considered before choosing cardiopulmonary support as a treatment of choice. Another challenging issue is the highly selective inclusion and exclusion criteria before a patient is eligible for the use of extracorporeal membranous oxygenation (ECMO). Therefore, the management of both HF and COVID-19 has to be tailored since the concept of one treatment fits all might not suitable in these patients.

HEART FAILURE AND COVID-19

The mechanism of cardiac function disturbance in COVID-19 is poorly understood and it is thought to be an interaction between several mechanisms including direct myocardial injury, cytokine release, prothrombotic state causing microvascular thrombosis and exacerbation of underlying cardiovascular disease[3,9-13]. In the context of COVID-19, CHF patients are vulnerable to acute exacerbation. These patients are at risk because of their lower baseline status which unable to cope with the increasing metabolic demand in systemic inflammation triggered by the infection[14]. In the settings of advanced HF with left ventricular assisted device (LVAD) support, functional capacity of the lung has already impaired and contributes even more to the decrease of the cardiopulmonary reserve[15,16].

Several studies have demonstrated more severe infections and higher mortality rate in patients with preexisting cardiovascular disease[6,7,14,17]. Older age along with other comorbid such as obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease and frailty are seems to

be more prevalent in the HF group and might contribute to an increased rate of mortality and morbidity[7,18]. Moreover, these patients generally have a reduced immunity, general frailty, an tend to be in an inflammatory state[14,19].

A lower pulmonary function is commonly found in HF patients and is contributed mainly by chronic obstructive pulmonary disease (COPD)[20]. Combination of underlying parenchymal disease and elevated left ventricular filling pressure leads to the development of pulmonary hypertension[21]. In COVID-19 infection, respiratory failure and acute respiratory distress syndrome (ARDS) further exacerbates pulmonary vasoconstriction and interstitial edema. This condition is further worsened by pre-existing biventricular failure and ARDS that eventually lead to right ventricular function impairment.

Recent studies have shown that COVID-19 is associated with acute myocardial involvement which described as an acute cardiac injury[3,12,13]. A suspicion of cardiac involvement in COVID-19 is best described by an elevation in cardiac biomarker [high-sensitivity troponin (hs-TnI)] above 99th percentile upper reference limit[13,22]. Early reports had been analyzed, with notable findings suggest an increased level of cardiac troponin was associated with admission to intensive care and higher in hospital mortality[12,23-26]. A careful observation of endomyocardial biopsy in COVID-19 patients has revealed an evidence of acute myocardial inflammation through the presence of viral particles and a diffuse myocardial edema on cardiac magnetic resonance, therefore raising the suspicion of direct viral myocardial invasion[27]. Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV2) binds with angiotensin-converting enzyme 2 (ACE2) receptor and with the help of transmembrane protease serine 2 (TMPRSS2), facilitates viral entry through the cell[28,29]. ACE2 and TMPRSS2 are widely expressed in various tissue, including the heart, and might explain the involvement of heart during the course of infection[29]. Viral inclusion bodies were found from the biopsy of myocardial tissue along with identification of SARS-CoV2 genomic RNA in patients with suspected COVID-19 myocarditis, therefore raising the possibility of direct viral invasion to the myocardium[30-33]. Although there was a high viral load which is associated with higher proinflammatory cytokine expression in the cardiac tissue, these findings were not accompanied with an elevated inflammatory cell infiltrates[34]. The exact proportion of myocarditis is still hard to be determined, mainly because of the lack of definitive diagnostic procedure done in the patients[13,27]. However, myocarditis is important to be considered as it may cause abnormal electrical conductance in the myocardium[10].

Myocardial infarction plays a significant role in the development of acute HF in COVID-19 infection. Both Type I and II myocardial infarction might occur in patient with COVID-19, worsening the function in an already impaired baseline function[3]. This may leads to worse outcome in patient with a history of HF[3].

Cardiac arrhythmia is a major concerning issue in the context of HF and COVID-19 infection. Careful observation of the heart rate and rhythm are vitals in the clinical settings. Atrioventricular block, atrial fibrillation, polymorphic ventricular tachycardia and pulseless electrical activity have been closely associated with COVID-19 despite of the unknown mechanism of how these rhythms abnormalities may develop[22,35]. QT prolongation is constantly a thread, considering that QT prolongation is an independent risk factor of adverse outcome in advanced heart failure[36]. Even though the use of hydroxychloroquine and azithromycin is no longer recommended due to the lack of evidence to reduce mortality and severity, patients with HF are often already have underlying structural abnormalities. These abnormalities are related to the delay of ventricular repolarization which is manifested on electrocardiogram (ECG) as prolonged QT interval[37-39]. The use of another agents such as loop diuretic, may promote electrolyte imbalance and increase the risk of developing malignant arrhythmia. Sepsis is a known risk factor for QT prolongation that has to be considered in these patients[40]. The proposed mechanism of cardiac function deterioration is depicted in Figure 1.

ROLE OF INFLAMMATORY RESPONSE IN HEART FAILURE PATIENTS WITH COVID-19

Profound cytokine release in the setting of severe COVID-19 infection is commonly found. The release of proinflammatory cytokines, increased metabolic demand and coagulation disorder in sepsis may contribute to the development of new onset HF and decompensation episodes in CHF[41]. Cytokine storm is observed in viral induced infection such as influenzae and COVID-19 and in the setting of graft-versus-host

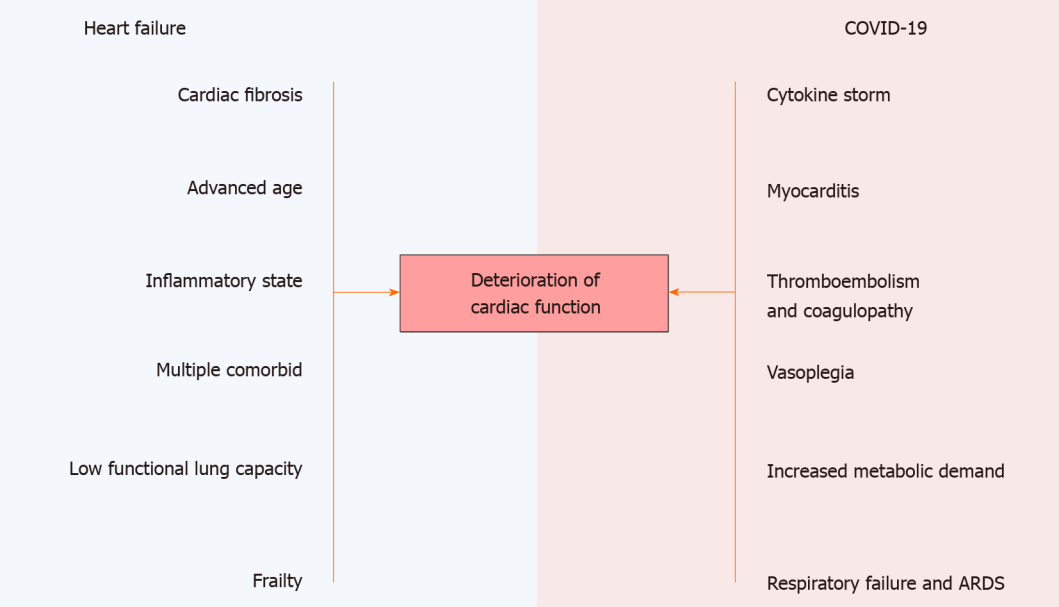


Figure 1 Proposed mechanism of deterioration of cardiac function in preexisting chronic Heart failure patient with coronavirus disease 2019 infection. CHF: Chronic Heart failure; COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome.

disease. Lymphopenia, C-reactive protein, lactate dehydrogenase, ferritin, D-dimer and troponin are among the biomarkers that reflect the severity of the hyperinflammatory state[42,43]. In HF, the inflammation happened as a response to the myocardial stressors. Multiple preexisting comorbidities that might further contribute to the profound inflammatory response are coronary artery disease, hypertension, arrhythmia, diabetes, and obesity. Increased level of inflammatory cytokine directly linked to the deterioration of the heart function[44,45]. The increased level of several cytokines such as tumor necrosis-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and galectin-3 may predict worse outcome in HF patients[46,47]. Interestingly, an elevation of IL-6 Level is also seems to be correlated with mortality in COVID-19 infection[48]. Moreover, the systemic hyperinflammation state that might occur in the setting of COVID-19 has extrapulmonary involvement and causing additional burden to the heart. The effect of hyperinflammation is well reflected by an elevation of cardiac biomarkers such as troponin and N-terminal pro B-type natriuretic peptide [43]. In this stage, vasoplegia and myocarditis might also occur[43].

Pro-inflammatory response which is induced by the infection might worsen hypoxia which in turn causing more stress to the damaged heart[42]. Hypoxia serves as a risk factor of survival in COVID-19 patients and should not be overlooked since it has deleterious effect in patients with HF and COVID-19[49]. Acute respiratory distress syndrome and exaggerated inflammatory response contributes to the development of hypoxia which may cause cardiac lesion and further exacerbates HF[50-53].

COAGULOPATHY IN THE WORSENING HEART DURING COVID-19

Coagulopathy is a common disorder found in COVID-19 infection. It is thought that the interaction between host defense mechanism and coagulation system during COVID-19 infection may lead to hypercoagulability and a high prevalence of thrombotic events[54-56]. This finding is reinforced by an elevated D-dimer level which is often present in the setting of COVID-19 infection[5,55]. The combination of endothelial dysfunction, inflammatory state, oxidative stress and platelet activation are thought to be responsible for a hypercoagulable state[1,5,55]. The true nature of the course is remain unknown to date, however the role of endothelial activation cannot be overlooked. It is thought that ACE2 receptor that serves as an entry point for the SARS-CoV-2 into the cell, plays an important role[57,58]. The presence of ACE2 receptors on the endothelial cells as well as antithrombin (AT), heparin and other anticoagulation might play an important role in regulating the inflammatory response [57]. AT interacts with heparin-like glycosaminoglycan (GAG) on endothelial surface and therefore involved in the release of prostacyclin which will inhibit leukocyte

activation by decreasing IL-6 Level[57,59]. The hypercoagulability state is also involved in the development of both micro- and macrovascular thrombus and may also plugs the extracorporeal circuits[5,55]. Grave consequence of thrombosis may occur in COVID-19 patients as it may present as pulmonary venous thrombosis leading to right heart failure and or microvascular thrombosis may leads to myocardial dysfunction, worsening the heart function[5,55,60-62].

Patients with a preexisting history of heart failure are already in an increased risk for developing thromboembolism due to venous stasis, endothelial injury, ischemic cardiomyopathy and atrial fibrosis[63,64]. This condition might be worsened by the presence of COVID-19 infection which may trigger coagulopathy and the presence of implantable device which also may trigger thrombosis[65,66]. The pre-existing cardiopulmonary support such as left ventricular assisted device (LVAD) alone might increase the risk of developing pump thrombosis, although the risk of stroke with co-existing COVID-19 infection has not been assessed yet[3,67].

CARDIOPULMONARY SUPPORT IN COVID-19 PATIENTS WITH HEART FAILURE

Patient with COVID-19 might require mechanical circulatory support as a consequence of COVID-19 induced cytokine release syndrome or cytokine storm[3]. Hypoxemic respiratory failure may cause circulatory collapse in a small subset of patients and the need of lung-protective ventilation (LPV) in these patients is evident [68,69]. The use of extracorporeal life supports (ECLS) is reserved for patients with refractory hypoxemia or hypercarbia, right ventricular failure as a consequence of hypercarbia and acidemia, and hypoxic pulmonary vasoconstriction. These patients might have benefit from the use of venovenous (V-V) ECMO while those who suffer from refractory cardiogenic shock might consider the use of venoarterial (V-A) ECMO which might improve cardiac condition by pronounced LV unloading[70-72].

However, the use of these devices is remain in question since significant resources such as specialized equipment and trained personnel are needed to plant and maintain the device[4,42]. The decision of implanting the device might be considered for patients with ARDS and or cardiogenic shock refractory to traditional management with favorable outcome with the use of the device[68]. Close monitoring is also essential and health care workers exposure is also needed to be looked closely[42]. Still, despite the use of cardiopulmonary support, management of patients with HF and COVID-19 infection remain difficult due to complex interaction between the volume status and the biventricular dynamics[42]. There are also strict criterias have to be met before implanting ECMO in COVID-19 patient. While there are no difference for indication of ECMO between COVID-19 and non-COVID-19 patient, there are several things to be remembered[68]. First, careful selection is needed as patients with advanced age and significant comorbidities might not have much benefit from the use of ECMO. Also, patient with underlying CHF tend to be older, have multiple existing comorbidities and often fall into profound clinical status in the natural course of COVID-19 infection[6,7,14]. Therefore, the use of ECMO should be restricted in these patients unless there are a reasonable chance of recovery[5]. The use of ECMO should be carefully taken, considering that the hospital capacities and resources are limited in most settings and the possible outcome that the patient might achieve[5,42,68].

There are some small subset of patient who may choose another options in regard to the treatment of advanced HF. Patients who are not eligible for the heart transplant might use the left ventricular assist device (LVAD). However, the use of this device is not without risk, especially in the context of COVID-19 infection. These patients are known to have different types of HF that may produce different inflammatory profile in response to the implanted device[47]. To the best of our knowledge, until now there are no specific indication of when to implant ventricular assist device (VAD) in the context of severe COVID-19. First reported case of VAD implantation in patient with COVID-19 infection demonstrate the possibility of VAD as an alternative in a setting of prolonged cardiogenic shock and hemodynamical instability with modest chance of VA ECMO weaning[65]. Careful consideration and assessment of patient's clinical status has to be put in top priority in determining when to implant the device. The indications and contraindications for ECMO in COVID-19 is described in Table 1.

The presence of hardware in the body and prolonged support such as LVAD may cause immune dysregulation, increase the risk of infection and cellular immunity impairment as prior studies had already demonstrated[47,66,73,74]. In COVID-19, severe inflammatory response might induce profound patient's clinical status and

Table 1 Indications and contraindications for Extracorporeal membranous oxygenation in coronavirus disease 2019

Indications for ECMO	Contraindications for ECMO
V-V ECMO; PaO_2/FiO_2 < 60 mmHg for > 6 h < 50 mmHg for > 3 h; pH < 7.2 with $PaCO_2$ > 80 mmHg for > 6 h V-A ECMO; Refractory cardiogenic shock; Persistent tissue hypoperfusion; Systolic blood pressure < 90 mmHg; Cardiac index < 2.2 L/min/m^2 while receiving noradrenaline > 0.5 mcg/kg/min; Dobutamine > 20 mcq/kg/ min or equivalent	Relative contraindications; Age ≥ 65 yr old; Body mass index ≥ 40; Immunocompromised status; No legal medical decision maker available; Advanced chronic underlying systolic heart failure; High dose vasopressor requirement (and not under consideration for VA or V-VA ECMO); Absolute contraindications; Advanced age; Clinical frailty scale category ≥ 3; Mechanical ventilation > 10 d; Significant comorbidities: Chronic kidney disease ≥ III; Cirrhosis; Dementia; Baseline neurological disease which might prohibit rehabilitation potential; Disseminated malignancy; Advanced lung disease; Uncontrolled diabetes with chronic end-organ dysfunction; Severe deconditioning; Protein-energy malnutrition; Severe peripheral vascular disease; Other preexisting life-limiting medical condition; Nonambulatory or unable to perform activities; Severe multiple organ failure; Severe acute neurologic injury (example: anoxic, stroke); Uncontrolled bleeding; Contraindications to anticoagulation; Inability to accept blood products; Ongoing cardiopulmonary resuscitation

ECMO: Extracorporeal membranous oxygenation; V-V: Veno-venous; V-VA: Veno-Venoarterial; V-A: Veno-arterial.

worse outcome. The pre-existing LVAD in severe COVID-19 infection may raise some concerns in the context of management. The risk of pump thrombosis has to be kept in mind, as hypercoagulability state in COVID-19 infection and the pump itself may induce thrombosis[65]. Despite of severe hypoxemia might improve by prone position, there is a specific concern of the outflow graft compression, driveline damage and elevated pressure in the right ventricle with subsequent right ventricular failure[66,67]. Moreover, additional load to the right ventricle may predispose to right heart failure which is well known as a potential etiology of hypotension in the setting of LVAD use and inflammatory surge[66,67]. However, prone position in patients with LVADs is not contraindicated in the management of hypoxemic respiratory failure although more data are needed[3].

Anticoagulant use in LVAD patient has to be closely monitored due to a high risk of thrombosis in this population[3,14]. More interestingly, patient with COVID-19 infection may often shows a hypercoagulability state despite therapeutic dose of anticoagulation and to overcome this state, requires an increase dose which will carry the risk of life-threatening bleeding[75]. Still, thromboembolism carries a significant risk of adverse outcome and the use of closely monitored anticoagulation might have a beneficial role[55].

Several biomarkers that reflect the severity of hyperinflammation in COVID-19 might be obtained before the infection and serves as a baseline markers in patient with LVAD. Baseline lactate dehydrogenase (LDH), absolute lymphocyte count, troponin and natriuretic peptide that are taken prior the infection might bring an important information that should not be overlooked[42]. These indicators are valuable in following LVAD patients with COVID-19 infection[42]. The role of cardiopulmonary support in COVID-19 infection is illustrated in Figure 2.

CONCLUSION

As discussed above, COVID-19 infection has deleterious effect on the heart function. In addition, exaggerated inflammatory response in severe COVID-19 infection in combination with preexisting impairment of the heart function and multiple comorbid as seen in the HF patients may severely affect the outcome. Cardiac function in patient with HF should not be overlooked as deterioration of the heart function may occur rapidly as a consequence of the infection. Therefore prompt diagnosis and early monitoring of the heart function are critical in the management. Careful monitoring of inflammatory marker during the course of the disease might also play an important role, as patient with advanced HF often have their baseline checked regularly. Any elevation of the inflammatory marker might serve as a clue of worsening inflammation and the heart function.

Another thing needs to be considered is the use of anticoagulation in severe COVID-19 patients with heart failure might have beneficial effect. Hypercoagulability state is often found in the patient, it is possibly because of the inflammatory response and the implanted device that may induce coagulation. However the risk of bleeding has to be kept in mind since fluctuant international normalized ratio and overt bleeding is not uncommon[55,76-78].

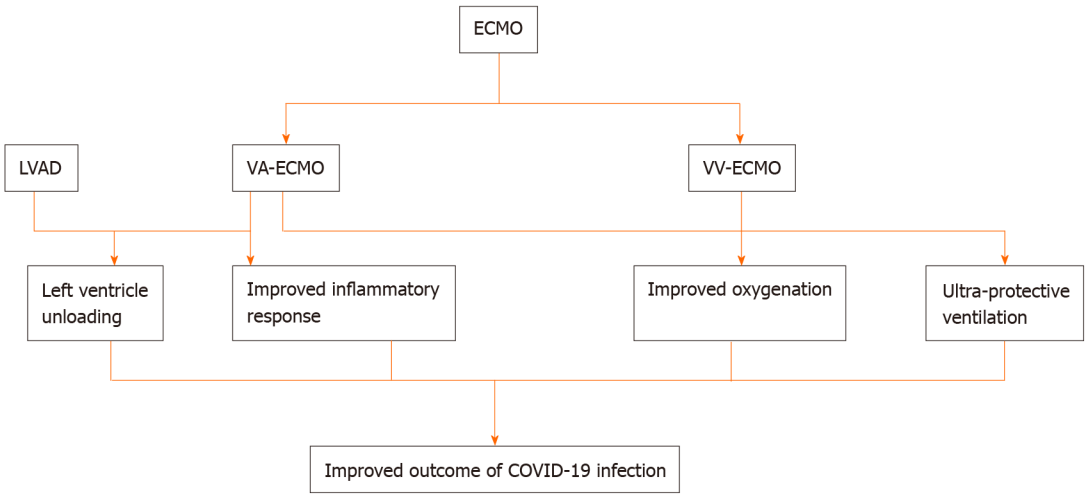


Figure 2 Proposed role of cardiopulmonary support in coronavirus disease 2019 infection. ECMO: Extracorporeal membranous oxygenation; LVAD: Left ventricular assist device; VV: Venovenous; VA: Venoarterial; COVID-19: Coronavirus disease 2019.

The use of cardiopulmonary support in this patient remains an issue. A small subset of patients with implanted LVAD also need to be concerned as unfamiliarity of the healthcare personnel to the device and the possible manipulation of the patient's position such as prone position might increase the right ventricular pressure and might lead to hypotension[66]. The use of ECMO and COVID-19 is very challenging due to its highly selective criteria and contraindicated in most patient with COVID-19 due to multiorgan dysfunction, significant comorbidities and the risk of bleeding[5,8].

Currently, supportive treatment remain the mainstay of treatment for COVID-19 infection. Focus is now directed on primary prevention and vaccination program. High burden and mortality rate was found in patient with preexisting cardiovascular disease, therefore American college of cardiology recommends to prioritize vaccination program in this high risk group[79].

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MINIREVIEWS

Surgical strategies for severely atherosclerotic (porcelain) aorta during coronary artery bypass grafting

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Abstract

Porcelain aorta (PA) is an asymptomatic atherosclerotic disease, characterized by circumferential calcification throughout the whole perimeter of the aorta. It is seen in 2% to 9.3% of patients undergoing elective coronary artery bypass grafting (CABG) and makes manipulation of the ascending aorta impossible. It has been clearly shown that most emboli seen and detected during the CABG procedure occur during aortic cross-clamping and aortic side-clamping. Manipulation of porcelain or a severely atherosclerotic aorta increases the risk of perioperative stroke. The incidence of stroke after CABG is between 0.48% and 2.9%, and the risk is correlated with the extent and severity of the atherosclerotic disease. A conventional CABG procedure involves successive steps that include cannulation of the ascending aorta, application of a cross-clamp to the aorta, and partial clamping of the aorta to create the proximal anastomosis. Therefore in procedures that involve cannulation, clamping, or proximal anastomosis, and where aortic manipulation is inevitable, preassessment of the atherosclerotic aortic plaques is crucial. Although many surgeons still rely on intraoperative manual aortic palpation, this approach has very low sensitivity and underestimates the severity of the atherosclerotic illness. Imaging methods including preoperative computed tomography or intraoperative epiaortic ultrasonography enable modification of the surgical technique according to the severity of atherosclerosis. Various surgical techniques have been described to reduce the risk of atheroembolism that may lead to cerebrovascular events in patients with severely atherosclerotic ascending aorta. Anaortic or "no-touch" techniques that do not utilize aortic manipulation may significantly decrease the development of neurological complications by avoiding aortic maneuvers known to cause emboli. In cases where severe atherosclerotic disease or other factors preclude safe use of the ascending aorta, modifications in the surgical techniques, such as switching to different cannulation sites including the axillary/subclavian, femoral and innominate arteries, or using hypothermic ventricular fibrillation and in-situ

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pedicled arterial grafts, or performing proximal anastomoses at alternative anatomical locations will enable CABG operations to be performed safely with low morbidity and mortality rates in patients with porcelain aortas.

Key Words: Coronary artery bypass grafting; Cardiopulmonary bypass; Severe atherosclerotic aorta; Porcelain aorta; Stroke; Mortality

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Core Tip: Porcelain aorta (PA) is a serious atherosclerotic disease that prevents manipulation of the aorta, and it is seen in 2% to 9.3% of the patients undergoing elective coronary artery bypass grafting (CABG). Although various mechanisms have been proposed to explain the development of stroke in cardiac surgery, embolic events resulting from manipulation of the ascending aorta are the main cause of stroke. Perioperative stroke is still among the most crucial complications of CABG surgery with its high patient morbidity and mortality. The best approach to prevent embolic events is the use of alternative surgical techniques which aim to minimize or eliminate the manipulation of a severely atherosclerotic or completely calcified aorta. Here, surgical strategies which are used for the management of patients with PA are summarized.

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INTRODUCTION

Coronary artery bypass grafting (CABG) remains the standard of management for the multi-vessel and left main coronary disease, however it is associated with an increased risk of postoperative complications. Severe circumferential calcification of the aorta is defined as porcelain aorta (PA) and its frequency has been reported as 2% to 9.3% in patients who are undergoing elective CABG[1-4]. PA is a serious atherosclerotic disease that, due to increased risk of perioperative embolic stroke, precludes manipulation of the aorta during CABG operations. It is expected that cardiac surgeons will encounter more patients with PA, due to the gradual aging of the world population, the increase in life expectancy, and the increase in the number of co-morbid diseases such as diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, and peripheral artery diseases.

A conventional CABG procedure involves cannulation of the ascending aorta, two-stage cannulation of the right atrium, insertion of antegrade cardioplegia cannula for cardiac arrest, application of a cross-clamp (CC) to the aorta, partial clamping of the aorta to create the proximal anastomosis, and finally removing these cannulas in a certain order. Although various mechanisms have been defined in the development of stroke in patients undergoing CABG surgery, embolic events caused by intraoperative aortic manipulations remain the main cause of stroke[5-7]. Embolic signals that are monitored by intraoperative transcranial Doppler (TCD) ultrasonography have demonstrated that most of the emboli in CABG procedures emerge during cross-clamping and side-clamping[5-8]. Perioperative stroke is still one of the most important complications of CABG surgery and causes an increase in economic costs, due to excessive consumption of resources in addition to high patient morbidity and mortality. Stroke after CABG is seen in approximately 0.48%-2.9%[3,9-11] of the operations, and stroke risk increases with the presence and prevalence of the atherosclerotic disease[4,12,13]. Some preoperative variables such as advanced age, peripheral vascular disease, and diabetes have been stated as risk factors for the development of postoperative stroke[4,10,11].

Clamping the aorta during CABG increases the risk of postoperative stroke regardless of the severity of aortic disease[6,14]. The best approach to prevent cerebral embolic complications is to modify the surgical techniques to minimize or eliminate

the manipulation of a severely atherosclerotic or fully calcified aorta. To safely perform CABG operations with low morbidity and mortality rates, various methods including the use of axillary/subclavian artery[15-17], femoral artery (FA)[4,18], or innominate artery (IA)[15,19] for cannulation, utilization of aortic "no-touch" or anaortic off-pump CABG surgery[4,20-23], use of in-situ pedicle arterial grafts[24-26], hypothermic ventricular fibrillation[4,21,26,27] and carrying out the proximal anastomoses in different anatomic locations[28-30], have been suggested. This review examines the relevant studies on patients who have a severe atherosclerotic disease of the ascending aorta or PA, and who need to undergo CABG surgery. The surgical strategies for the prevention of perioperative atheroembolic events and management of severe aortic atherosclerotic disease or PA are summarized in detail.

DEFINITION OF PA

PA is an asymptomatic atherosclerotic disease that is characterized by circumferential calcification of the aorta and which renders manipulation of the ascending aorta impossible (Figure 1). It is detected incidentally in patients evaluated for cardiovascular or pulmonary diseases. The use of different diagnostic methods and differences in the definition makes it difficult to determine the true prevalence of PA[31]. Severe atherosclerosis of the ascending aorta is reported to be present in 2.0% of CABG patients[32]. Studies have shown that atherosclerotic disease most frequently affects the distal part of the ascending aorta, and calcified plaques are significantly more common than complex plaques[12,13]. This may be associated with a large number of patients (75%) treated with lipid-lowering drugs, which can lead to increased calcification of the atherosclerotic plaques.

Hangler *et al*[3] found that atherosclerosis in the ascending aorta was normal or mild in 151 patients (42.9%), moderate in 167 patients (47.5%), and severe in 34 patients (9.6%). Also, by using epiaortic ultrasound (EU) before manipulating the aorta, Daniel *et al*[2] graded atherosclerotic disease within the ascending aorta using an ordinal variable (grade 1–5), according to the presence and thickness of mobile atheroma. Grade 1: normal (< 2 mm thickness); Grade-2: minimal disease (2–3 mm); Grade-3: moderate disease (3-5 mm); Grade-4: severe disease (> 5 mm); and Grade-5: the presence of a mobile plaque within any part of the ascending aorta. Grade 1-2 aortic disease was detected in 450 (85.7%) patients and grade 3–5 disease in 75 (14.3%) patients. In another study, it was observed that 22% of patients had simple intraluminal atheroma and 2% of them had complex intraluminal atheroma[7].

Amorim *et al*[1] divided aortic calcifications into two types; Type 1 (circumferential calcification of the ascending aorta) and Type 2 (calcification of the descending aorta including the aortic arch, and no involvement in the ascending aorta). Also, Type I has been divided into two subgroups as Type Ia (the type in which calcified aorta is not likely to be clamped) and Type Ib (calcified aorta with possible clamping).

DIAGNOSIS: PREOPERATIVE AND INTRAOPERATIVE EVALUATION

The presence of an aortic plate thicker than 4 mm is associated with a significant risk of stroke[33,34]. Therefore, a preassessment of atherosclerotic aortic plaques should be performed before procedures such as cannulation, clamping, or proximal anastomosis during which aortic manipulation is unavoidable[13]. Calcification of the arch the ascending aorta may be visible on chest x-ray or fluoroscopy during coronary angiography, however, these are not adequate for evaluating the degree and extent of the disease. Frequently used diagnostic methods are computed tomography (CT), intraoperative epiaortic ultrasonography (EU), and transesophageal echocardiography (TEE).

Chatzikonstantinou *et al*[35] advocated that conventional CT angiography, with efficacy proven to be superior to TEE, should be the reference method for imaging the ascending aorta. Similarly, Park *et al*[36] stated that CT angiography significantly affected the perioperative management or follow-up plan of the patients, and they recommended the use of preoperative CT angiography as a routine test unless contraindicated. Park *et al*[36] obtained a multislice CT scan before CABG in 284 patients and found severely atherosclerotic aorta in 36 patients (12.7%) and severe left subclavian artery stenosis in 18 patients (6.3%) that would alter the conduit selection or grafting strategy. CT accurately diagnoses PA and provides information on the location and extent of aortic calcification. Also, it provides detailed information about the distribution of the disease through 3-dimensional images of the aortic wall[1,31].

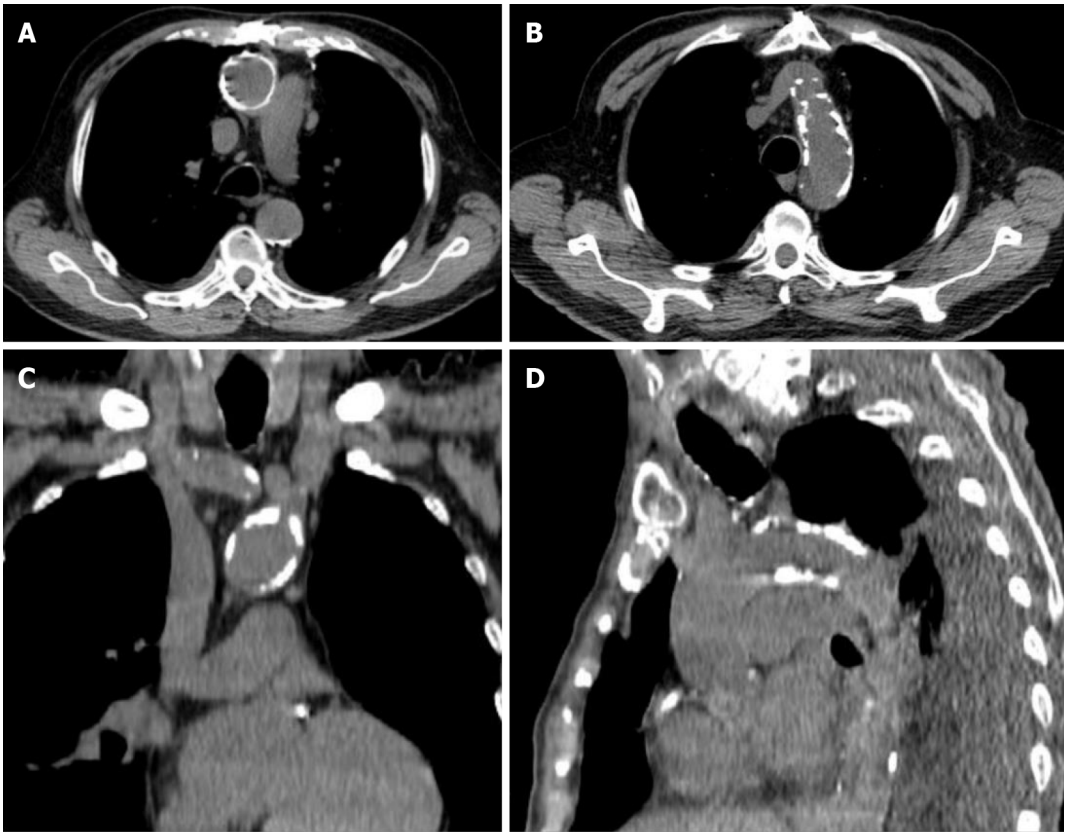


Figure 1 Porcelain aorta. Computed tomography reconstructions demonstrate circumferential calcification of the ascending aorta (A) and severe calcification of aortic arch (B-D).

There is evidence that EU is superior to manual palpation of the aorta and TEE in the detection of atherosclerotic disease of the ascending aorta and the aortic arch[37-39]. TEE evaluation of the distal ascending aorta, especially the CC and cannulation sites, is limited because the interposition of the left main bronchus between the esophagus and the aorta obstructs the vision[40]. Although many surgeons still rely on manual aortic palpation, this approach has a very low sensitivity and underestimates the severity[41]. EU is a simple and reliable solution to accurately scan the entire ascending aorta for the presence of intraluminal atheroma and has a sensitivity superior to both TEE and palpation[2,42,43].

INTRAOPERATIVE EPIAORTIC ULTRASONOGRAPHY

EU scanning is a fast, non-invasive and sensitive technique that provides information about the ascending aorta. Its use is limited because it does not allow preoperative planning, provides intraoperative information after the surgical incision has been made, extends the duration of surgery, needs special equipment, and requires trained personnel for both uses of the device and interpretation of the acquired data[7,44].

To determine any potential effect on intraoperative surgical decision-making, 6051 consecutive patients, who underwent EU of the aorta during cardiac operations have been analyzed retrospectively by Rosenberger *et al*[44] The overall effect of the EU on surgical decision-making is 4.1%. This effect was stated as 0.6% for off-pump CABG requirement, 0.5% for the avoidance of aortic CC, 0.2% for change in arterial cannulation area, or avoidance of aortic cannulation. In patients whose surgical plans changed, aortic atheroma was more common in the anterior aspect of the aorta than the posterior. The overall stroke rate is lower in patients in whom intraoperative EU was used, compared to all patients undergoing the surgical procedures[44]. Shapeton *et al*[7] prospectively evaluated the impact of EU on surgical cannulation strategy and cerebrovascular events, as well as its use in cardiac surgery. EU was performed by the surgeon using a high frequency (> 7 MHz) ultrasound transducer, and two-dimensional images of the ascending aorta were obtained in multiple planes before aortic cannulation and CC application. Aortic cannulation or CC strategy were altered based

on EU findings in 7% (19/269) of the cases. No difference was found between patients with and without EU in terms of stroke (1.9% *vs* 1.2% $P = 0.523$).

Hangler *et al*[3] performed EU screening in 352 patients who underwent primary CABG and modified the applied surgical strategy according to the severity of atherosclerosis. In the presence of moderate atherosclerosis (maximum aortic wall thickness between 3 and 5 mm), single aortic CC is preferred first, while in severe atherosclerosis (maximum aortic wall thickness > 5 mm) no-touch techniques (aortic no-touch techniques on the beating heart) were used. The surgical technique was modified in 31% of patients with moderate aortic atherosclerosis and 91% of patients with severe aortic sclerosis. While there was no perioperative mortality for mild disease, mortality rates were 3% for moderate disease and 9% for severe disease ($P = 0.005$). Stroke rates were 2.0%, 2.4% and 2.9%, respectively ($P = 0.935$). Similarly, Djaiani *et al*[45] showed that the use of EU led to changes in intraoperative surgical management in patients undergoing CABG surgery [16 (29%) of 55 patients in the EU group and 7 (12%) of 58 patients in the control group]. However, they showed that the use of EU did not lead to a decrease in the number of cerebral emboli detected by TCD before or during cardiopulmonary bypass (CPB). Bolotin *et al*[38] also showed that the EU led to a change in the surgical procedure in 28% of 105 patients undergoing CABG procedures.

In a retrospective study involving 2292 patients who underwent isolated off-pump coronary artery bypass (OPCAB), patients were divided into two groups [the non-EU group with OPCAB under intraoperative TEE only ($n = 1019$) and the EU group with OPCAB under the EU ($n = 1273$)]. In both groups, OPCAB was performed with or without a partial aortic clamp. There was no statistically significant difference in the incidence of early stroke between the groups with and without EU (non-EU 1.7% (17/1019) *vs* EU 0.8% (10/1273); $P = 0.052$). However, in subgroups of patients with partial aortic clamps, the incidence of early stroke was significantly lower in the EU group (2.8% (9/317) *vs* 0.7% (2/301) $P = 0.041$)[39].

Konstadt *et al*[46] reported 100% sensitivity and 60% specificity for TEE in the assessment of the ascending aorta for atherosclerotic disease. A TEE study showed that negative findings for an atherosclerotic plaque suggested that the presence of a significant plaque is not high, whereas when the TEE study showed positive findings the possibility of having a significant disease in the ascending aorta was 34%. Therefore, they stated that the EU should be considered in cases where an atherosclerotic plaque is detected by TEE. On the other hand, it has been reported that routine intraoperative TEE identifies patients with the severe atherosclerotic aortic disease [47], and EU may be required when the insertion of a TEE probe is difficult or contraindicated[48].

CANNULATION STRATEGIES

The standard cannulation site in conventional CABG is the ascending aorta[27,32,49-51]. If the ascending aorta cannot be used safely because of severe atherosclerotic disease or other reasons, alternative cannulation sites may be used. The most preferred sites for the arterial inflow in CPB are the femoral arteries, axillary/subclavian arteries, and IA[51]. When choosing the arterial cannulation area, the risk profiles and benefit/cost ratios of the patients should be evaluated separately.

Femoral artery cannulation

FA cannulation is routinely used for extracorporeal circulation and constitutes the most common alternative to ascending aorta cannulation. The coexistence of severe atherosclerosis in the abdominal aorta or iliofemoral arteries limits its use[27,49,50]. The main disadvantages are the risk of cerebral atheroembolism and retrograde dissection caused by retrograde perfusion[17,27,51]. Grossi *et al*[47] showed that retrograde perfusion had no significant effect on the incidence of stroke in patients under 50 years of age, but it was an important risk factor for the occurrence of neurologic events in high-risk patients with aortic disease. Intraoperative malperfusion, arterial dissection, vascular injury, or limb ischemia are complications that are associated with cannulation. Femoral cannulation-related local wound complications occurred in only 1% of the patients, while the stroke rate was found to be 2%[18].

Axillary/subclavian artery cannulation

The axillary artery (AA) is a safe and effective path to maintain adequate arterial flow during CPB[17,27,51]. Because they are less affected by the atherosclerotic disease process, the axillary/subclavian arteries are safe access places, even in patients with

the severe atherosclerotic disease[51]. However, critical stenosis of the axillary, subclavian, or innominate arteries[52], inadequate AA diameter, AA dissection, and morbid obesity limit its usage[53]. AA cannulation is a safe method that offers shorter mean operative times, shorter average lengths of stay in the intensive care unit and hospital. Minor complications of axillary cannulation include seroma, hematoma, chronic pain, and pectoralis major muscle atrophy[53]. Brachial plexus injury, arterial dissection[16,54], and AA thrombosis requiring thrombectomy[51] are other complications.

The AA can be cannulated either directly or using a side graft[16,55-57]. Sabik *et al*[16] investigated whether the use of side grafts reduced morbidity in patients with 399 AA cannulations. In more than half of the patients (212 patients, 53%) the AA had been cannulated directly, and the remainder (187 patients / 47%) were cannulated using a side graft. Complications related to cannulation were brachial plexus injury in 7 (1.8%), AA injury in 7 (1.8%), aortic dissection in 3 (0.8%), and arm ischemia in 3 (0.8%) patients. These complications were statistically lower in the side graft group (2.1% *vs* 7.0%, $P = 0.03$). Carino *et al*[55] recommend the open Seldinger-guided approach for axillary cannulation (52/404, 13%) because of its safety, efficacy, speed, and simplicity.

Axillary inflow using a lateral graft reduces stroke and is a preferred method for complicated cardiac operations requiring circulatory arrest[57]. No superiority of AA cannulation over IA cannulation concerning perioperative outcomes in thoracic aortic surgery has been demonstrated[58]. In a study where they compared the early and late postoperative outcomes of patients who underwent axillary ($n = 107$) and FA($n = 198$) cannulation during the repair of acute Type A aortic dissection, Stamou *et al*[59] found that operative mortality was not affected by the cannulation site (16% for axillary cannulation *vs* 19% for femoral cannulation, $P = 0.64$) and that stroke rates were similar between the two techniques. On the contrary, Etz *et al*[60] reported on their 10-year experience with over 869 patients who were surgically treated for complicated aortic pathology. They compared aortic cannulation ($n = 157$) with femoral ($n = 261$), and direct right axillary ($n = 451$) cannulation. The right axillary cannulation was found to be superior regarding the rates of stroke and mortality. Similarly, Svensson *et al*[57] found a higher mortality risk in the femoral cannulated group compared to the group that was cannulated using a side graft to the AA.

Innominate artery cannulation

IA cannulation is an easy-to-apply technique that is used as an alternative to AA cannulation and enables selective antegrade cerebral perfusion. Its important advantages are the absence of a need for an extra incision in contrast to femoral and axillary cannulations, and the wide diameter which enables ideal flow without high pump pressures during CPB. Its large diameter is also a safe and advantageous technique for complex aortic repair, allowing faster cooling and rewarming in patients requiring circulatory arrest[15]. Other advantages of IA cannulation include the presence of the cannulation site within the same surgical field, ease of application in obese patients, lack of risk of brachial plexus injury or arm ischemia, prevention of malperfusion and retrograde cerebral atheroembolism associated with femoral cannulation, and the possibility of antegrade cerebral perfusion[15,19]. It can be cannulated either directly[61] as in AA cannulation or using a side graft[19,62].

In a retrospective study evaluating the surgical results of 206 patients with complex aortic pathology, axillary and IA cannulations accounted for 37% ($n = 77$) and 67% ($n = 129$) of the cases, respectively. Shorter times for CPB (189 *vs* 150 min, $P < 0.001$) and circulatory arrest (22.5 *vs* 11 min, $P < 0.001$) were found in the group which underwent IA cannulation. Blood transfusion rates were also found to be lower compared to the AA group[15]. Harky *et al*[58] reported shorter CPB times (173.12 ± 51.85 min for AA cannulation and 167.45 ± 54.67 min for IA cannulation, $P = 0.004$) in patients who underwent AA and IA cannulation. However, they did not find a significant difference between the two patient groups in terms of mean deep hypothermic circulatory arrest (DHCA) durations (29.14 ± 23.55 min for right AA cannulation and 38.48 ± 31.32 min for IA cannulation; $P = 0.06$). It was observed that axillary and IA cannulation were responsible for 3.5% and 4.48% of permanent neurological deficits and 3% and 9.70% of transient neurological deficits, respectively, and there was no significant difference detected between the two groups concerning cannulation-related complications ($P > 0.05$).

In IA cannulations using side grafts, Preventza *et al*[19] reported neurological complication rates of 4.4% and mortality rates of 1.5%, while Huang *et al*[62] reported transient neurological dysfunction in 5 (10.9%) of 46 patients. Di Eusanio *et al*[54] also reported that their patients who underwent IA cannulation (44 patients) had no morbidity due to cannulation, and neurologic complication and hospital mortality

rates in these patients were 6.8%. IA cannulation is a safe and effective alternative to femoral or axillary cannulation for arterial flow in proximal aortic surgery[19]. However, there are no high-quality data to prove that it is superior to AA cannulation in providing cerebral protection[57].

Other cannulation areas

The arch of the aorta[4,63,64], carotid artery[52,65], and brachial artery[66,67] are reported as alternative cannulation sites. Carotid artery cannulation was first performed by Urbanski *et al*[52] for acute aortic dissection surgery and has become the standard approach for surgical interventions requiring circulatory arrest. It has been noted as a fast, safe, and effective method of arterial cannulation, even in very obese patients.

AORTIC MANIPULATION AND CLAMP RELATED NEUROLOGIC COMPLICATIONS IN PATIENTS UNDERGOING CONVENTIONAL CABG AND OPCAB

It has been demonstrated that most emboli detected during CABG operations occur during the manipulation of the aorta[5,8]. Barbut *et al*[68] studied the formation of transient microembolisms during different maneuvers in on pump-CABG. They found that, in addition to a much smaller number of microembolisms during clamp application, CC and side-biting clamp removal was responsible for 58% of the total cerebral microembolic load (34% and 24%, respectively). In another study, 39% of the total microembolisms occurred during side-biting clamp application, and 46% during clamp removal[5]. Lev-Ran *et al*[69] compared 429 patients who underwent the aortic no-touch technique with 271 patients who underwent PC, they found a significantly lower incidence of stroke in the no-touch group and identified PC as an independent predictor of stroke.

In a meta-analysis comparing the results of different CABG techniques; (anaortic off-pump, off-pump with the clampless Heartstring device, off-pump with a PC, traditional on-pump CABG with aortic CC) the anaortic off-pump is an effective treatment method to reduce the risk of postoperative stroke, mortality, renal failure, bleeding complications, atrial fibrillation and to shorten the length of stay in intensive care unit[6]. The degree of EU, postoperative stroke score, operative approach, and aortic clamping were independently associated with an increase in postoperative stroke compared to the no-touch technique. Also, the observed-expected stroke rate increased as the degree of aortic manipulation increased[14].

In a study investigating the effect of different clamping strategies on postoperative stroke incidence during CABG; the double clamp (CC + PC) on-pump strategy showed a 2.5-fold increase in the risk of postoperative stroke compared to the single CC technique. In the OPCAB group, no difference was found between PC and no-clamping. The authors stated that the rate of clamp use generally decreased over the years, nonclamped techniques were used in 93.3% of patients with grade 3–5, and none of these patients developed postoperative stroke. Also, surgery year and surgeon identity were not found to be associated with postoperative stroke risk[2].

Avoiding aortic manipulation may reduce the risk of postoperative stroke, especially in patients at high risk of stroke[6]. In these patients, OPCAB, which is a less invasive method, may be preferred to reduce mortality and morbidity. Motallebzadeh *et al*[70] randomized a total of 212 patients [on-pump (104 patients) and off-pump (108 patients)] undergoing CABG, and assessed embolic signals from the middle cerebral artery by bilateral TCD ultrasonography. A better neurocognitive score (P = 0.01) and decreased cerebral embolism rates were observed in patients in the off-pump group at discharge, and they found no significant difference in the neurocognitive score at the sixth week and sixth month. Also, age (P = 0.02), length of education (P = 0.03), and on-pump status (P = 0.006) were found to be independent predictors of pre-discharge neurocognitive score. In another study, no significant difference was found between off-pump and on-pump CABG in the 30-day composite result ratio (7.0% and 5.6%, respectively; P = 0.19), the ratio of patients who ended up with less number of completed grafts than previously planned was higher in off-pump patients compared to on-pump CABG (17.8% *vs* 11.1%, P < 0.001). Follow-up angiograms revealed a lower overall graft patency rate in the off-pump group compared to the on-pump group (82.6% *vs* 87.8%, P < 0.01)[71]. In contrast, in their study where they shared the results of patients who underwent OPCAB (13 889 patients) and on-pump CABG

surgery (35 941 patients), Hannan *et al*[72] showed that OPCAB patients had a significantly lower 30-day mortality (adjusted OR 0.81, 95% confidence interval [CI] 0.68 to 0.97) and a lower incidence of postoperative stroke (adjusted OR 0.70, 95%CI 0.57 to 0.86). While there was no difference in three-year mortality between the groups (hazard ratio 1.08, 95%CI 0.96 to 1.22), higher rates of subsequent revascularization (hazard ratio 1.55, 95%CI 1.33 to 1.80) were found in OPCAB patients.

In another report; Emmert *et al*[73] similarly reported that the mortality and stroke rates were significantly lower in patients who underwent OPCAB compared to on-pump CABG. A meta-analysis of seven observational studies comparing unclamped OPCAB with conventional CABG and OPCAB regarding the use of partial clamp avoidance during OPCAB, the conventional CABG (0.38 *vs* 1.87% RR 0.27; 95%CI 0.14-0.58; $P < 0.0001$) rate showed a significant reduction in stroke risk compared to OPCAB using partial clamps (0.31 *vs* 1.35%; RR 0.34; CI 95% 0.18–0.65; $P = 0.001$)[74]. A similar meta-analysis comparing neurologic complications in off-pump surgery with and without aortic manipulation showed that post-surgical neurologic complications were reduced by half in anaortic OPCAB grafting cases (OR 0.46;% 95 CI, 0.29–0.72; $P = 0.008$)[22]. Another study compared the patients who underwent CABG without aortic manipulation (1201/1758, 68%) with those who underwent a minimum of one proximal anastomosis using a side-biting aortic clamp or no-clamp proximal anastomotic device (557/1758, 32%). In the anaortic group, the incidence of perioperative neurologic deficits was lower than in the aortic manipulation group (0.25% *vs* 1.1%, $P = 0.037$). It was also found that advanced age is associated with peri-operative neurologic injury (OR 1.1, 95%CI 1.01-1.20, $P = 0.017$)[75].

Douglas and Spaniol[76] emphasized the role of unclamped OPCAB as an important tool in the prevention of postoperative stroke and also reported that assistive techniques (such as anastomotic assist devices) may be an important factor in reducing stroke occurrence for patients with significant atherosclerosis. On the other hand, large randomized controlled trials have reported similar neurologic results after on-pump and off-pump CABG[71,77,78].

PA AND CABG

Various techniques have been described and implemented in patients with atherosclerotic ascending aorta to reduce the risk of atheroembolism that may cause cerebrovascular events. The "no-touch" technique avoids all types of clamps in the aorta. Also when using this technique, no cardioplegia is applied, no grafts are anastomosed to the aorta, and deep hypothermia is not necessary[20,21]. Anaortic or no-touch techniques without aortic manipulation can significantly improve the development of neurologic complications by avoiding aortic maneuvers known to cause embolism[22,23]. Halbersma *et al*[24] compared the 4-year results with those in the surgical arm of the SYNTAX trial in 400 consecutive non-touch total arterial OPCAB patients without touch, and there was a clear trend towards a reduction in stroke rate in the no-touch group (0.8%) compared to the surgical arm of the SYNTAX trial (2.2%). Also, there was no significant difference in the stroke rates between the non-touch OPCAB group and the PCI arm of the SYNTAX trials. Based on these results, they recommended off-pump in situ grafting as "standard care" to reduce neurologic complications. OPCAB no-touch with total arterial Y-graft and composite graft revascularization is an effective method for preventing thromboembolic events[23-25].

The internal mammary artery (IMA) can be used as an inflow site for saphenous vein (SV) grafts as in the total arterial T, or Y-shaped graft technique[28,32]. Mills *et al*[32] reported the frequency of severe atherosclerosis of the ascending aorta as 2.0% for patients undergoing CABG, and by using the "no-touch" technique they anastomosed the SV to the IMA in an end-to-side-fashion in 26 patients. They did not encounter any recurrence of angina in the patients. The "no-touch" technique has been used in 18 patients with heavily calcified and atherosclerotic ascending aorta who had myocardial revascularization. With this technique, 37 pedicled arterial grafts (22 IMA and 15 gastroepiploic arteries) were anastomosed proximally to the internal thoracic artery. Fifty-two distal anastomoses were performed using 15 free grafts, and no patients had neurologic complications[20]. However, accompanying subclavian artery stenosis may limit the use of these grafts both in situ and as Y-grafts. In this situation, the preoperative diagnosis becomes even more crucial, and preoperative subclavian artery stenting may be required, as in the cases of Adesanya and Kilic[79].

One of the methods used to achieve optimal coronary revascularization is hypothermic ventricular fibrillation or hypothermic fibrillatory arrest[4,21]. The hypo-

thermic fibrillatory arrest also allows easy proximal anastomosis to a disease-free area of the ascending aorta in patients with a high risk of cerebral embolic complications and significant ascending aortic disease[21,27]. Gaudino *et al*[4] could not find a difference between hypothermic ventricular fibrillation and beating heart in terms of the overall in-hospital mortality rate. To achieve optimal coronary revascularization and minimize cerebrovascular events, Akpinar *et al*[80] also used the moderate degree hypothermic fibrillatory arrest technique with pedicled arterial grafts (internal mammary and gastroepiploic artery) in 21 patients with severe calcification of the ascending aorta, and they did not encounter any neurologic complications. However, the hypothermic ventricular fibrillation technique was associated with a greater incidence of neurologic complications (stroke and transient ischemic attack), renal insufficiency, and stay in the intensive care unit and hospital[4].

In conventional and OPCAB, the standard proximal anastomosis site or location is the ascending aorta itself. In advanced stages, the presence of PA makes it difficult to perform proximal anastomoses, and when in situ grafts cannot be used due to limited graft flow resources or T/Y grafting techniques cannot be applied, free grafts that require proximal anastomosis should be used. In this situation, using alternative inflow areas such as IA[27,29,30], subclavian artery, AA[28,30,81] and carotid artery [23,82] may be considered. Extra-anatomic CABG procedure is a safe and reliable method to minimize the prevalence of perioperative stroke and systemic embolization [29,30]. Demirsoy *et al*[30] preferred IA as the proximal anastomosis site in six of eight patients who underwent extra-anatomic bypass surgery because of the PA, they preferred the AA in one patient and the subclavian artery in another. Postoperative graft patency was evaluated by contrast-enhanced electron beam coronary angiography, and only one saphenous vein graft to the right coronary artery was occluded. Bonatti *et al*[28] have also demonstrated patency in 11 out of 13 extra-anatomic vein grafts with a 3D multislice CT scan performed in 13 patients during the first postoperative year. Agrifoglio *et al*[82] have identified a case in which CABG was performed off-pump and the saphenous vein graft was anastomosed proximally to the left common carotid artery. In addition to these methods, the coronary - coronary bypass is an alternative technique that can be used to bypass isolated atherosclerotic coronary lesions in the presence of PA[83,84]. In hemodynamically unstable patients or in whom aortic manipulation cannot be performed due to severely atherosclerotic aorta, performing CABG with the off-pump technique under CPB support and without application of CC can be a good choice to prevent neurologic complications [29,30].

Anastomotic support devices

The use of anastomosis support devices allows proximal aortic anastomoses to be performed without a side-clamp. The use of a sutureless proximal anastomotic device during OPCAB is safe and significantly reduces cerebral microembolism compared with the conventional bypass method[5,8,9]. Guerrieri *et al*[5] used TCD ultrasound to determine and compare the number and nature of microembolisms in patients. These patients underwent off-pump coronary artery bypass grafting during proximal anastomosis with three different techniques (aortic side-clamps and two separate unclamped devices Enclose II and Heartstring). It was seen that most of the microembolisms occurred during the application/insertion and removal of each device into the ascending aorta. During the anastomosis using the Heartstring device, the median number of total microembolisms was found to be higher than the other two groups, but there was no statistically significant difference (P = 0.239). The solid microembolism rate was significantly higher in the side-clamping group (23%) compared to 6% and 1% in the Enclose and Heartstring groups (P < 0.01). Avoiding aortic side clamping resulted in a significant reduction in the rate of solid microembolism detected by TCD. Similarly, Akpinar *et al*[80] found that the use of side-biting-clamps causes more microembolic load than Enclose II device [the median number of microemboli: 68 (range 35-290) *vs* 15 (range 5-48), P < 0.05)]. Hilker *et al*[9] performed 542 off-pump proximal anastomoses using the Heartstring device in 412 consecutive patients. The overall postoperative stroke incidence was lower than the predicted stroke risk score (0.48% observed *vs* 1.37% predicted), and a 35% reduction in solid particle embolism has been observed.

In a study in which proximal anastomoses were performed using a sutureless Symmetry aortic connector device (St Jude Medical, St Paul, Minn); OPCAB was compared with conventional coronary artery bypass (cardiopulmonary bypass and hand-stitched proximal anastomoses). Patients were evaluated by intraoperative TCD ultrasonography to determine right- and left-sided cerebral microembolic counts. Patients in the OPCAB group experienced fewer left-sided cerebral embolic events

intraoperatively (mean, 24.9 ± 19.2; median, 26.0) compared to the patients who are in the conventional CABG group (mean, 189.9 ± 60.4; median, 180.0; $P < 0.0001$). A similarly significant difference in embolic counts was also noted in the right cerebral circulation (mean of 21.9 ± 20.7 and median of 18.0 for the OPCAB group *vs* mean of 181.6 ± 85.3 and median of 173.0 for the S-CABG group, $P < 0.0001$)[8].

CROSS-CLAMPING, ENDARTERECTOMY OR REPLACEMENT OF PA

Aortic CC is associated with high mortality and morbidity rates in patients with PA. Different techniques have been described to clamp the PA. Hartert *et al*[63] have reported the results of aortic cross-clamping in 42 patients with PA who underwent valve replacement [aortic valve (n = 33) or mitral valve (n = 9)] by using the open proximal ascending aorta technique. Longitudinal aortotomy was performed under total CPB after distal aortic arch or FA cannulation. The aorta was gently clamped, allowing the mobilized atherosclerotic material to leave the aorta through the open incision. After the main operation, the aorta was opened gradually and the plaques were cleared through the aortotomy which was still open. Surgical revision was required in three patients (7.1%) due to major bleeding and aortic dissection was not observed in any patients. The stroke rate was 7.1% and the 30-day mortality rate was 6.9%. The authors have suggested that cross-clamping with the "open proximal ascending aorta" technique is an effective method, with a low incidence of stroke and low risk of systemic embolization in patients with PA.

Another method used to avoid an embolic event in patients with PA is the "staged aortic clamp" procedure. This procedure includes (1) Short-term cessation of circulation and aortotomy during moderate hypothermia; (2) Balloon occlusion of the ascending aorta during low flow CPB; (3) Endarterectomy using an ultrasonic surgical aspirator to allow aortic CC; and (4) Felt reinforced CC and full-flow CPB steps[85]. The authors stated that they did not encounter any thromboembolic events with this method.

Nishi *et al*[86] suggested that by carefully selecting the direction of cross-clamping of the aorta with the help of preoperative CT and EU, they could successfully overcome the problem of the severely calcified ascending aorta. They performed a preoperative CT assessment for developing the clamping strategy in a severely calcified aorta. They found that the degree of calcification just below the IA was significantly less compared to the ascending aortic clamp site. After confirming that the extent of calcification in this area is less than 75% of the entire circumference, a soft CC calcification was carefully placed in the ascending aorta. All surgeries were completed under normal CPB with mild hypothermia, and no postoperative neurologic complications were observed in the patients. However, the utility of this technique is questionable, since aortic cross-clamping may cause an increase in the frequency of postoperative cerebrovascular events when calcification covers the entire aortic wall.

In high-risk patients with severe atherosclerosis of the ascending aorta short-period (3.4 ± 1.5 min) and moderately hypothermic (29.0 ± 2.3 ° C) circulatory arrests allow internal inspection or debridement of atheroma plaques, thus allowing safe aortic cross-clamping[87]. Culliford *et al*[88] have also cooled 13 patients, with excessive calcification in the ascending aorta and transverse arch, to 18 degrees during CPB, and manipulation of the aorta during cooling was not allowed**.** During DHCA (for 3.5 to 12 min), the aorta was widely opened to remove ulcerated plaques and friable debris and to find a safe place for CC. In 12 patients the presence of PA was known before surgery, whereas one patient was found to have PA after CC. In this latter patient, occipital infarctions developed, and ascending aortic endarterectomy was necessary. Endoaortic balloon occlusion of the atherosclerotic ascending aorta has been proposed as an alternative to conventional CC to prevent vascular damage and distal embolization of atherosclerotic plaques. However, Zingone *et al*[89] found that endoaortic occlusion was ineffective, and associated with a significantly higher risk of in-hospital death (25%) and a higher risk of stroke (3.8%).

In patients undergoing cardiac surgery, hypothermic circulatory arrest enables safe resection of the severely atherosclerotic ascending aorta and graft replacement with an acceptable postoperative stroke rate and provides long-term protection from subsequent embolic cerebrovascular events[49,90]. Replacement of the atherosclerotic aorta with graft during DHCA is a radical option and has high mortality rates (14%) [64]. In the study by Rokkas *et al*[90], among 81 patients who were noted to have severe atherosclerosis of the ascending aorta on epiaortic screening and who un-

derwent CABG, 80 received [partial (5) or complete (75)] ascending aorta replacement by using hypothermic circulatory arrest. In the remaining patient, resection of a protruding aortic atheroma was performed. The 30-day mortality rate was reported as 8.6% (for 7 patients) and the incidence of stroke has been reported as 4.9%. Zingone *et al*[91] replaced the ascending aorta in 36 out of 152 patients who were noted to have severe aortic atherosclerosis which was detected on EU screening and CT. In 13 of them (36.1%), the aortic replacement was extended to the aortic arch. While DHCA was used in 34 patients, proximal aortic disease allowed conventional CC administration in 2 patients. The hospital mortality rate was 5.6%, one patient had a stroke (2.8%) and five patients (13.9%) had a neurocognitive impairment. Four patients (11.1%) experienced excessive bleeding requiring re-exploration.

Aortic endarterectomy may be an option in the management of patients with calcification of the aorta[64,92]. Vogt *et al*[93] performed complete thromboendarterectomy to the ascending aorta and the aortic arch during hypothermic circulatory arrest on 22 patients (CABG, n = 21 and aortic valve replacement, n = 8), and reported a 4.5% mortality rate and a 9% adverse neurologic event (one early and one late) rate. The follow-up of the patients was performed by magnetic resonance imaging and transthoracic echocardiography, and the endarterectomized aorta did not develop a dilation. The authors above have suggested that for patients with advanced-stage (Grade IV and V) plaques, ascending aorta and transverse arch thromboendarterectomy can be performed with acceptable surgical risk and a low recurrence rate for cerebrovascular events. On the contrary, Takami *et al*[87] performed reoperations in two patients (2/40, 5%) during the follow-up period, at postoperative 8th month in one and 44th month in the other, due to pseudoaneurysm in the suture line of the aortic patch. The authors suggested that the aortic wall undergoing endarterectomy should be considered as a risk factor for pseudoaneurysm formation and that the aortic suture line should be enforced during surgery.

CONCLUSION

Perioperative stroke is still one of the most crucial complications of CABG surgery with its high patient morbidity and mortality. During CABG, most emboli occur during active aortic clamp applications (cross-clamps, side-biting clamps) or the insertion and removal of unclamped aortic anastomotic devices. Therefore, in procedures that involve cannulation, clamping, or proximal anastomosis where aortic manipulation is inevitable, preassessment of the atherosclerotic aortic plaques is crucial. Imaging methods including preoperative CT or intraoperative EU enable modification of the surgical technique according to the severity of atherosclerosis. The use of anastomosis support devices to prevent lateral clamping and to support the proximal anastomosis may be an important strategy to minimize cerebral damage during proximal anastomoses in, especially high-risk groups. Since a soft or non-calcified aortic segment is needed to use anastomotic support devices, the need for aortic manipulation cannot be eliminated. The best approach to prevent embolic events is the utilization of alternative surgical techniques which aim to minimize or eliminate the manipulation of a severely atherosclerotic or completely calcified aorta.

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MINIREVIEWS

Angiotensin receptor blocker neprilysin inhibitors

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Abstract

Heart failure (HF) is a clinical syndrome that results from a structural or functional cardiac disorder that reduces the ability of the ventricle of the heart to fill with, or eject, blood. It is a multifaceted clinical condition that affects up to 2% of the population in the developed world, and is linked to significant morbidity and mortality; it is therefore considered a major concern for public health. Regarding the mechanism of HF, three neurohumoral factors - the renin-angiotensin-aldosterone system, the sympathetic nervous system, and natriuretic peptides — are related to the pathology of chronic HF (CHF), and the targets of treatment. Angiotensin receptor blocker and neprilysin inhibitor (angiotensin-receptor neprilysin inhibitor), namely sacubitril/valsartan (SAC/VAL), has been introduced as a treatment for CHF. SAC/VAL is an efficacious, safe, and cost-effective therapy that improves quality of life and longevity in patients with HF with reduced ejection fraction (HFrEF), and reduces hospital admissions. An in-hospital initiation strategy offers a potential new avenue to improve the clinical uptake of SAC/VAL. In the last five years, SAC/VAL has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. On the other hand, further work, with carefully designed and controlled preclinical studies, is necessary for understanding the molecular mechanisms, effects, and confirmation of issues such as long-term safety in both human and animal models.

Key Words: Angiotensin receptor blocker and neprilysin inhibitor; Chronic heart failure; Renin-angiotensin-aldosterone-system; Sympathetic nervous system; Natriuretic peptide;

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Core Tip: Heart failure (HF) is a multi-faceted clinical condition that affects up to 2% of the population in the developed world, and is linked to significant morbidity and mortality; it is therefore considered a major concern for public health. In 2014, a newly developed angiotensin receptor blocker and neprilysin inhibitor (angiotensin-receptor neprilysin inhibitor), namely sacubitril/valsartan (SAC/VAL), was introduced as a treatment for chronic HF (CHF), and it proved to have the efficacy, safety, and cost-effectiveness to improve quality of life and longevity in patients with heart failure with reduced ejection fraction and reduces hospital admission. In this review, we first summarize the current knowledge regarding HF, then provide an overview of the current knowledge on SAC/VAL for CHF, together with relevant clinical trials and future perspectives.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome resulting from a structural or functional cardiac disorder, diminishing the ability of the cardiac ventricle to fill with, or eject, blood[1-3]. It is a multi-faceted clinical condition that affects up to 2% of the population in the developed world, and it is linked to both significant morbidity and mortality; it is therefore considered a major concern for public health[4].

According to several researches in Japan, HF results from myocardial injury due to a variety of causes, including age > 80 years old, male, underlying heart disease; ischemic, hypertensive, cardiomyopathy, vulver heart disease, medical history; prior hospitalization for HF, hypertension, dyslipidemia, diabetes mellitus (DM), smoking, atrial flutter/fibrillation, chronic respiratory disease, stroke/transient ischemic attack, continuous positive airway pressure, pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy, and hemodialysis[1,5,6]. The etiology and frequency of HF is shown in Table 1.

Regarding the mechanism of HF, vasoconstriction and fluid retention are caused by the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), and the natriuretic peptides (NPs) secreted by the myocardium, which is itself both volume- and pressure-overloaded, promote vasodilation and diuresis[7,8]. The three neurohumoral factors related to the pathology of chronic heart failure, and the target of conventional remedies, are shown in Figure 1.

In this review, we first summarize the current knowledge of HF, then provide an overview of the current knowledge on angiotensin receptor blocker and neprilysin inhibitor [angiotensin-receptor neprilysin inhibitor (ARNI)], namely sacubitril/valsartan (SAC/VAL) for chronic HF (CHF), together with the structure, expression, regulatory roles, effects on CHF and other diseases, relevant clinical trials, and future prospects.

HF

Classification

HF is associated with a number of symptoms, including shortness of breath, breathing difficulties, nausea, diminished appetite, fatigue, intolerance to exercise, retention of fluid, coughing, weight gain from pulmonary congestion, and peripheral edema and

Table 1 The etiology of heart failure

Arrhythmia
Cardiomyopathy
Cardiotoxic drug
CKD
Congenital heart disease
DM
Hypertensive heart disease
Hypertension
Infection
Ischemic heart disease
Myocardial disease
Pericardial disease
Pulmonary hypertension
Systemic toxins
Valvular disease

CKD: Chronic kidney disease; DM: Diabetes mellitus.

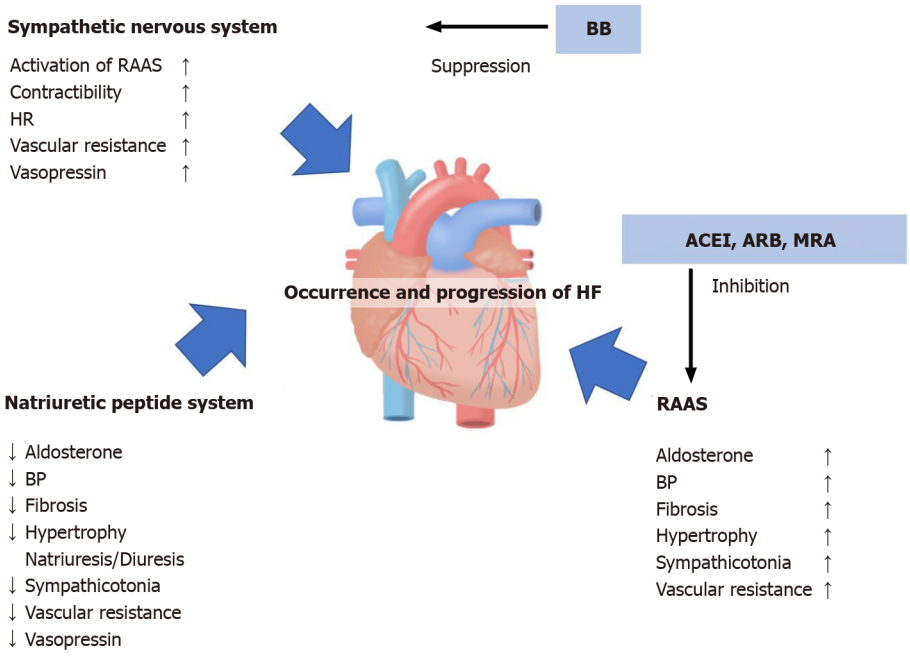


Figure 1 Three neurohumoral factors related to the pathology of chronic heart failure, and the targets of conventional remedies. ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; BB: β-blocker; BP: Blood pressure; HF: Heart failure; HR: Heart rate; MRA: Mineralocorticoid receptor antagonist; RAAS: Renin-angiotensin-aldosterone-system.

ascites due to impaired venous return[1,3]. HF severity can be classified under the New York Heart Association (NYHA) classification system as follows: Class I, no symptoms; Class II, symptoms with ordinary activity; Class III, symptoms with less than ordinary activity; and Class IV, symptoms at rest or with any minimal activity[3].

HF can be further categorized based on ejection fraction (EF)[3]. In 2013, The American Heart Association (AHA) and American College of Cardiology (ACC) assigned an EF range to HFrEF and HFpEF[3,9]. This classification created a "gray area" of patients who have EF of 41–49%; this has ultimately come to be known as "HF with mid-range" (HFmrEF)[3,9]. "HF with preserved EF" (HFpEF) is defined as left

ventricular (LV) EF (LVEF) of 50% or greater; HFmEF is defined as LVEF of 41%–49%, and HF with reduced EF (HFrEF) is defined as LVEF of up to 40%[3,9]. Of these, HFmrEF patients represent a group with heterogeneous clinical characteristics, sometimes resembling HFrEF, sometimes resembling HFpEF, and sometimes even resembling a unique phenotype entirely[9]. There are no randomized controlled trials (RCTs) for patients with HFmrEF, though HFrEF and HFpEF studies that include overlap suggest some potential benefits from β-blockers (BBs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and ARNI[9]. HFrEF occurs at LVEF of 40% or below, and is accompanied by progressive LV dilatation and adverse cardiac remodeling[2]. HF assessment begins with obtaining the patient's medical history and performing a physical examination[2]. Other key factors for diagnosis are NPs that are elevated above age- and context-specific thresholds, and identifying LV systolic dysfunction with LVEF of 40% or less using echocardiography [2]. Worldwide, HF now affects an estimated 23 million people, approximately 50% of whom are HFrEF cases[2].

Management

Management of HF depends on each individual's NYHA classification and EF, but generally, treatment involves pharmacotherapies[3]. HF treatment strategies include the use of diuretics for symptom relief, and the application of an expanding armamentarium of disease-modifying drug and device therapies[2].

The foundation of HFrEF treatment is a number of pharmacotherapies that have been shown in large multinational RCTs to reduce morbidity and mortality[10]. With the exception of cases with specific contraindications, patients with HFrEF should be treated with BB, and one of ARNI, an angiotensin-converting enzyme (ACE) inhibitor (ACEI), or ARB, as foundational therapy, as well as diuretics, and additionally MRA which is recommended to reduce mortality and hospitalization in all the patients with HFrEF and EF ≤ 35%; until recently, however, it was unclear how to augment the beneficial effects of NPs in HF patients[2,7,10]. Of these, this review article covers ARNI in more detail below. In some cases, digoxin, ivabradine, ivabradine and hydralazine with isosorbide dinitrate, and hydralazine/isosorbide dinitrate also play roles in the care of some HFrEF patients[2]. More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have led to further improvements in disease outcomes, bringing about significant reductions in cardiovascular and all-cause mortality, regardless of patient diabetes status; additionally, the soluble guanylate cyclase stimulator vericiguat has reduced hospitalization for HF in high-risk HFrEF patients [2]. Pharmacotherapy efficacy does not vary by age; therefore, each of these therapies should be considered for every patient, no matter their age[10]. Other factors, including co-morbidities such as renal dysfunction, may limit use of some of these drugs for elderly patients[10]. Building on this foundation, other, more advanced treatments, including implantable cardioverter defibrillators and cardiac resynchronization therapy, are recommended by HFrEF treatment guidelines; for a select few, mechanical circulatory support and cardiac transplantation also remain options[2,10]. Conversely, there are only limited options for HFpEF[10]. In the absence of robust outcome data from large randomized trials, MRA is a reasonable therapy for the reduction of hospitalization risk for HF in patients with HFpEF[10].

New therapeutic strategies that aim to tackle the rising socio-economic burden of HF have become a significant priority, and timely, efficient drug treatments play key roles in improving quality of life (QOL) and prognosis for HF patients[11,12]. Enhancing NP bioavailability through exogenous NP administration, and inhibiting neutral endopeptidase, are valuable therapeutic strategies for HF; current therapeutic concepts combine inhibition of the RAAS with blockage of the sympathetic system[8, 12]. New therapeutic approaches, including selective heart rate reduction, attenuation of NP degradation through neutral endopeptidase inhibition, and treatment of comorbidities (such as iron deficiency, DM, or hyperkalemia) have led to further improvements to affected patient survival, time out of hospital, and QOL[8,12]. In addition, this approach has been proven to demonstrate beneficial effects, and reduce adverse events, in HF patients[8].

Prognosis

Typically, the natural course of HF is associated with repeated hospitalizations and the subsequent deterioration of patient prognosis[13,14]. In the past twenty years, the prognosis for HFrEF has steadily improved due to drug treatment advances and consistent implementation of evidence-based drug therapy as recommended by guidelines[12]. Therefore, a history of multiple previous admissions for HF was found to be a strong independent risk factor for adverse events following index admission,

and number of hospitalizations could serve as a simple yet valuable surrogate indicating subsequent adverse events in HF patients[13]. Furthermore, another study conducted in Japan reported a 23.6%–26.2% HF readmission rate within one year after discharge for HF[15]. Overall, despite the underlying pathophysiological mechanisms of HF being well understood, the disease still has significant morbidity, with three-year mortality of 30% and five-year mortality of 50%[1,3,16].

As a classification of HF, HFrEF is a major public health concern that has substantial morbidity and mortality; however, recent developments such as SGLT2 inhibitors, vericiguat, and transcatheter mitral valve repair all incrementally improve prognosis beyond what was possible through foundational neurohormonal therapies[2]. On the other hand, one of the most common reasons for prolonged hospital admission is poor management of HF symptoms from decompensated HFpEF[17]. The high morbidity and mortality rates associated with HFpEF are compounded by poor understanding of the underpinning pathophysiology[17].

CHF

Though CHF is a common condition, if untreated, it will markedly impair QOL; it is associated with a high risk of recurrent hospitalization and death[18]. Availability of evidence-based treatment options is limited to congestive HF with low EF; the medication has been approved in the United Stated by the Food and Drug Administration (FDA) for the treatment of chronic HFrEF patients of NYHA class II, III, or IV [18,19]. Alongside the past decade's marked progress in device therapy, more recent advances in CHF management have led to exciting new pharmacological options[20]. Pharmacotherapy is based on neurohumoral inhibition of the RAAS and the adrenergic system[18]. Previously, it has been reported that higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk in CHF patients, and that these confer complementary and incremental prognostic value[21]. On the other hand, a recent article reported further prognostic improvements for patients with this condition by introducing ARNI[18]. Modern implantable devices serve as another component of treatment[18]. The use of implantable defibrillators and special pacemakers for cardiac resynchronization is well established; there is still a need for further studies to investigate the utility of alternative devices (such as baroreflex modulation or cardiac contractility modulation) [18]. The treatment of chronic systolic HF as recommended in relevant guidelines, using drugs and implanted devices as indicated, can greatly improve clinical outcomes [18].

INTRODUCTION OF ARNI

In the early 1980s, the NP system was extensively characterized, with investigations into its potential influence on the development and progression of HF; in recent years, the NP system has drawn increasing attention[22]. Indeed, this new class of drugs for HF management is supported by recent results and a vast clinical development program, and may prompt a paradigm shift in HF treatment, moving from inhibition of RAAS and SNS, to more integrated targeting of rebalanced neurohormonal dysregulation in HF[22]. The study of NPs has become highly relevant, as they mediate beneficial effects at the cardiovascular level, such as diuresis, natriuresis, and decreased cardiac remodeling; their metabolism is mediated by neprilysin, a metalloproteinase that is widely expressed in humans, and which is capable of catalyzing various substrates[23]. One of these, neprilysin, is an endopeptidase that breaks down endogenous vasoactive peptides, including NP, bradykinin, and adrenomedullin[3]. Neprilysin inhibition increases the levels of vasoactive substances, helping to counter the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and other maladaptive processes of HF[3]. The modulation of these functions has been studied for decades, giving rise to the use of sacubitril, the first neprilysin inhibitor; in conjunction with ARB, it has demonstrated high efficacy and tolerability among HF patients[23].

The association of an angiotensin II receptor antagonist and a neprilysin inhibitor is a new actor in HF management; recently, a newer pharmacotherapy, SAC/VAL, has become available for this purpose[3,24]. The stimulation of counter-regulatory systems, in addition to neurohormonal blockade, constitutes a new paradigm, known as "neurohormonal modulation," and SAC/VAL is the first example of this new approach[3,8,16,19]. This new pharmacological class of ARNI has prompted a substantial conceptual change in HF treatment, with a transition from only inhibition

of the RAAS and SNS, to a strategy built around concomitant pharmacological enhancement of endogenous NPs[11].

STRUCTURE, EXPRESSION, AND REGULATORY ROLES OF ARNI

The ARNI, namely SAC/VAL, is a single molecule that is synthesized through the co-crystallization of valsartan and the neprilysin inhibitor prodrug sacubitril (1:1 molar ratio)[25]. The substrates for neprilysin are multifarious, and include biologically active NPs, adrenomedullin, substance P, endothelin, and angiotensin II, among others; it is unclear which of those substrates, or combination(s) of substrates, might be responsible for the benefit observed[26]. In addition, it can exert an additive action, because it may increase the levels of compounds that can protect against lung and heart injury (NPs, adrenomedullin, substance P, bradykinin, and apelin)[27].

In humans, this peptidase is widely distributed throughout the body, expressed with broad substrate specificity that preferentially hydrolyses oligopeptide substrate [28,29]. It is also an endogenously induced peptidase, for modulation of the production and degradation of various peptides; it present in the most abundance in the kidneys, and regulates the intrinsic renal homeostatic mechanism[30]. However, despite intensive research into neprilysin structure in different organisms, it is still not fully understood when it comes to changes in its expression and regulation during brain development and aging, especially for age-related pathologies, as well as the exact mechanisms underlying therapeutic benefit[26,28].

However, despite intensive research into neprilysin functions in various organisms, and into changes in how it is expressed and regulated during brain development and ageing, especially in age-related pathologies, concrete resolution is still not fully understood[28]. Currently, it is known that neprilysin regulates the cardiovascular, nervous, and immune systems[28,29]. SAC/VAL modulates the neurohormonal axis through inhibition of both angiotensin receptors and neprilysin, which additionally improves neurohormonal balance more than blocking the RAAS alone would[31]. Of these, unfavorable outcomes are attributed primarily to NP degradation[30]. NPs are involved in the RAAS inhibition and sympathetic system activation contributing to tubular and glomerular injury, and ARNI possesses the ability to counteract the effects of angiotensin II, as well as to increase NP activity[30,32]. Neprilysin exerts a beneficial effect by converting angiotensin-1 to angiotensin-(1-7), which activates the MAS-related G-protein coupled receptor[30]. Mas-related genes antagonize the angiotensin type 1 receptor (AT1R), reducing reactive oxygen species and inflammation, which ameliorates renal injury[30]. Neprilysin expression is increased by cytokines on the surface of the lung fibroblasts[27]. The current understanding of the mechanism of SAC/VAL, progressing to HF, is shown in Figure 2. According to the latest knowledge, neprilysin activity is elevated in acute respiratory distress syndrome; it is conceivable that it is also high in severe acute respiratory syndrome coronavirus 2 — namely, infections of coronavirus disease-2019 (COVID-19) — and neprilysin/AT1R inhibitor SAC/VAL may increase the levels of these molecules, blocking AT1Rs required for ACE2 endocytosis in COVID-19 infections[27]. In addition, green tea and various other natural compounds that are capable of upregulating neprilysin expression have been proposed as preventive medicine for both prostate cancer and Alzheimer's disease[28].

EFFECTS OF ARNI ON CHF

The approval of SAC/VAL, a first-in-class ARNI, marked the first novel pharmacological class in over a decade for HFrEF treatment[28,30,33]. Neprilysin plays a role as its mechanism, degrading the gross excess of circulating NPs in HF patients[7]. Compared to enalapril, SAC/VAL leads to reductions in symptoms of HF, cardiovascular death or HF hospitalization, sudden cardiac death, and disease progression, and improved QOL, in patients undergoing evidence-based contemporary medical therapy for HFrEF, and the NP assays for B-type NP (BNP) and N-terminal-proBNP (NT-proBNP) assays have been shown to have similar diagnostic accuracy for the differentiation of HF from other etiologies of shortness of breath[11,17,32,34-36]. In real-world settings, SAC/VAL was found to be associated with improved survival and reduced HF-related hospitalization compared to enalapril in Asian HF patients, with consistent effectiveness even in older populations[37]. SAC/VAL use has been shown to result in a modest, chronic elevation of BNP while

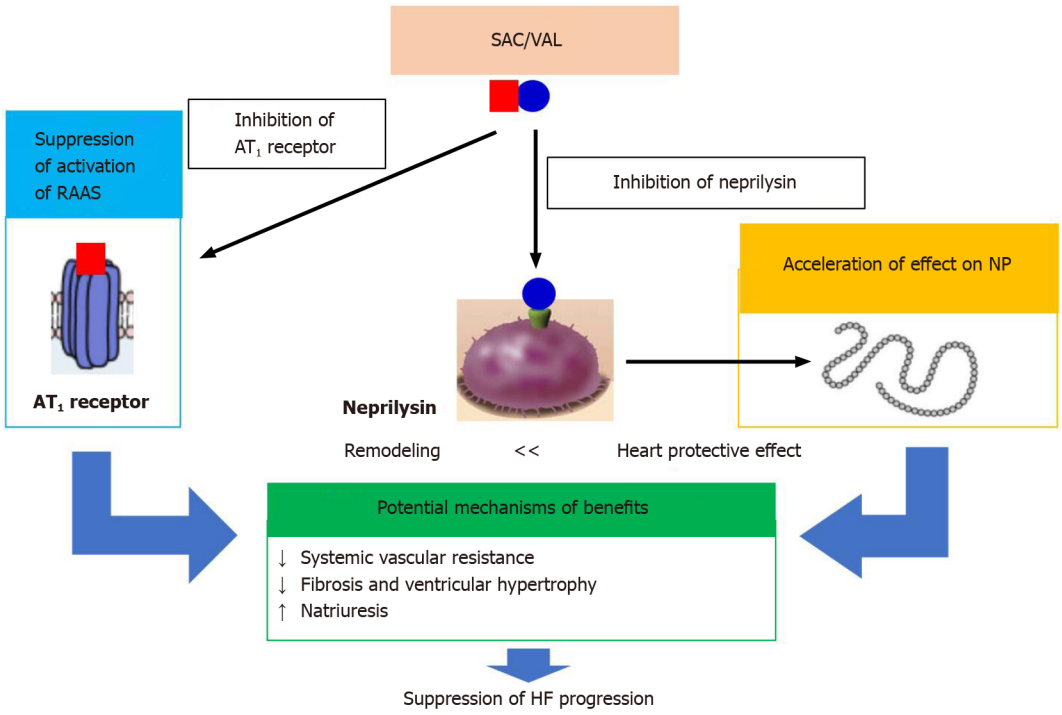


Figure 2 Mechanism of sacubitril/valsartan on heart failure progression. AT1: Angiotensin II type 1; HF: Heart failure; NP: Natriuretic peptide; RAAS: Renin-angiotensin-aldosterone-system; SAC/VAL: Sacubitril/valsartan.

reducing levels of NT-prBNP[35].

The European Society of Cardiology, the Canadian Cardiovascular Society, and the ACC HF guidelines all currently recommend the use of ACEI or ARB and BB in HFrEF treatment[38]. In addition, HFrEF patients should first be treated with a BB and an ACEI or ARB (or ARNI), followed by add-on therapy with MRA and a diuretic, based on volume status[19,38-40]. Due to the different mechanisms of action in SAC/VAL, this combination may be regarded as a potential treatment option for patients who remain symptomatic despite optimized therapy with other alternatives[3]. While SAC/VAL is indicated for HF NYHA class II or III severity, it is unclear whether there is sufficient evidence from clinical trials or observational studies to support their use in combination, from the perspectives of both effectiveness and safety[3]. On the other hand, although it remains unclear what the optimal timing is for initiation of SAC/VAL, early use seems likely to positively impact patient outcomes[3,33]. We present the therapeutic options and treatment lines of CHF, especially HFrEF, based on the European Society of Cardiology, the Canadian Cardiovascular Society, and the ACC HF guidelines, in Figure 3.

Other point of discussion regarding ARNI for HF include evaluating the prevalence and significance of hyperkalemia in HF patients, which is essential for optimized use of potassium sparing agents, such as RAAS inhibitors or ARNI and MRA, which represent a well-established cornerstone of life-saving therapy[41]. SAC/VAL has already proven highly effective for HFrEF, and there is convincing data available regarding the cardioprotective effects of dapagliflozin, an SGLT2 inhibitor[20,38]. These two treatments have earned class I and class II recommendations, respectively, in the European Society of Cardiology guidelines for the diagnosis and treatment of HF[20]. However, more research is necessary on the mechanisms of action of disease modification[38]. Another point of discussion, raised in 2017, is that it was recommended that "patients who are eligible for treatment with ivabradine may also be eligible for treatment with SAC/VAL", but there was no evidence evaluating the combination of SAC/VAL and ivabradine, or assessing the comparative safety and efficacy of the two treatments[3]. An additional novel point of discussion is that SAC/VAL also has a positive impact on acute HF, as observed very frequently in deceased COVID-19 patients[27].

On the other hand, there seems to be no evidence of a difference between SAC/VAL and valsartan in patients with HFpEF[17,39]. Therefore, there are, at present, no universal treatment strategies recommended for HFpEF; instead, management should take an individualized approach, with consideration given to each patient's

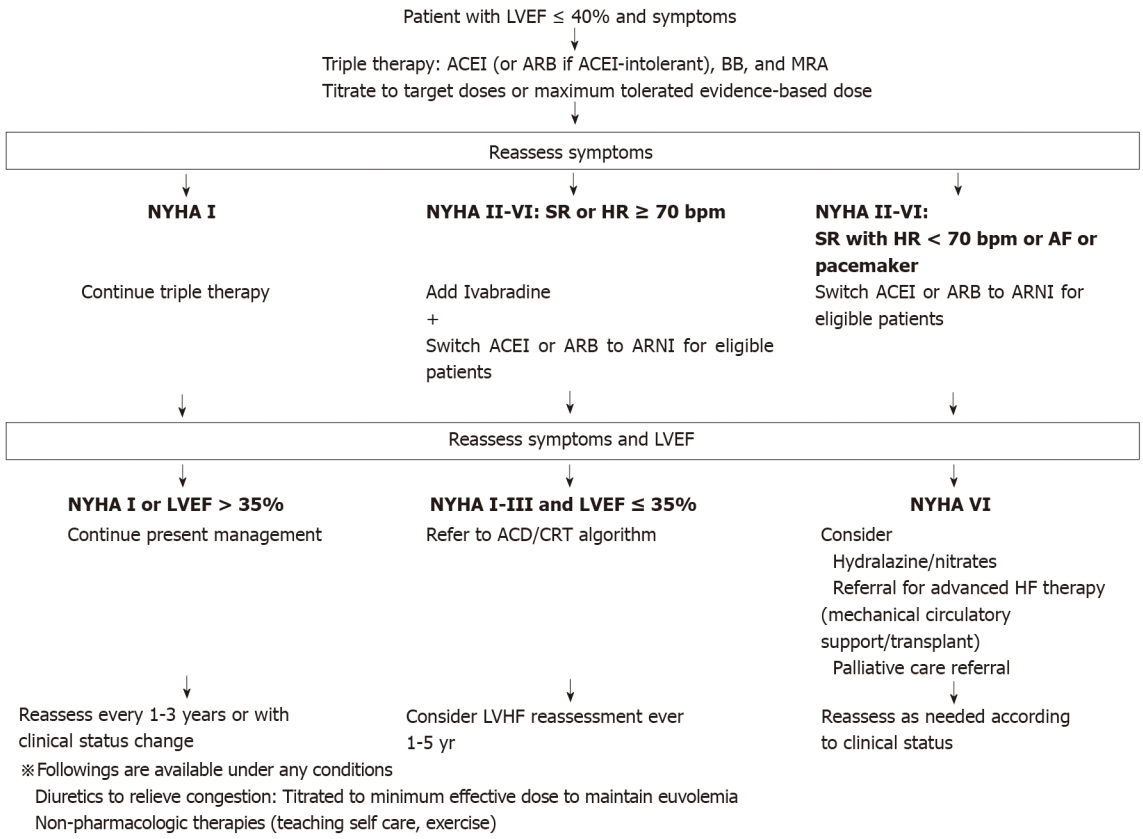


Figure 3 The therapeutic options and treatment lines of patients with symptoms of heart failure with reduced ejection fraction. ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; BB: β-blocker; bpm: Beats per minute; CRT: Cardiac resynchronization therapy; HR: Heart rate; ICD: Implantable cardioverter defibrillator; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SR: Sinus rhythm.

comorbidities[17]. Additionally, modern guidelines should emphasize this lack of evidence for the combined use of ARB and BB for HFrEF, with the exception of candesartan[42]. Even as practice moves towards widespread adoption of ARNI (which contain the ARB valsartan) for HF, this distinction has significant implications for the ongoing role of combination therapy with BB, which has, to date, only been assumed, but not proven[42].

OTHER EFFECTS OF ARNI

ARNI plays an important role in proteolytic processes in the kidney, as well as in cardiovascular regulation, immune response, cell proliferation, fetal development, and more[28]. First, in an exploratory study of patients with HFrEF who were treated with SAC/VAL using echocardiography, it was demonstrated to significantly decrease the ratio of early transmitral doppler velocity to early diastolic annular velocity (E/e') ratio, a simple, straightforward parameter of heart diastolic function[43]. Further, SAC/VAL may improve cardiac volume and function markers at twelve months[43]. Secondly, SAC/VAL is effective in treatment of hypertension, and short-term RCTs have found that the highest doses of SAC/VAL (200 and 400 mg q.d.) are more effective at lowering both office and ambulatory blood pressure than either ACEI or ARB alone; it should particularly be used as a first-line therapy for hypertensive patients with HFrEF[25,44]. They seem promising as antihypertensive agents for HFpEF, but investigation is ongoing[44]. Thirdly, although no effect was found on kidney function (compared to the irbesartan control), allocation to SAC/VAL did cause more reduction in cardiac biomarkers than irbesartan did, which suggests that this treatment could improve cardiovascular outcomes for this population[5]. Fourthly, there is growing evidence of neprilysin's role in glucose homeostasis: Because its activity in type 2 DM (T2DM) and obesity may potentially negatively impact metabolic processes in various tissues, it therefore plays a preventive role in the development of obesity and T2DM[28,29]. Thus, by raising the levels of various

peptides that exert beneficial effects on glucose metabolism, such as glucagon-like peptide-1 (GLP-1), NPs, and bradykinin, the inhibition of neprilysin in nutrient excess conditions could prove to be a powerful strategy for improving glucose homeostasis [29]. However, because of the action of other enzymes (such as DPP-4) on neprilysin substrates, which results in reduced inhibitor efficacy, as well as the concomitant elevation of neprilysin substrates that can impair sensitivity to insulin and function of beta cells, the use of a combination of drugs is preferable to the use of a neprilysin inhibitor alone for the treatment of T2DM[29]. Moreover, the increased angiotensin II levels that are associated with neprilysin inhibition limit its utility as a monotherapy for T2DM patients; a neprilysin inhibitor should always be prescribed along with an ARB, which is preferred over ACEI in order to avoid angioedema[29]. Fifthly, in some cases, administering SAC/VAL at appropriate doses has allowed for recovery of the sinus rhythm; consequently, upstream therapy of atrial fibrillation may demonstrate good results[45]. Sixthly, it may play a preventive role in cancer development[28]. Seventhly, viral dependence on ACE-2, as entry receptors, has been a recent focus, driving research into the impact of RAAS on COVID-19 pathogenesis[46]. Several pieces of evidence have pointed to neprilysin as a pulmonary RAAS components[46]. Considering neprilysin's protective effects against pulmonary inflammatory reactions and fibrosis, this suggests that future efforts should be directed towards its potential role in the pathophysiology of COVID-19[28,46].

On the other hand, the most frequently reported adverse events are hypotension and hyperkalemia[47]. Other adverse effects include teratogenicity from the ARB component; this medication should therefore be avoided during pregnancy[48]. In addition, though it was reported in 2018 that SAC/VAL could increase the risk for dementia, the risk was lower than the proportions reported for other medications[48].

EVIDENCE FROM TRIALS

To date, there have been a number of global clinical trials regarding SAC/VAL: PARAMOUNT, PARADIGM-HF, TRANSITION, PIONEER-HF, PARAGON-HF, and PARALLEL-HF. The detail is shown in Supplement material.

PARAMOUNT trial

PARAMOUNT was a phase-2, randomized, parallel-group, double-blind multicenter trial in patients of NYHA class II-III HF, LVEF 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1), by a central interactive voice response system, to either ARNI LCZ696 titrated to 200 mg twice daily, or valsartan titrated to 160 mg twice daily, and treated for 36 wk[49]. The primary endpoint was changes in NT-proBNP, a marker of LV wall stress, from baseline to twelve weeks; the analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment[49]. The trial concluded that, in patients with HFpEF, SAC/VAL reduced NT-proBNP to a greater extent at twelve weeks than valsartan, and that it was well tolerated[49]. In this trial, the most common adverse event reported with SAC/VAL was symptomatic hypotension, with 19% frequency[48].

PARADIGM-HF trial

In the 2014 PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial of 8399 outpatient subjects with HFrEF, SAC/VAL was found to be more effective than enalapril for slowing disease progression by decreasing the risk of worsening HF leading to the need for hospitalization or emergency admission and the need for intensified therapy; it also reduced the rates of 30-day HF readmission, as well as all-cause readmission after HF hospitalization, HF devices, or cardiac transplantation[24,31,37]. In addition, treatment with SAC/VAL was associated with statistically important reductions in cardiovascular death, a 16% reduction in all-cause mortality, and a 20% reduction in the composite of cardiovascular-related death or HF-related hospitalization (composite primary endpoint) compared to treatment with enalapril [16,26,33,37,47,48,50-52].

Accordingly, in 2016, the European and American cardiology societies (ACC/AHA/Heart Failure Society of America) simultaneously issued a class I recommendation to replace ACEI with SAC/VAL for management of patients with HFrEF NYHA II-IV[4,16,26,33,48,50,52]. The results indicate that SAC/VAL should be started from the earliest symptomatic stages of the disease[31,37]. However, more, longer-

term trials may be necessary in order to conclusively compare the efficacy of the two drugs, as well as their safety; though this is beyond the scope of this review, it is nevertheless in crucial need of evaluation[4]. Moreover, the results of the above trials should be taken with caution, as several limitations have been identified that may affect the generalizability and applicability of these results in real-life clinical practice [4].

Biomarker-based mechanistic studies have also provided further insight into potential pathways that may prove relevant to the benefits that have been observed with ARNI[26]. In this trial, treatment with SAC/VAL was associated with greater increases in BNP and urinary levels of cyclic guanosine monophosphate compared to treatment with enalapril; the latter reflects the increased intracellular second-messenger levels that result from NP action, as well as the other direct and indirect effects of mediators increased by inhibition of neprilysin[26]. However, most of the patients treated showed only a modest increase in BNP levels after initiation of SAC/VAL[26]. In contrast, neprilysin has a greater affinity for A-type NP (ANP) than for BNP, and after SAC/VAL initiation, ANP increased more consistently and robustly [26]. It is conceivable that ANP or perhaps other neprilysin substrates (such as C-type NP, urodilatin, adrenomedullin, substance P, apelin, bradykinin, vasoactive intestinal peptide, calcitonin gene-related peptide, or GLP-1) may play a predominant role in the mechanism of action of SAC/VAL; indeed, further mechanistic studies are currently ongoing, in order to elucidate the processes that underlie the clinical benefits that were observed in this study[26]. In addition, treatment with SAC/VAL led to significantly reduced levels of aldosterone, soluble ST2, matrix metalloproteinase-9, and its specific inhibitor (tissue inhibitor of metalloproteinases-1), reflecting reduced profibrotic signaling[26]. The levels of procollagen amino-terminal propeptide types I and III also were lower than with enalapril, reflecting reduced synthesis of collagen[26].

This study also compared safety outcomes: the SAC/VAL group had a higher risk of hypotension compared to conventional therapy (OR, 3.14; 95%CI, 0.94–10.55), with 18% frequency[48,53]. Thus, in order to prevent serious adverse advents, clinicians must monitor for hypotension, dizziness, cough, angioedema, hyperkalemia, and renal dysfunction[53]. The risk of other adverse effects of ARNI use, such as hyperkalemia, cough, and diminished renal function, have been demonstrated to be lower than when using ACEI on its own[48,53].

TRANSITION trial

The TRANSITION trial was a randomized, multi-center, open-label study comparing two treatment initiation modalities of SAC/VAL, to assess tolerability and optimal time point for initiation of SAC/VAL in patients stabilized after acute HF: Either at least twelve hours pre-discharge, or days 1–14 post-discharge[54]. In summary, approximately half of the HFrEF patients who had stabilized after an acute HF decompensation event were able to achieve the recommended target dose of SAC/VAL within ten weeks, and at least 86% were able to maintain any dose of SAC/VAL for more than two weeks, following the label recommendations for initiation and up-titration[54]. There were few adverse events or permanent treatment discontinuations, particularly given the extreme vulnerability of the post-acute decompensated HF population[54]. The findings from this study complement those from the PIONEER-HF study, showing that early initiation of SAC/VAL in a wide range of HFrEF patients who have recently been admitted for acute decompensated HF is feasible, either as hospital patients or shortly after discharge[54].

PIONEER-HF trial

The PIONEER-HF trial (Comparison of SAC/VAL Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute HF Episode) was a multicenter, randomized, double-blind trial of in-hospital initiation of SAC/VAL (n = 440) compared to enalapril (n = 441), in patients who were stabilized during hospitalization for acute decompensated HF[55]. In this trial, a heterogeneity in the effect of SAC/VAL on these efficacy and safety outcomes were evaluated in the following selected subgroups of clinical concern: Patients with baseline systolic blood pressure ≤ 118 mmHg, baseline NT-pro BNP > 2701 pg/mL, estimated glomerular filtration rate < 60 mL/min per 1.73 m^2, ≥ 1 additional hospitalization for HF within the prior year, admission to the ICU during the index hospitalization, inotrope use during the index hospitalization, and severe congestion[55]. As a result, the trial found that treatment with SAC/VAL after initial stabilization led to a consistent reduction in cardiovascular death or rehospitalization for HF in high-risk subpopulations admitted for acute decompensated HF, and that SAC/VAL was well tolerated[55].

PARAGON-HF trial

The recently completed PARAGON-HF trial found that SAC/VAL modestly reduced total HF hospitalization and cardiovascular death risks, compared to valsartan, in patients with HFpEF, although this finding fell just short of being statistically significant[7,26,56]. Clinical benefits were observed in secondary endpoints, including QOL and kidney endpoints; more specifically women and patients who are at the lower end of the LVEF spectrum appeared to preferentially benefit[26]. In addition, the safety profile of SAC/VAL was found to be largely consistent with prior trials[26]. In this trial, 15.4% of the SAC/VAL group discontinued use of the trial drug due to an adverse event, and 58.9% patients had at least one serious adverse event; the most common serious adverse events (n ≥ 2% in the group) during the double-blind period, regardless of study drug relationship, by preferred term and SAC/VAL group, were cardiac failure (14.6%), atrial fibrillation (6.7%), pneumonia (6.7%), acute kidney injury (6.7%), congestive cardiac failure (3.6%), acute cardiac failure (3.5%), anemia (2.8%), acute myocardial infarction (2.5%), urinary tract infection (2.2%), hypotension (2.2%), and unstable angina (2.1%)[56]. By the time of the final visit, among the patients continuing therapy, the target dose was being taken by 82.0% of the SAC/VAL group [56].

SAC/VAL group patients had a greater likeliness of having hypotension, but were less likely to demonstrate creatinine and potassium level increases than valsartan group patients, and the mean systolic blood pressure at eight months was 4.5 mmHg (95%CI, 3.6–5.4), or lower in the SAC/VAL group than in the valsartan group; however, this difference did not correlate with the potential treatment effect[56].

PARALLEL-HF trial

The objective of the PARALLEL-HF trial was to describe the baseline characteristics and treatment of Japanese HFrEF patients[57]. The trial concluded that the patients studied were largely representative of contemporary ambulatory HFrEF patients who were well treated using evidence-based therapies[57]. In addition, PARALLEL-HF will assist in determining whether SAC/VAL provides clinical outcome improvements in Japanese HFrEF patients similar to those that were observed in the PARADIGM-HF study[57].

FUTURE PROSPECTS

Though guidelines have changed worldwide to include SAC/VAL for HFrEF patients, even now, some seven years after PARADIGM-HF trial, there remains some uncertainty regarding when to start SAC/VAL, and in whom[7]. A treatment's estimated long-term effects can serve as a helpful adjunct to clinical trial results, in order to provide patients with easily understood information regarding one treatment's potential benefits compared to those of another[26]. Furthermore, both HFpEF diagnosis and treatment remain challenging, as do the management of advanced and acute HF[7,34]. Though progress remains slow with respect to HFpEF, both ARNI and SGLT2 inhibitors also hold great promise for this condition, and there are currently large clinical trials underway (PARALLAX)[20,26,32]. In addition, the recent development of new diagnostic algorithms, to improve HFpEF diagnostic accuracy, will assist in future clinical trials' efforts to find effective therapies[20].

There are currently several other ongoing trials that aim to clarify and explore the benefits of SAC/VAL for HF management, as well[48]. It is unclear whether inhibition of neprilysin has a direct effect on extracellular matrix homeostasis, or if these profibrotic benefits reflect hemodynamic improvement; the completed PROVE-HF trial (prospective study of biomarkers, symptom improvement, and ventricular remodeling during SAC/VAL therapy for HF) will continue to examine a wide variety of biomarkers, including collagen homeostasis markers, in 795 HFrEF patients being treated with open-label SAC/VAL[26]. The currently ongoing PARADISE-MI trial (prospective ARNI *vs* ACEI trial to determine superiority in reducing HF events after myocardial infarction (MI)) aims to evaluate the effects of inpatient SAC/VAL compared to ramipril, for reducing cardiovascular death and HF hospitalization in post-acute MI patients who have evidence of LV systolic dysfunction (EF < 40%) and/or pulmonary congestion, and who have no known prior history of CHF[26,48]. Another dedicated, randomized, cardiac-magnetic-resonance-based trial, comparing SAC/VAL to valsartan in patients who have asymptomatic LV systolic dysfunction and a history of MI, RECOVER-LV (effects of SAC/VAL compared to valsartan on LV remodeling in asymptomatic LV systolic dysfunction after MI), is also expected to

provide further insight into ARNI's potential remodeling effects[26].

The effects of SAC/VAL on hypertensive organ damage have only been sparsely investigated; to date, no studies have established SAC/VAL's impact on cardiovascular event rates[25]. Therefore, future studies should focus on comparing SAC/VAL to combination therapies already in use, such as ARB and calcium channel blockers[25]. Additionally, COVID-19 is an ongoing viral pandemic disease that induces severe pneumonia in human patients[46]. A report has aimed to elucidate the potential beneficial effects of neprilysin pathways, as a novel target for COVID-19 therapy, through a summary of its possible molecular mechanisms[46]. Additional experimental and clinical studies that further explain the relationships between neprilysin and COVID-19 will be of great benefit when designing future treatment approaches[46].

Finally, the barriers that prevent SAC/VAL from being prescribed for eligible patients may include practitioners' unfamiliarity with ARNI, safety concerns, and payer reimbursement issues[53].

CONCLUSION

SAC/VAL is an efficacious, safe, and cost-effective therapy that improves QOL and longevity in patients with chronic HFrEF, and reduces hospital admission. An in-hospital initiation strategy offers a potentially new avenue to improve clinical uptake of SAC/VAL. In the last five years, SAC/VAL has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. In the next five years, we should see SAC/VAL being brought into wider implementation in practice, with potential expansion of its therapeutic indications. Further work is necessary, with carefully designed and controlled preclinical studies, in order to better understand its molecular mechanisms and effects, and to confirm issues such as long-term safety in both human and animal models.

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ORIGINAL ARTICLE

Case Control Study

Association of marital status with takotsubo syndrome (broken heart syndrome) among adults in the United States

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Abstract

BACKGROUND

The pathophysiology of takotsubo syndrome (TTS) is not well understood, however, it is often precipitated by psychological or physical stress. Marital status is related to emotional stress, but its associations with TTS are limited.

AIM

To explored the potential association between marital status and TTS.

METHODS

We conducted a case-control study using data on patients aged ≥ 40 years with marital status data in the National Hospital Discharge Survey (2006-2010). The International Classification of Diseases Ninth Revision codes were used to identify cases with TTS and other comorbid conditions. Each case was matched to 5 controls by age, sex, year of TTS diagnosis and bed size of hospital. Two sets of controls were selected: Acute myocardial infarction (AMI) controls and non-cardiovascular disease (CVD) controls. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of marital status with TTS.

RESULTS

The 59 patients with TTS who had information on marital status were matched to 295 controls with AMI and 295 non-CVD controls, resulting in a sample of 649

patients. The average age of cases was 69.7 ± 11 years with 90% being women and 88% reporting White race. In multivariable-adjusted models, compared to singles, patients who were married had lower odds of TTS (OR = 0.86, 95%CI: 0.79–0.93) while those who were widowed (OR = 1.14, 95%CI: 1.05–1.23) or divorced/separated (OR = 1.32, 95%CI: 1.21–1.45) had elevated odds for TTS when compared to non-CVD controls. Similar results were observed when cases were compared to controls with AMI.

CONCLUSION

In this study, being married was associated with lower odds for TTS while being divorced/separated or widowed was related to elevated odds for TTS. These novel findings that underscore the potential importance of social factors like marital status in the development of TTS need confirmation in larger studies.

Key Words: Stress-induced cardiomyopathy; Takotsubo syndrome; Marital status; Epidemiology; Case-control; Marriage

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Core Tip: Being married was associated with lower odds for takotsubo syndrome (TTS) while being divorced/separated or widowed was related to elevated odds for TTS.

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INTRODUCTION

Takotsubo syndrome (TTS), also known as "broken heart syndrome" is a transient dysfunction of the left ventricle (LV)[1]. Its initial presentations are similar to acute coronary syndrome, and it is characterized by varying combinations of chest pain, ischemic electrocardiographic changes pertaining to ST-segment elevation and/or T-wave inversion, and moderate elevations in cardiac biomarkers such as troponin[2]. Almost 80% of all cases occur in older women[1,3]. In the United States, the incidence of TTS has been increasing over the years. During the period of 2007 to 2012, the incidence of TTS increased by more than 300% from 52 per 1000000 discharges to 178 per 1000000 discharges[4]. Although the pathophysiology is not well understood, it is often precipitated by psychological or physical stress[5], as well as acute neurologic and psychiatric diseases[6].

While the prognosis is favorable with recovery of LV function in some patients, growing evidence suggests that TTS is associated with severe morbidity and mortality [7]. Patients with TTS are at high risk for recurrence after the first events[6]. Emerging evidence suggest that more than half of patients with TTS develop severe complications, and that TTS-related mortality is comparable to those amongst patients with myocardial infarction or acute coronary syndrome[8,9].

Due to the observed stress triggers, it has been suggested that TTS may be related to some social and emotional factors that influence psychological wellbeing. Marital status is related to emotional stress[10]. However, investigations into the relation of marital status with TTS are limited, with most of these being case reports[11,12].

We aimed to explore the association of marital status with TTS in a national sample of hospitalized adults from the United States.

MATERIALS AND METHODS

The National Hospital Discharge Survey (NHDS) which is administered by the National Center for Health Statistics is a continuous survey of inpatient utilization of

because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: All data are from the National Hospital Discharge Survey and are publicly available through the Centers for Disease Control and Prevention: https://www.cdc.gov/nchs/nhds/index.htm.

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short-stay (< 30 d) hospitals in the United States. The NHDS which was conducted from 1965-2010 used a multistage cluster sampling technique to provide nationally representative data. All procedures were approved by the institutional review board of the National Center for Health Statistics with all patients providing written informed consent for their information to be included in this database. All data from the NHDS are publicly available through the Centers for Disease Control and Prevention: https://www.cdc.gov/nchs/nhds/index.htm. Because the NHDS data is deidentified and publicly available, the Texas Tech University Health Sciences Center Institutional Review Board determined that this current study did not require a review

We conducted a case-control study using discharge records from 2006 to 2010. Patients who were aged ≥ 40 years with no missing data on marital status and did not have a diagnosis of myocarditis or pheochromocytoma were eligible for this study. Marital status information which was obtained from the National Center for Health Statistics was classified as single, married, divorced, separated or widowed. Similar to other reports from national samples[2,4,13], the International Classification of Diseases Ninth Revision codes were used to identify cases with TTS (ICD-9-CM: 429.83) and other comorbid conditions. Acute myocardial infarction (AMI) was identified using ICD-9 codes: 410 while stroke was defined with ICD-9 codes 430 to 438.

Cases were defined as patients with TTS who underwent diagnostic coronary angiography and did not receive any percutaneous coronary interventions or revascularizations. A control was defined as any patient without TTS diagnosis during hospitalization. Each case was matched to 5 controls by age, sex, year of TTS diagnosis and bed size of hospital. Hospital bed size, defined as the number of beds per hospital, was used as a measure of hospital volume. The greedy matching strategy with a fixed number of controls per case was used[14]. Matched controls were selected from among all patients' who met the eligibility criteria listed above. Two sets of controls were selected for each case. Thus, for each case, 5 controls with AMI were selected (considered as AMI controls) and also 5 non-cardiovascular disease (CVD) controls were selected (considered as non-CVD controls). Patients with AMI or stroke were considered eligible for CVD controls.

Means and percentages were used to describe the characteristics of patients. Conditional logistic regression incorporating sampling weights was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of marital status with TTS. Besides the matching variables of age, sex, year of TTS diagnosis and bed size of hospital, adjustments were made for race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes and chronic obstructive pulmonary disease. Additional analyses were performed with further adjustment for neurological and psychiatric disorders. A 2-tailed p value less than 0.05 was used to determine statistical significance, and all analyses were performed with SAS version 9.4 (SAS Institute Inc).

RESULTS

The 59 patients with TTS who had information on marital status were matched to 295 controls with AMI and 295 non-CVD controls, resulting in a sample of 649 patients. Characteristics of the 649 participants included in the study are presented in Table 1. The average age of cases was 69.7 ± 11 years with 90% being women and 88% reporting White race. Overall, a greater proportion of participants were from the southern region of the United States with about two-thirds of participants having Medicare as their principal expected source of payment. Approximately 39% of cases were married, 17% were single, and 27% were widowed. There were significant differences in race/ethnicity between cases and AMI controls or non-CVD controls. Although AMI controls and non-CVD controls had higher prevalence of neurologic and psychiatric disorders than patients with TTS, these differences did not meet statistical significance ($P > 0.05$).

A significant association was observed between marital status and TTS (Table 2) in multivariable models. Compared with singles, patients who were married had lower odds for TTS (OR = 0.86, 95%CI: 0.79–0.93) while those who were widowed or divorced/separated had 14% (OR = 1.14, 95%CI: 1.05-1.23) and 32% (OR = 1.32, 95%CI: 1.21-1.45) elevated odds for TTS, respectively, when compared to non-CVD controls. Similar results were observed when cases were compared with controls with AMI. Compared to patients who were currently married, non-married patients (single, widowed or divorced/separated) were at elevated risk for TTS, whether compared to AMI controls (OR = 1.66, 95%CI: 1.58-1.75) or non-CVD controls (OR = 1.40; 95%CI:

Table 1 Characteristics of participants according to case-control status, National Hospital Discharge Survey 2006-2010

Characteristics	Cases (*n* = 59)	AMI controls (*n* = 295)	*P* value[2]	Non-CVD controls (*n* = 295)	*P* values[3]
Age, (mean ± SD, yr)[1]	69.7 (11.4)	(69.8 (11.1)	-	69.7 (11.3)	-
Sex, female[1]	89.8%	89.8%	-	89.8%	-
Race			0.009		0.021
White	88.1%	67.1%		70.5%	
Black	5.1%	16.3%		14.6%	
Other	6.8%	16.6%		14.9%	
Current smoker	15.3%	8.5%	0.104	17.3%	0.701
Type of insurance			0.424		0.537
Medicaid	8.5%	5.8%		5.8%	
Private	22.0%	29.2%		27.8%	
Medicare	69.5%	65.1%		66.4%	
Health condition					
Obese	6.8%	8.8%	0.597	5.1%	0.593
Hypertension	42.4%	50.5%	0.241	52.5%	0.133
Dyslipidemia	20.3%	15.9%	0.404	27.1%	0.272
Diabetes	15.3%	16.3%	0.845	17.6%	0.660
COPD	27.1%	16.3%	0.051	22.0%	0.390
Neurological disorders	6.8%	13.2%	0.178	13.2%	0.173
Psychiatric disorders	3.4%	7.1%	0.295	5.1%	0.577
Marital status			0.375		0.583
Married	39.0%	45.1%		42.7%	
Not married	61.0%	54.9%		57.3 %	

[1]These variables are among the characteristics by which cases were matched to controls.
[2]*P* values for comparison of characteristics between cases and AMI controls.
[3]*P* values for comparison of characteristics between cases and non-CVD controls. AMI: Acute myocardial infarction; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease.

1.34–1.46). These associations remained largely the same when additional adjustments were made for neurological and psychiatric disorders (Table 3).

DISCUSSION

In this case-control study using a nationally representative sample, being married was associated with lower odds for TTS while being divorced/separated or widowed was associated with elevated odds for TTS. These novel findings corroborate previous reports of marriage being related to good cardiovascular health while being single or encountering marital disruptions such as divorce/separation or widowhood is associated with poor overall and cardiovascular health outcomes[10].

To our knowledge, this is the first observational study to evaluate the association of marital status with TTS. Although the relationship of family or social history with TTS have not been extensively investigated, previous case reports and case series have observed TTS among elderly women who were recently widowed[11,12] or had loss of a close family member[15]. Emotional stresses such grief, interpersonal conflicts, fear, panic, anxiety and anger have been frequently observed in women with TTS compared to physical stressful event[16]. Among the few studies on TTS that obtained marital status information, TTS was more common among patients who were not married compared to those who were currently married[3], results that are similar to findings of the current study.

Table 2 Adjusted estimates for the association of marital status with takotsubo syndrome by acute myocardial infarction and non-cardiovascular disease controls, National Hospital Discharge Survey 2006-2010[1]

Marital status	Cases (*n* = 59)	AMI controls (*n* = 295)	Non-CVD controls (*n* = 295)	Odds ratios (95%CI) for AMI controls	Odds ratios (95%CI) for non-CVD controls
Single	10	53	40	1	1
Married	23	133	126	0.69 (0.63-0.75)	0.86 (0.79-0.93)
Widowed	16	76	93	1.09 (1.01-1.19)	1.14 (1.05-1.23)
Separated/divorced	10	33	36	1.27 (1.16-1.39)	1.32 (1.21-1.45)
Married	23	133	126	1	1
Not married	36	162	169	1.66 (1.58-1.75)	1.40 (1.34-1.46)

[1]Each case was matched to five controls based on age, sex, year of takotsubo cardiomyopathy diagnosis and bed size of hospital. Adjusted for age, sex, year of TTS diagnosis, bed size of hospital, race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes and chronic obstructive pulmonary disease. AMI: Acute myocardial infarction; CI: Confidence interval; CVD: Cardiovascular disease.

Table 3 Estimates from fully adjusted models for the association of marital status with takotsubo syndrome by acute myocardial infarction and non-cardiovascular disease controls, National Hospital Discharge Survey 2006-2010[1]

Marital status	Cases (*n* = 59)	AMI controls (*n* = 295)	Non-CVD controls (*n* = 295)	Odds ratios (95%CI) for AMI controls	Odds ratios (95%CI) for non-CVD controls
Single	10	53	40	1	1
Married	23	133	126	0.62 (0.57-0.68)	0.86 (0.79-0.93)
Widowed	16	76	93	1.04 (0.96-1.14)	1.19 (1.10-1.28)
Separated/divorced	10	33	36	1.30 (1.18-1.43)	1.36 (1.25-1.49)
Married	23	133	126	1	1
Not married	36	162	169	1.80 (1.71-1.91)	1.44 (1.38-1.51)

[1]Each case was matched to five controls based on age, sex, year of takotsubo cardiomyopathy diagnosis and bed size of hospital. Adjusted for age, sex, year of TTS diagnosis, bed size of hospital, race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, neurologic and psychiatric disorders. AMI: Acute myocardial infarction; CI: Confidence interval; CVD: Cardiovascular disease.

There are several plausible explanations for these observations. Marriage offers certain behavioral, social and psychological benefits that may help in the prevention of TTS. Many married couples tend to have better CVD risk profiles namely healthier meals, physical activity, adequate sleep and better financial benefits that often lead to less stress than singles, divorced/separated or widowed persons[10,17]. Married couples often have larger social networks and support, and are known to report greater happiness and life satisfaction as well as higher compliance with medical screenings and uptake of medications[10]. The protective benefits of marriage for TTS and other CVD may also simply reflect the fact that healthy individuals usually select other healthy individuals for marriage[17].

Marital disruptions (*i.e.*, divorce/separation or widowhood) typically have deleterious effects on health. Acute events like widowhood, especially if unexpected, can lead to sudden heightened psychological stress, depression and loss of some social support[10]. Persons in troubled marriages which often end in divorce/separation may also experience these conditions. Some studies have observed high levels of catecholamines especially epinephrine in individuals experiencing marital conflicts [17]. Evidence from animal studies and histologic findings suggest that a surge in circulating epinephrine may induce transient LV dysfunction due to their toxicity on myocardial cells resulting from a rise in cyclic AMP-mediated calcium overload of cardiocytes[12,18]. This calcium overload of cardiocytes triggers the formation of free oxygen radicals, expression of stress response genes, and also the induction of apoptosis in a subset of myocardial cells[12]. However, with the full resumption of LV function weeks after the occurrence of TTS in some patients, it holds to reason that this cascade of molecular activities leading to apoptosis in some cardiomyocytes may not

fully explain the role of catecholamines in the development of TTS[12,19].

Other factors such as neurologic and psychiatric disorders at the time of admission have been reported to be significantly associated with in-hospital complications among patients with TTS[6,20]. Some studies have reported higher prevalence of neurologic and psychiatric disorders in patients with TTS compared to controls; however, results for the association of these disorders with TTS have been mixed[21]. In the current study, there was no significant difference between patients with TTS and AMI controls or non-CVD controls, and additional adjustment for neurologic and psychiatric disorders did not appreciably change the reported estimates between marital status and TTS. The discrepancy in findings between the current study and some prior studies may, in part, be explained by differences in sample size and study designs. Patients with TTS often have recurrent events, with the risk of reoccurrence being higher among patients with pre-admission psychiatric disorders[22]. With about 39% of patients with TTS reporting a neurological disease and 50% of patients with TTS reporting at least one mental disorder about 17.5 mo from their index event[23], future studies are warranted to investigate the potential role of therapeutics in preventing the incidence or reoccurrence of TTS in patients with neurologic and psychiatric disorders.

A strength of this study is the usage of a population representative sample that enhance the generalizability of the findings. Limitations of this study include the small sample of TTS cases due to exclusion of patients without data on marital status, and the inability to study the quality of marriage or sex differences on the relation of marital status with TTS. Also, data on the severity of the acute disease between cases and controls were not available. Finally, ICD codes which are susceptible to error during the coding process were used to identify diseases and comorbid conditions. However, the use of ICD codes is the standard procedure for identifying TTS cases in national samples from the United States[2,4,13]. For TTS, information for confirming the diagnosis such as cardiac enzymes as well as echocardiographic or electrocardiographic readings were not available. Therefore, patients with conditions like coronary spastic angina could not be excluded. Finally, even though we controlled for several potential confounders, the possibility of residual confounding influencing these results cannot be entirely ruled out.

CONCLUSION

In conclusion, these novel findings show that being married is associated with lower odds for TTS, whereas the occurrence of divorce/separation, or widowhood is associated with higher odds of TTS. These results have substantial clinical and public health importance. Given that growing evidence suggests that TTS is associated with severe morbidity and mortality[7], understanding the specific pathophysiologic pathways that may be involved in the association of social stress factors and TTS holds promise in providing avenues to prevent this disease. Therefore, confirmation of these observed associations from prospective studies are warranted to better understand the relation of marital status with TTS and elucidate specific pathophysiologic pathways that are involved in the association between marital status and TTS.

ARTICLE HIGHLIGHTS

Research background

The incidence of takotsubo syndrome (TTS) is increasing in the United States. However, the pathophysiology of TTS is not well understood, although, it is often precipitated by psychological or physical stress.

Research motivation

Marital status is related to emotional stress. However, not many studies have been conducted to evaluate the association of family relationships or social history with TTS.

Research objectives

The objective of this study was to evaluate the association of marital status namely being single, married, widowed or divorced/separated with TTS in an elderly population.

Research methods

A case-control study was performed using data on 649 patients from the United States National Hospital Discharge Survey.

Research results

Findings from this study showed that being married was associated with lower odds for TTS while being divorced/separated or widowed was associated with elevated odds for TTS.

Research conclusions

With marital status associated with TTS, understanding the underlying mechanisms for this association is of substantial clinical and public health importance.

Research perspectives

Confirmation of these observed associations from prospective studies are warranted to better understand the relation of marital status with TTS.

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ORIGINAL ARTICLE

Clinical Trials Study

Nutritional supplement drink reduces inflammation and postoperative depression in patients after off-pump coronary artery bypass surgery

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Abstract

BACKGROUND

Coronary artery bypass grafting is a surgical treatment for ischemic heart disease. Although development in surgical technique and improvement of perioperative management reduced the postoperative complications, some patients still delayed in progress of postoperative rehabilitation. In this study, we aimed to investigate the effect of daily intake of an herbal medicine-containing drink for rehabilitation after surgery in patients with ischemic heart disease.

AIM

To investigate the effect of taking an herbal medicine-containing, commercially available drink for postoperative rehabilitation in those patients.

METHODS

Patients who underwent isolated off-pump coronary artery bypass (OPCAB) surgery were divided into two groups depend on the timing of the admission to the hospital: the Yunker (YKR) group, that consumed one bottle of a caffeine-free nutritional supplement drink on a daily basis and the control group (CTL) that

underwent regular rehabilitation.

RESULTS

A total of 229 patients (CTL = 130, YKR = 99) were enrolled. No significant differences were observed in the baseline characteristics between the two groups. The YKR group had a significantly increased number of daily steps postoperatively ($P < 0.05$) and had significantly lower postoperative serum tumor necrosis factor-alpha levels ($P < 0.01$), while no significant differences were observed in the levels of other inflammatory or stress-related cytokines (interleukin-6, adiponectin, superoxide dismutase, and urine 8-hydroxy-2′-deoxyguanosine) between the two groups. Also, the YKR group showed a significant improvement in the Hospital Anxiety and Depression Score ($P < 0.05$). Moreover, there were no differences in postoperative complications and the duration of postoperative hospital stay between the two groups.

CONCLUSION

Our results demonstrated that the daily intake of an herbal medicine-containing drink after OPCAB surgery may have beneficial effects on cardiac rehabilitation by reducing inflammation markers and depression.

Key Words: Herbal medicine; Inflammation; Cardiac rehabilitation; Moderate-to-vigorous intensity physical activity; Off-pump coronary artery bypass

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Core Tip: Ischemic heart disease is still a major cause of death in the developed country. Cardiac rehabilitation for the patients who underwent coronary artery bypass grafting surgery has known to be associated with early recover. Daily intake of an herbal medicine-containing drink after the surgery enhances the postoperative cardiac rehabilitation by reducing inflammation and improving depression.

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INTRODUCTION

Ischemic heart disease is still a major cause of death in the developed country. Coronary artery bypass grafting (CABG) is a surgical treatment for ischemic heart disease. Although postoperative complications are reduced with the technical development of the surgery, such as the off-pump technique[1,2], or with the improvement of perioperative management, variable amounts of physical and mental stress still occur after surgery. Postoperative rehabilitation following cardiac surgery is highly recommended since it increases motion tolerability[3,4], improves cardiac function[5,6], and reduces postoperative depression[7,8]. The recent guideline recommended the early induction of postoperative rehabilitation for the prevention of perioperative heart or respiratory failure, resulting in short hospital stay and early social recovery[9]. Despite the abovementioned recommendation, patients with low cardiac function, high age, frail, or complicated conditions often show delay. With the recent increase in the elderly population, the number of octogenarians who underwent CABG has also increased. These patients are potentially frail and exhibit systemic deterioration.

Consuming a commercially available nutritional supplement "energy" drink when a person experiences fatigue or develops illnesses such a cold is a widely accepted practice in the Japanese society. Some people habitually consume this type of drink as a treatment for chronic fatigue or to maintain motivation. Various kinds of nutritional supplement drinks are commercially available in Japan. Although, many of these

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

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products commonly contain multiple vitamins, caffeine, and sugar, only few contain herbal products, of which some have been known to reduce the physical and mental stresses. In this study, we aimed to investigate the effect of taking an herbal medicine-containing drink for postoperative rehabilitation in patients with ischemic heart disease.

MATERIALS AND METHODS

Design and participants

Adult patients (≥ 20 years of age) who were scheduled for elective isolated off-pump coronary artery bypass (OPCAB) surgery at Juntendo University Hospital were enrolled consecutively in the study from January 2014 to December 2017. The patients were assigned to one of two groups as follows: Those enrolled from January to June 2014 and September 2016 to December 2017 were assigned to the control group (CTL), and those enrolled from June 2014 to September 2016 were assigned to the treatment group. Patients in the treatment group consumed 30-mL of a caffeine-free, herbal nutritional supplement from a commercially available bottle, (Yunker DCF, Sato Pharmacy. Co. Ltd, Tokyo, Japan) every day after being granted permission to resume a liquid diet following surgery (YKR group). Patients with liver dysfunction (defined by tests exceeding the normal value in any of the following markers at the time of administration: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, or γ-glutamyl transpeptidase), who underwent hemodialysis due to kidney dysfunction, or who experienced preoperative gait disturbance were excluded from the study. The contents of the drink are shown in Table 1. Patients in the CTL underwent the regular post-cardiac surgery course and did not consume the supplement drink. Both groups were treated according to our post-CABG clinical path. In addition, patients who received concomitant surgery due to the surgeon's decision during surgery and those who experienced stroke (including transient ischemic attack) or infections such as pneumonia postoperatively were excluded from the study.

Activity measurements

The primary endpoint of the study was whether the YKR enhanced the activity postoperatively. To evaluate perioperative activity, we used an accelerometer (Omron HJA-350IT, Kyoto, Japan). As indices of the activity, the number of daily steps, daily total activity [metabolic equivalent (MET) × hour], and moderate-to-vigorous intensity physical activity (MVPA) were used. Total activity was determined by calculating the integrated METs per minute for 1 h (60 min), while MVPA was calculated using more than three METs of total activity.

The maximum value in each period (pre-/postoperative) was compared between the two groups. If preoperative or postoperative data were lacking, they were excluded from the activity analysis.

Laboratory measurements

Results of blood tests performed upon admission and on the 2nd and 7th postoperative day (2 POD and 7 POD, respectively) were used in this study. In addition, the levels of the following inflammatory cytokines were measured in serum and urine (SRL, Inc., Tokyo, Japan) and compared between the two groups: interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), adiponectin, superoxide dismutase (SOD), and the ratio of urine 8-hydroxy-2′-deoxyguanosine and creatinine (8-OHdG/Cre).

Anxiety and depression scores

Before and on 7 POD, the levels of depression and anxiety were assessed. We used the Hospital Anxiety and Depression Scale (HADS) and Geriatric Depression Scale-15 (GDS). The HADS has two subscales: HADS_A, used to measure the level of anxiety; and HADS_D, used to measure the degree of depression. Each value and changes in intra-patient values were compared between the groups.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of data distribution, and further statistical analyses were subsequently performed. Patients' baseline data were compared using the chi-square test and Student's *t*-test. In the development data set, we formulated a predictive equation based on sex, age, body mass index, ischemic heart disease, treatment with cardiopulmonary bypass, hypertension, diabetes

Table 1 Contents of the nutritional supplement drink (per 120 mL)

Contents	
Agkistrodon meat and bones tincture	100 mg
Civet tincture	250 mg
Ginseng fluid extract	600 mg
Hawthorn flower extract	30 mg
Rehmannia root extract	120 mg
Royal jelly	100 mg
Vitamin B1 nitrate	10 mg
Vitamin B2 phosphate ester	5 mg
Vitamin B6	10 mg
Tocopherol acetate	10 mg
Nicotinamide	25 mg
Panthenol	10 mg
Chondroitin sulfate sodium	120 mg

mellitus, dyslipidemia, preoperative hemodialysis, smoking (present/history), persistent atrial fibrillation (AF), serum brain natriuretic peptide level, New York Heart Association classification, left atrial diameter, and left ventricular ejection fraction. Multicollinearity among the variables in the predictive equation was considered. Data were analyzed using SPSS 22.0 (SPSS, Tokyo, Japan). All data are expressed as mean ± SE. Statistical significance was set at a level of $P < 0.05$. The statistical methods of this study were reviewed by an expert Biostatistician Dr. Minematsu K.

RESULTS

Characteristic of the patients

Altogether, 280 patients were eligible to enroll in this study (Figure 1). Fifteen patients did not consent for enrollment and 10 were excluded preoperatively because of liver dysfunction. Thirteen patients who were initially eligible did not undergo isolated OPCAB surgery due to their physician's decision, one withdrew from the study, and four other patients were excluded because they developed hemiplegia of the right hand, postoperative pneumonia, pneumothorax, or a drug allergy. Furthermore, eight patients were excluded for missing data. In total, 229 patients were analyzed; 130 were in the CTL group and 99 were in the YKR group. The characteristics of the patients are shown in Table 2. There were no differences in these indices between the two groups.

Activity

Figure 2 shows the number of preoperative and postoperative steps, activity, and MVPA, which were recorded using an accelerometer, in each group. The mean number of postoperative steps (Figure 2A) was increased in both groups, but only the increase in the YKR group was significant (preoperative *vs* postoperative: CTL, 2301 ± 253 steps *vs* 2787 ± 257 steps, $P = 0.096$; YKR: 2223 ± 225 steps *vs* 2943 ± 272 steps, $P < 0.05$).

The total activity (Figure 2B) significantly increased both in the CTL and YKR groups postoperatively (preoperative *vs* postoperative: CTL, 45.6 ± 1.9 METs·h *vs* 55.1 ± 2.8 METs·h, $P < 0.01$; YKR, 44.8 ± 2.6 METs·h *vs* 56.6 ± 3.4 METs·h, $P < 0.01$). The postoperative MVPA, an integrated activity of >3 METs, showed a nonsignificant decreasing trend in both groups (Figure 2C; preoperative *vs* postoperative: CTL, 0.76 METs·h *vs* 0.61 METs·h, $P = 0.275$; YKR, 0.83 METs·h *vs* 0.79 METs·h, $P = 0.749$). Despite the decreasing trend of the MVPA, the ratio of the MVPA to the total activity in the individual patients (Figure 2D) increased postoperatively in the YKR group. By contrast, it decreased in the CTL group, although no significant differences were found in the two groups (CTL, 0.084% ± 0.014% *vs* 0.055% ± 0.010%, $P < 0.094$; YKR, 0.081% ±

Table 2 Patient characteristics

	CTL	YKR	*P* value
Number of patients	130	99	
Age, yr	69.4 ± 0.8	68.5 ± 1.0	0.437
Female (%)	20 (15.4)	12 (12.1)	0.481
BMI	24.5 ± 0.3	24.7 ± 0.3	0.644
Hypertension (%)	90 (69.2)	74 (74.7)	0.360
Diabetes mellitus (%)	70 (53.8)	49 (49.5)	0.407
Dyslipidemia (%)	94 (72.3)	75 (75.8)	0.791
Smoking history (%)	78 (60.0)	59 (59.6)	0.950
Preoperative AF (%)	4 (3.1)	1 (1.0)	0.261
NYHA	1.6 ± 0.1	1.7 ± 0.1	0.725
LAD, mm	37.3 ± 0.4	37.9 ± 0.5	0.316
LVDd, mm	47.8 ± 0.5	49.1 ± 0.7	0.131
LVDs, mm	32.0 ± 0.6	32.7 ± 0.8	0.537
IVST, mm	9.7 ± 0.1	9.9 ± 0.1	0.266
PWT, mm	9.8 ± 0.1	10.0 ± 0.1	0.195
LVEF, %	61.0 ± 0.8	60.0 ± 1.4	0.540
Operation time, min	253.6 ± 5.7	248.4 ± 6.8	0.555
Intubation time, h	6.7 ± 0.7	5.6 ± 0.4	0.176
Number of distal anastomosis	3.2 ± 0.1	3.2 ± 0.1	0.964
Right gastroepiploic artery graft (%)	66 (50.8)	52 (52.5)	0.793
Saphenous vein graft (%)	47 (36.2)	32 (32.3)	0.470
Blood transfusion (%)	23 (17.7)	19 (19.2)	0.662
Postoperative AF (%)	31 (23.8)	24 (24.2)	0.936
ICU stay, d	1.2 ± 0.0	1.2 ± 0.0	0.895
Hospital stay, d	10.1 ± 0.3	10.7 ± 0.4	0.187

AF: Atrial fibrillation; BMI: Body mass index; ICU: Intensive care unit; IVST: Interventricular septum thickness; LAD: Left atrium diameter; LVDd: Left ventricular diastolic diameter; LVDs: Left ventricular systolic diameter; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association classification; PWT: Posterior wall thickness; CTL: Control group; YKR: Yunker group.

0.013% *vs* 0.091% ± 0.025%, $P < 0.690$).

Blood and urine test

The results of blood tests performed upon admission and on 2 POD and 7 POD are shown in Table 3. No significant differences were observed in the investigated indices between the groups at any period.

Next, the levels of inflammatory or stress-related cytokines (IL-6, TNF-α, adiponectin, and SOD, Figure 3A-D) and urinary stress hormones (8-OHDG/Cre ratio, Figure 3E) were measured on 2POD and 7POD. IL-6 Level significantly decreased in both groups (CTL: 81.5 ± 4.9 pg/mL to 21.5 ± 2.9 pg/mL, $P < 0.01$; YKR: 75.8 ± 7.2 pg/mL to 17.3 ± 2.7 pg/mL, $P < 0.01$, 2 POD to 7 POD, respectively). In addition, there were no significant differences between the two groups on 2 POD ($P = 0.498$) and on 7 POD ($P = 0.301$). A nonsignificant increasing trend was observed in TNF-α level in the CTL group, while a nonsignificant decreasing trend was observed in the YKR group (CTL: 3.2 ± 0.7 pg/mL to 5.0 ± 1.2 pg/mL, $P = 0.686$; YKR: 3.7 ± 0.9 pg/mL to 1.9 ± 0.2 pg/mL, $P = 0.052$, 2 POD to 7 POD, respectively). Notably, the TNF-α level in the YKR group was significantly lower than that in the CTL group ($P < 0.01$) on 7 POD, although no significant difference was observed on 2 POD ($P = 0.623$). Adiponectin level significantly increased in both groups (CTL: 6.8 ± 0.3 μg/mL to 8.5 ± 0.4 μg/mL,

Table 3 Perioperative blood test results

	Group	Pre	*P* value	2 POD	*P* value	7 POD	*P* value	7-2 POD	*P* value
WBC, × 10^9/L	CTL	6.1 ± 0.3	0.991	12 ± 0.3	0.962	7.6 ± 0.2	0.534	-4.4 ± 0.2	0.568
	YKR	6.1 ± 0.2		12 ± 0.4		7.8 ± 0.2		-4.2 ± 0.3	
Hb, g/dL	CTL	13.3 ± 0.1	0.645	11.2 ± 0.1	0.876	11.7 ± 0.1	0.130	0.5 ± 0.1	0.027[a]
	YKR	13.4 ± 0.2		11.3 ± 0.1		11.5 ± 0.1		0.2 ± 0.1	
Hct, %	CTL	39.2 ± 0.4	0.315	33.3 ± 0.3	0.854	34.6 ± 0.3	0.194	1.3 ± 0.2	0.053
	YKR	39.8 ± 0.5		33.4 ± 0.4		34.0 ± 0.4		0.6 ± 0.3	
TP, g/dL	CTL	6.8 ± 0.0	0.616	5.7 ± 0.0	0.904	6.1 ± 0.1	0.789	0.4 ± 0.1	0.684
	YKR	6.8 ± 0.0		5.7 ± 0.1		6.2 ± 0.1		0.5 ± 0.0	
Alb, g/dL	CTL	4.0 ± 0.0	0.482	3.5 ± 0.0	0.337	3.4 ± 0.0	0.385	-0.1 ± 0.0	0.821
	YKR	4.0 ± 0.0		3.5 ± 0.0		3.3 ± 0.0		-0.1 ± 0.0	
ChE, IU/L	CTL	301.7 ± 6.9	0.953	176.3 ± 4.0	0.258	183.0 ± 4.0	0.227	6.7 ± 2.4	0.934
	YKR	302.3 ± 7.8		183.3 ± 4.7		190.5 ± 4.6		7.0 ± 2.3	
CK, IU/L	CTL	101.3 ± 6.9	0.565	482.4 ± 22.7	0.443	67.8 ± 5.3	0.736	-391.7 ± 16.9	0.878
	YKR	95.3 ± 7.6		458.0 ± 19.8		70.2 ± 4.3		-387.8 ± 18.2	
ALP, IU/L	CTL	217.2 ± 6.1	0.491	142.7 ± 3.1	0.734	201.4 ± 6.0	0.103	58.7 ± 5.3	0.097
	YKR	210.8 ± 6.9		141.0 ± 4.1		222.8 ± 13.0		81.9 ± 12.8	
T-Bil, mg/dL	CTL	0.8 ± 0.1	0.194	1.2 ± 0.1	0.100	0.9 ± 0.0	0.580	-0.3 ± 0.1	0.123
	YKR	0.7 ± 0.0		1.0 ± 0.1		0.8 ± 0.1		-0.2 ± 0.0	
AST, IU/L	CTL	21.8 ± 0.7	0.133	28.9 ± 0.9	0.748	20.1 ± 0.9	0.245	-8.8 ± 1.1	0.556
	YKR	23.6 ± 1.0		29.3 ± 1.0		21.6 ± 0.8		-7.9 ± 1.0	
ALT, IU/L	CTL	21.4 ± 1.1	0.388	16.4 ± 1.0	0.543	20.3 ± 1.2	0.101	3.9 ± 1.3	0.244
	YKR	23.1 ± 1.6		17.4 ± 1.3		23.7 ± 1.7		6.2 ± 1.5	
γGTP, IU/L	CTL	33.1 ± 2.0	0.352	24.3 ± 1.3	0.555	38.2 ± 3.2	0.540	14.0 ± 2.7	0.489
	YKR	36.0 ± 2.5		25.5 ± 1.6		41.4 ± 3.9		16.9 ± 3.2	
BUN, mg/dL	CTL	16.8 ± 0.5	0.814	20.6 ± 0.5	0.667	17.7 ± 0.8	0.619	-2.9 ± 0.7	0.840
	YKR	16.6 ± 0.6		21.0 ± 0.7		18.3 ± 1.0		-2.7 ± 0.9	
Cre, mg/dL	CTL	0.9 ± 0.0	0.606	1.0 ± 0.0	0.954	1.0 ± 0.1	0.828	0.0 ± 0.0	0.633
	YKR	0.9 ± 0.0		1.0 ± 0.0		0.9 ± 0.0		0.0 ± 0.0	
eGFR	CTL	72.1 ± 1.9	0.219	68.0 ± 2.2	0.688	68.2 ± 2.0	0.816	0.2 ± 1.1	0.726
	YKR	68.7 ± 2.0		66.7 ± 2.3		67.5 ± 2.3		0.8 ± 1.3	
Na, mmol/L	CTL	140.9 ± 0.2	0.752	140.9 ± 0.3	0.269	140.7 ± 0.2	0.604	-0.2 ± 0.3	0.101
	YKR	140.8 ± 0.3		140.4 ± 0.3		140.9 ± 0.3		0.5 ± 0.3	
K, mmol/L	CTL	4.3 ± 0.0	0.768	4.1 ± 0.0	0.416	3.9 ± 0.0	0.792	-0.1 ± 0.3	0.360
	YKR	4.3 ± 0.0		4.1 ± 0.0		3.9 ± 0.0		0.2 ± 0.3	
CRP, mg/dL	CTL	0.3 ± 0.1	0.407	15.7 ± 4.4	0.176	3.8 ± 2.4	0.586	-11.9 ± 4.0	0.233
	YKR	0.4 ± 0.1		14.9 ± 4.4		3.7 ± 1.8		-11.2 ± 4.1	
BNP, pg/mL	CTL	90.4 ± 15.8	0.692	346.0 ± 30.1	0.554	264.0 ± 23.6	0.881	-72.0 ± 12.6	0.653
	YKR	99.0 ± 13.3		321.6 ± 24.5		258.6 ± 27.4		-63.0 ± 15.7	

[a]$P < 0.05$. Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; ChE: Cholinesterase; CK: Creatine kinase; Cre: Creatinine; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; γGTP: Gamma-glutamyl transpeptidase; Hb: Hemoglobin: Hct: Hematocrit; K: Potassium; Na: Sodium; T-Bil: Total bilirubin; TP: Total protein; WBC:

White blood cells; POD: Postoperative day; CTL: Control group; YKR: Yunker group.

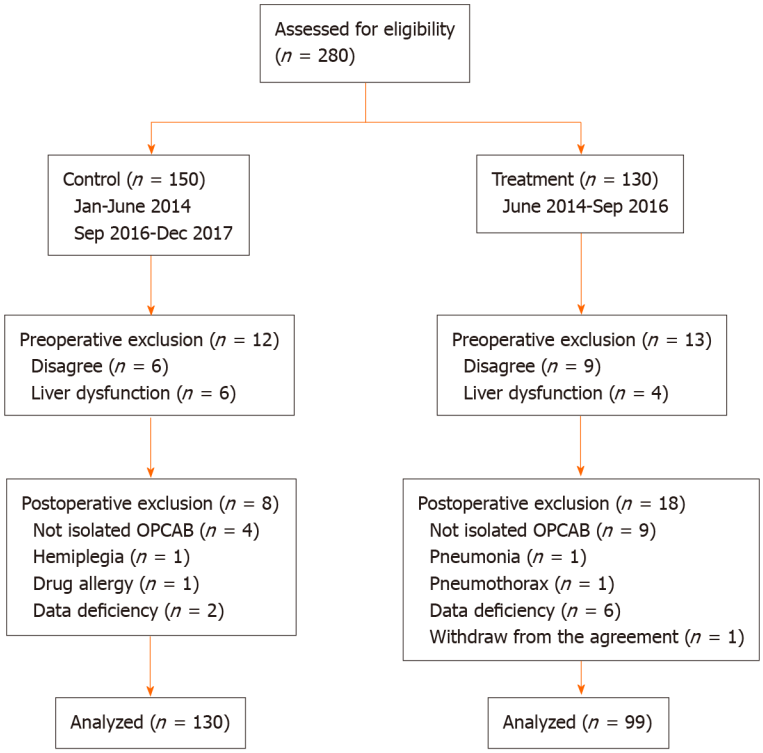


Figure 1 Flow diagram of the study. OPCAB: Off-pump coronary artery bypass.

P < 0.01; YKR: 6.0 ± 0.3 μg/mL to 7.4 ± 0.4 μg/mL, P < 0.01, 2 POD to 7 POD, respectively). In addition, there was no significant difference between the two groups in each time point (P = 0.085 at 2 POD, P = 0.056 at 7 POD). SOD activity did not change significantly in the CTL and YKR groups (CTL: 3.1 ± 0.2 U *vs* 3.0 ± 0.2 U, P = 0.263; YKR: 2.9 ± 0.2 U *vs* 2.9 ± 0.2 U, P = 0925, 2 POD to 7 POD, respectively) and neither at each time point between the two groups (P = 0.392 at 2 POD; P = 0.831 at 7 POD). Urine 8-OHdG/Cre ratio significantly decreased in both groups (CTL: 11.5 ± 0.8 ng/mgCre to 9.4 ± 0.4 ng/mgCre, P < 0.01, YKR: 10.4 ± 0.7 ng/mgCre to 9.0 ± 0.4 ng/mgCre, P < 0.01, 2 POD to 7 POD, respectively). In addition, there was no significant difference between the two groups at each time point (P = 0.349 at 2 POD, P = 0.986 at 7 POD).

Depression and anxiety score

To assess anxiety and depression, the HADS and GDS were administered the patients were enrolled (preoperative) and on 7 POD. If the questionnaire was not completed, the sheet was considered as void and the answers were not included in the results. Finally, 144 of 229 (87 from the CTL group and 57 from the YKR group) HADS sheets and 151 of 229 (92 from the CTL group and 60 from the YKR group) GDS sheets were eligible for analyses. The HADS can assess both anxiety and depression. If each score was more than 11 points, the patients was considered "positive" for anxiety and depression. For GDS, a score of > 5 was considered as "positive" for anxiety and depression. The number of patients with positive anxiety and depression is shown in Table 4, while the actual points (Figure 4A-C) and changes in scores (Figure 4D) are shown in Figure 4. HADS_A (anxiety) significantly increased postoperatively in the CTL group (12.6 ± 0.2 points *vs* 13.4 ± 0.3 points, preoperative *vs* postoperative, P < 0.01). YKR also showed an increasing trend in HADS_A; however, the trend was not statistically significant (12.8 ± 0.3 points *vs* 13.3 ± 0.3 points, preoperative *vs* postoperative, P = 0.078; Figure 4A). In addition, as shown in Figure 4D, there was no significant difference in perioperative HADS_A between the two groups (0.8 *vs* 0.5, CTL *vs* YKR, respectively, P = 0.317).

Table 4 Number of positive patients in the Hospital Anxiety and Depression Scale and Geriatric Depression Scale-15 tests

	Group	Pre (%)	Post (%)	Pre *vs* post	Improve	Worsen
HADS_A (≥ 11)	CTL	74 (85.1)	82 (94.3)	< 0.05	3 (3.4)	11 (12.6)
	YKR	50 (87.7)	50 (87.7)	1.00	4 (7.0)	4 (7.0)
HADS_D (≥ 11)	CTL	31 (35.6)	43 (49.4)	< 0.05	7 (8.0)	19 (21.8)
	YKR	29 (50.9)	23 (40.4)		14 (24.6)	9 (15.8)
GDS (≥ 5)	CTL	26 (28.3)	25 (27.2)		10 (10.9)	9 (9.8)
	YKR	14 (23.7)	12 (20.3)		6 (10.5)	3 (5.3)

GDS: Geriatric Depression Scale-15; HADS_A: Anxiety scale of Hospital Anxiety and Depression Scale; HADS_D: Depression scale of Hospital Anxiety and Depression Scale; CTL: Control group; YKR: Yunker group.

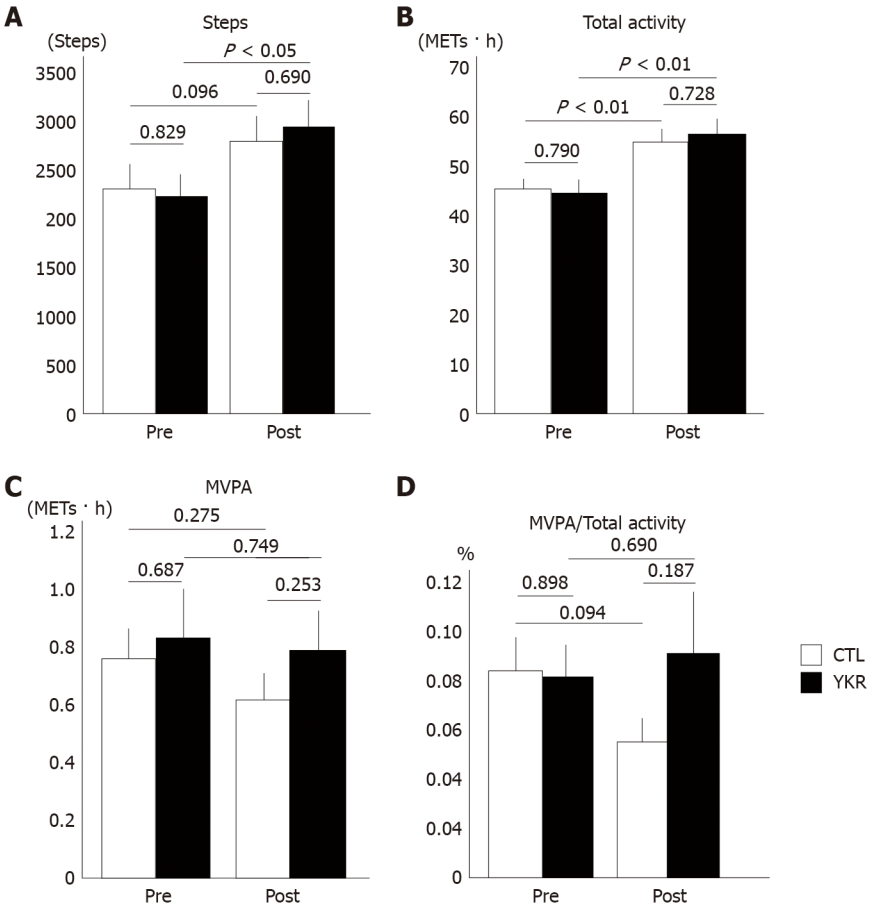


Figure 2 Perioperative activity was assessed using an accelerometer. A: Daily steps increased significantly in Yunker group postoperatively ($P < 0.05$), while control group (CTL) did not reach statistical differences ($P = 0.096$); B: Total activity increased significantly in both groups ($P < 0.01$, respectively); C: Moderate-to-vigorous intensity physical activity (MVPA) tended to decrease in both groups, although there were no significant differences; D: The ratio of the MVPA to the total activity was decreased in the CTL group. By contrast, it increased in the Yunker group, although no statistically significant differences were found in both groups. MET: Metabolic equivalent; MVPA: Moderate-to-vigorous intensity physical activity; CTL: Control group; YKR: Yunker group.

Similarly, HADS_D (depression) significantly increased postoperatively in the CTL group (9.8 ± 0.3 points *vs* 10.3 ± 0.2 points, preoperative *vs* postoperative, $P < 0.05$, Figure 4B). In contrast, HADS_D decreased in the YKR group (10.5 ± 0.3 points *vs* 10.1 ± 0.3 points, preoperative *vs* postoperative, $P = 0.192$), and the change was statistically significant compared with that in the CTL group (Figure 4D, $P = 0.018$).

The GDS score in both groups showed a decreasing trend, although no significant difference was observed between the two groups (CTL: 3.0 ± 0.3 points *vs* 3.0 ± 0.3 points, preoperative *vs* postoperative, $P = 0.849$, YKR: 3.0 ± 0.3 points *vs* 3.0 ± 0.3 points, preoperative *vs* postoperative, $P = 0.327$). In addition, the change in HADS_D

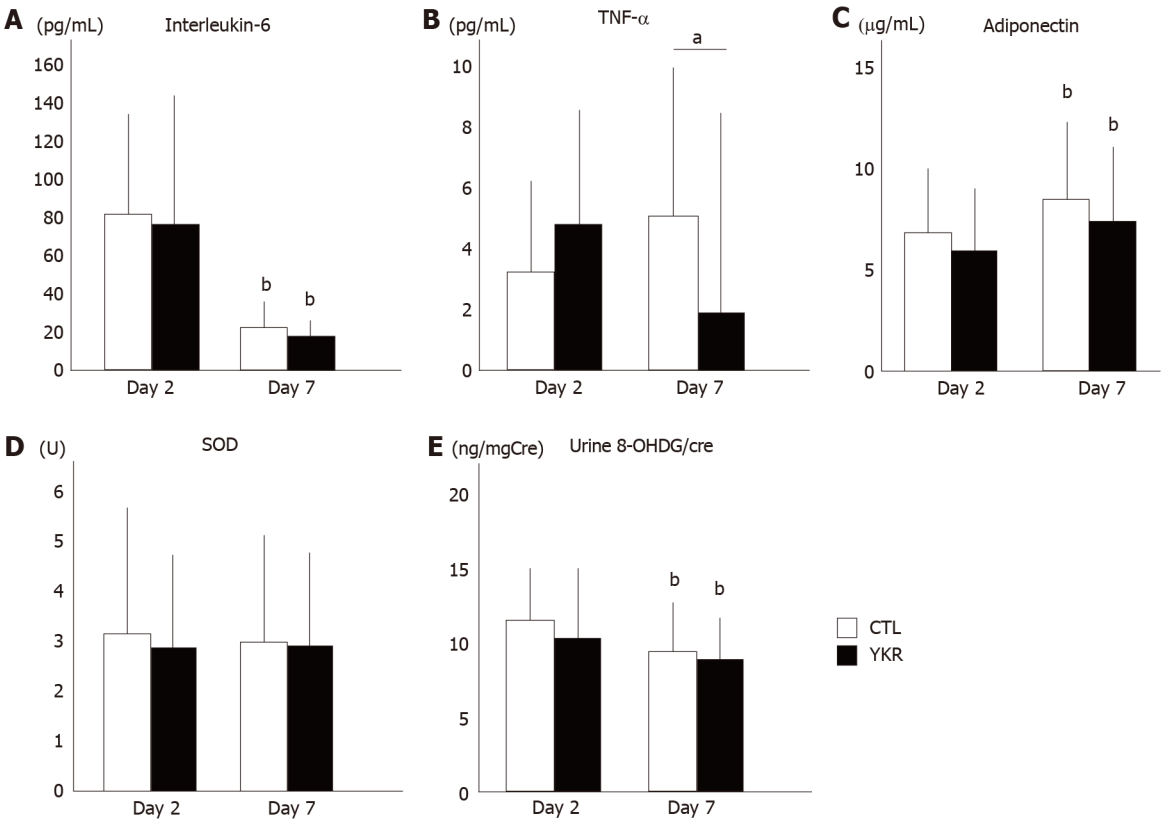


Figure 3 The levels of cytokines in serum and urine are shown. A: Interleukin-6 decreased significantly at 7th postoperative day in both groups ($P < 0.01$), although there were no differences between the two groups; B: Tumor necrosis factor-alpha level was significantly lower in the Yunker group ($P < 0.05$); C: Adiponectin increased significantly in both groups, while there were no differences between the groups; D: No significant differences were observed in the levels of superoxide dismutase in both groups; E The ratio of urine 8-hydroxy-2'-deoxyguanosine and creatinine decreased significantly in both groups, while there were no differences between the groups. [a]$P < 0.05$; [b]$P < 0.01$. TNF-α: Tumor necrosis factor-alpha; SOD: Superoxide dismutase; 8-OHDG/Cre: 8-Hydroxy-2'-deoxyguanosine and creatinine; CTL: Control group; YKR: Yunker group.

was not statistically different between the two groups ($P = 0.588$), although the YKR group seemed to show a more decreasing trend in score change.

DISCUSSION

In this study, we demonstrated that the daily intake of a nutritional supplement drink postoperatively has positive effects including enhancement of rehabilitation, reduction of inflammation, and improvement of anxiety score in patients who underwent OPCAB surgery.

Anxiety and depression after surgery

Previous studies revealed that 30%-50% of patients who experience coronary artery disease are likely to show depression[10]. In our experiment, 41.7% of the patients experienced depression (HADS_D positive) and 86.1% felt anxious (HADS_A positive) preoperatively. Unexpectedly, the number of patients who expressed anxiety and depression increased after rather than before surgery in the CTL group. As the mean length of postoperative hospital stay was around 10 days, many patients at 7 POD might feel anxiety concerning their lives after returning to home in a few days. By contrast, the number of patients who experienced depression (HADS_D) decreased in the YKR group, which suggests that consuming the drink may alleviate depressive moods. In fact, some of the contents of the drink (Table 1) are reported to improve stress and depression. Crude medicines, such as the extract from Ginseng roots or leaves, Rehmannia root, or royal jelly, have been widely used as herbal medications, especially in East Asian countries. Although the mechanism of the effect has not been fully elucidated, it has been demonstrated that the administration of ginseng saponin (ginsenoside Rb1) reduced stress and anxiety in both animal[11] and human models after a few days[12]. Catalpol, a major compound found in Rehmannia roots, showed

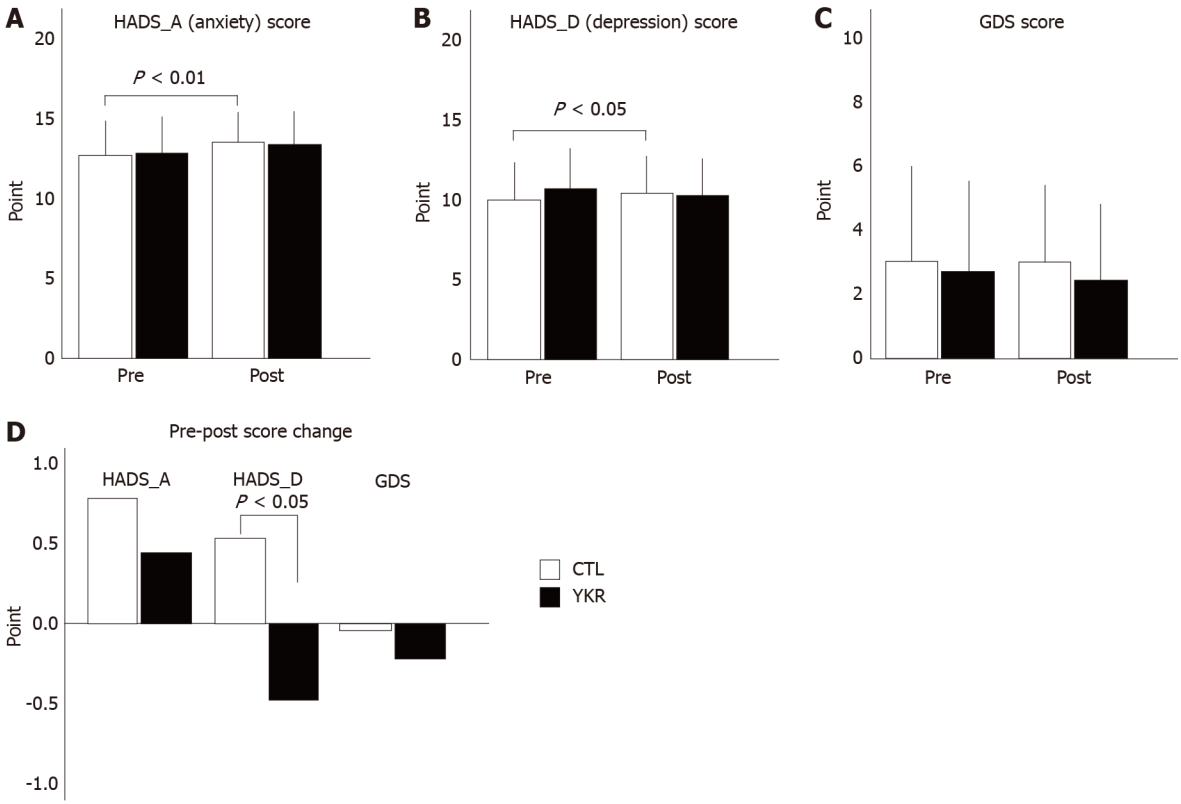


Figure 4 Perioperative anxiety and depression levels were assessed using the Hospital Anxiety and Depression Score and Geriatric Depression Scale-15. A and B: The control group showed significant increase in anxiety scale of Hospital Anxiety and Depression Scale (A) and depression scale of Hospital Anxiety and Depression Scale (B) postoperatively ($P < 0.01$ and $P < 0.05$, respectively), while Yunker (YKR) group showed no statistical differences; C: Geriatric Depression Scale-15 showed no significant differences between the groups; D: While comparing the changes in the scores pre- and postoperatively, the HADS_D score was significantly decreased in the YKR group ($P < 0.05$). HADS_A: Anxiety scale of Hospital Anxiety and Depression Scale; HADS_D: Depression scale of Hospital Anxiety and Depression Scale; GDS: Geriatric Depression Scale-15; CTL: Control group; YKR: Yunker group.

antidepressant properties in rat models[13]. In addition, consuming Melbrosia, a mixture of royal jelly and bee pollen, improved depression and irritability scores in postmenopausal women[14]. These findings suggest that consuming these contents can improve the anxiety score, although it was difficult to specify which content was effective or if ingestion of multiple contents may enhance the effect. In addition, another study reported that women were more likely experience depression; however, our analysis did not show sex differences in preoperative depression or anxiety as well as in score change (data not shown).

Activity

We evaluated the patients' level of physical activity using an accelerometer. The device used in this study can measure both the number of steps and activity. Recently, MVPA (3 > METs × hour) has been shown to be important[15-17].

In this study, the number of steps was significantly increased postoperatively in the YKR group, but no significant differences were found between the groups preoperatively and postoperatively. In addition, the postoperative total activity increased in both groups. By contrast, the MVPA decreased in the postoperative period in both groups, indicating that vigorous movement was limited postoperatively owing to the presence of pain, intravenous catheters, or drains. However, the ratio of the MVPA to the total activity was increased in the YKR group, despite that it was decreased in the CTL group, indicating that the YKR group had more vigorous and quantitative movements than the CTL group. These results indicate that the YKR group can perform more favorable postoperative rehabilitation.

Inflammation

Inflammation plays an important role in maintaining homeostasis against injury, which can be due to surgical stress. Especially for cardiac surgery, extracorporeal perfusion is one of the important factors that can enhance inflammation due to exposure to artificial materials and non-physiological blood flow to the organs.

Excessive activation and prolongation of inflammation may cause organ dysfunction. The expression of inflammatory cytokines, such as TNF-α and IL-6, is associated with postoperative complications[18,19]. Although the reports were controversial, the off-pump technique attenuates increase in inflammatory cytokine levels, such as TNF-α, IL-6, and IL-8[19-24], which may decrease the risk of renal dysfunction or surgical complications[25-28]. The levels of these inflammatory cytokines peaked during or within 48 h postoperatively in patients who underwent OPCAB, with an IL-6 Level of 35-400 pg/mL[25,26] and TNF-α level of 4-25 pg/mL[20,23,29].

In this study, we recruited patients who underwent OPCAB surgery, which was our standard procedure for isolated CABG cases (97.9% in last five years). We measured the cytokine levels on 2POD and 7POD; the average IL-6 level was 80 pg/mL, while the average TNF-α level was < 5 pg/mL. Compared with results of previous studies, our results exceeded the peak value. Under these conditions, the levels of one of the inflammatory markers, TNF-α, was significantly reduced in the YKR group (2 POD *vs* 7 POD), while they remained high in the CTL group. Some herbal medicines, contained in the drink, such as ginseng, Jiou, and royal jelly, have been reported to reduce the inflammation[12,30]. This result indicates that YKR prevents the prolongation of inflammation, although the level of other cytokines did not reach significance.

One of the most common complications after cardiac surgery is AF, which occurs in 20%-40% of patients postoperatively. The occurrence of AF has been shown to be associated with inflammation. In this study, despite the reduction in inflammation after consuming the supplement drink, no differences were observed in the occurrence of postoperative AF between the two groups. In addition, no differences were observed in the length of hospital stay and other postoperative complications. Importantly, results of perioperative blood tests suggest that the drink had no harmful effects on the kidney, liver, or other organs. In addition, a caffeine-free drink was used in this study since caffeine enhances sympathetic activity, which may increase the risk of arrhythmia.

Limitation

This study has some limitations. First, the drink contains several crude medications; hence, it is difficult to detect which contents contributed to the effect. Furthermore, since no placebo group was included in this study, it was unclear whether the behavior of "consuming a special drink" affected the results. Second, although the characteristics of the patients were not different between the groups, the social backgrounds of the patients varied. This difference may have an effect on a patient's level of anxiety or may motivate them to discharge early from the hospital. Third, we did not assess the seasonal effect of taking these medications in these patients. Last, we did not assess the long-term effect of the medications in the patients.

CONCLUSION

We demonstrated that consuming commercially available nutritional supplement drinks after OPCAB surgery reduced inflammation and mental deterioration. This may be associated with enhancement of postoperative rehabilitation as well as improvement of outcome and postoperative quality of life. Consuming the drink may be a novel option as a supplemental medication for high-risk patients.

ARTICLE HIGHLIGHTS

Research background

Some patients who underwent coronary artery bypass graft surgery still suffered from depression and prolongation of hospital stay after surgery, although postoperative complications are reduced with the technical development such as the off-pump technique. Recently, patients with low cardiac function, high age, frail, or complicated conditions who often delayed postoperative rehabilitation are increased. These patients are potentially frail and exhibit systemic deterioration.

Research motivation

Consuming nutritional supplement drink when a person experiences fatigue or develops illnesses such a cold is a widely accepted practice in our society. Various

kinds of nutritional supplement drinks are commercially available in Japan. These drink should be safe and useful for these patients after surgery.

Research objectives

We aimed to investigate the effect of taking an herbal medicine-containing, commercially available drink for postoperative rehabilitation in those patients.

Research methods

Patients who underwent isolated off-pump coronary artery bypass (OPCAB) surgery were divided into two groups: (a) consumed one bottle of a caffeine-free nutritional supplement drink on a daily basis (YKR group), and (b) underwent regular rehabilitation (CTL group).

Research results

Although there were no differences in postoperative complications and the duration of postoperative hospital stay between the two groups, the YKR group had a significantly increased number of daily steps postoperatively ($P < 0.05$) and had significantly lower postoperative serum tumor necrosis factor-alpha levels ($P < 0.01$), while no significant differences were observed in the levels of other inflammatory or stress-related cytokines (interleukin-6, adiponectin, superoxide dismutase, and urine 8-hydroxy-2′-deoxyguanosine) between the two groups. Also, the YKR group showed a significant improvement in the Hospital Anxiety and Depression Score ($P < 0.05$).

Research conclusions

The daily intake of an herbal medicine-containing drink after OPCAB surgery may have beneficial effects on cardiac rehabilitation by reducing inflammation markers and depression.

Research perspectives

The drink contains herbal medicine, vitamin and other materials. We should investigate what contain works the most effectively.

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ORIGINAL ARTICLE

Observational Study

Role of coronary angiogram before transcatheter aortic valve implantation

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Abstract

BACKGROUND

Coexistent coronary artery disease is commonly seen in patients undergoing transcatheter aortic valve implantation (TAVI). Previous studies showed that pre-TAVI coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA).

AIM

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

METHODS

This was a retrospective non-randomised single-centre analysis of consecutive patients undergoing TAVI. A selective approach for performing CA tailored to patient clinical need was developed. Clinical outcomes were compared based on whether patients underwent CA. The primary endpoint was a composite of all-cause mortality, myocardial infraction, repeat CA, and re-admission with heart failure.

RESULTS

Of 348 patients (average age 81 ± 7 and 57% male) were included with a median follow up of 19 (9-31) mo. One hundred and fifty-four (44%) patients, underwent CA before TAVI procedure. Patients who underwent CA were more likely to have previous myocardial infarction (MI) and previous percutaneous revascularisation. The primary endpoint was comparable between the two group (22.6% *vs* 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and MI ($P = 0.007$). In those who underwent CA, the presence of flow

collected data were anonymised during the analysis

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limiting lesions did not affect the incidence of primary endpoint, or its components, except for increased rate of repeat CA.

CONCLUSION
Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials

Key Words: Transcatheter aortic valve implantation; Angiogram; Revascularisation; Coronary angiogram

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Core Tip: Previous studies showed that pre-transcatheter aortic valve implantation coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA). A selective approach for performing CA tailored to patient clinical need was developed. In 348 patients, the primary endpoint of all-cause mortality, myocardial infraction, repeat CA, and re-admission with heart failure was comparable between patients who underwent CA *vs* no CA (22.6% *vs* 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and myocardial infarction ($P = 0.007$). The clinical value of routine CA should be challenged in future randomised trials.

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INTRODUCTION

Aortic stenosis is the most common valve disease requiring intervention in Europe and North America and is largely a disease of older adults[1]. Transcatheter aortic valve implantation (TAVI) is now a standard treatment option for management of severe aortic stenosis[1,2]. Given the ageing population and increasing prevalence of disease, the volume of patients requiring valve intervention is likely to increase. Moreover, a paradigm shift towards the use of TAVI in lower-risk patients is becoming more evident[3,4].

Coexistent coronary artery disease (CAD) is commonly seen in those with severe aortic stenosis, with shared traditional cardiovascular risk factors[5,6]. Whether revascularisation for bystander coronary artery disease pre-TAVI can improve procedural and long-term outcomes remains a matter of debate. Current guidelines recommend routine coronary angiography and revascularisation of proximal lesions with ≥ 70% stenosis prior to TAVI[1,2]. These recommendations are largely extrapolated from data in patients who underwent surgical aortic valve replacement[7-9]. Nonetheless, previous meta-analyses highlighted that pre-TAVI revascularisation was not associated with improved one-year mortality, and demonstrated increased 30-d major vascular complications and mortality[10,11]. Similarly, there was no significant difference between TAVI plus revascularisation verses TAVI alone in terms of 30-d mortality or morbidity with similar resolution of symptoms between the groups[12].

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram (CA) before TAVI procedure. However, there has not been any previous report on the safety of such approach or an attempt to identify a group of patients who may benefit from coronary angiography before TAVI. We report a single-centre experience using a selective approach to coronary angiography in patients with severe aortic stenosis referred for TAVI.

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MATERIALS AND METHODS

Study population

This was a retrospective observational analysis of consecutive patients undergoing TAVI at the Freeman Hospital in Newcastle-upon-Tyne over 4 years. Patients with inaccessible electronic follow-up were excluded. The TAVI programme is a regional service and ascertaining clinical follow up was an essential criterion to be included in this study.

The TAVI procedure and valve choice was left to the operators' discretion. Clinical, echocardiographic and procedural characteristics were prospectively entered into a dedicated TAVR database which was retrospectively interrogated. All patients had an echocardiogram and computed tomography (CT) prior to TAVI procedure.

Angiographic prior to TAVI

A selective approach to perform CA was developed during the study period. This was tailored to patient's clinical status and invasive angiogram was performed if: (1) Patient reported typical exertional chest pain which was relieved at rest and was suggestive of angina; (2) Impaired left ventricle systolic function (ejection fraction ≤ 50%), particularly if there were regional wall motion abnormalities; or (3) Extensive calcifications (> 70% of lumen diameter stenosis) involving the proximal segments of left or right coronary arteries detected on CT as part of TAVI work up.

Coronary revascularisation was recommended prior to TAVI, if patients had angiographically flow limiting lesions.

Study endpoints and follow up

The primary endpoint was a combination of all-cause mortality, myocardial infarction (MI), repeat CA, and re-admission to hospital with heart failure. Secondary endpoints included the individual or combination of two components of the primary endpoint. Procedural MI was excluded, and only spontaneous MI was included. Repeat CA after TAVI was indicated in the presence of symptoms, signs of ischaemia, or elevated cardiac biomarkers. Flow limiting lesion was defined as degree of stenosis ≥ 70% on epicardial coronary artery of ≥ 2.5 mm in size.

Mortality data were provided by the Office of National Statistics. Other clinical endpoints were retrieved using dedicated electronic databases for clinical follow up. MI events were cross-checked by evaluating troponin measurements and referral letter for invasive CA. Heart failure readmissions were similarly assessed using reported chest X-ray.

Statistical analysis

Data were assessed for normality of distribution using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± SD or as median accompanied by interquartile range for non-parametric data. Continuous variables were compared by using unpaired T test or Mann-Witney *U* test as appropriate, while frequencies comparisons were made using Chi square test or Fisher's exact test, as appropriate. Kaplan–Meier methodology and the associated log-rank test were performed to determine the differences in the primary endpoint. All statistical analysis was performed using SPSS 26.0 (SPSS, Inc Chicago, IL, United States) and a $P < 0.05$ was considered statistically significant.

RESULTS

Of 480 patients undergoing TAVI, 348 (73%) patients with accessible electronic records were included in this analysis. Patients were followed for a median of 19 (9-31) mo.

The average age was 81 ± 7 and 57% of patients were male. Two-thirds of patients were markedly symptomatic with NYHA class III/IV. 295 (85%) patients received balloon expanding valve and 34 (10%) had self-expanding valves. Less than half of the cohort, 154 (44%) patients, underwent coronary angiography before TAVI procedure. Almost three-quarters of patients had their TAVI procedure in an elective setting. There were no differences between patients who did or did not undergo CA in terms of age, gender, cardiovascular risk, body mass index, kidney function, or other vascular disease. Baseline clinical characteristics stratified according to CA pre-TAVI are presented in Table 1. Patients who underwent CA were more likely to have previous MI (14% *vs* 8%, $P = 0.07$), and previous percutaneous coronary intervention

Table 1 Baseline clinical characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (*n* = 348)	No coronary angiogram group (*n* = 194)	Coronary angiogram group (*n* = 154)	*P* value
Age (mean ± SD)	81 ± 7	82 ± 7	81 ± 7	NS
Male gender, *n* (%)	197 (57)	109 (56)	88 (57)	NS
Obesity, *n* (%)	83 (34)	43 (31)	40 (37)	NS
Hypertension, *n* (%)	136 (55)	79 (57)	57 (53)	NS
NYHA III/IV, *n* (%)	232 (67)	127 (66)	105 (68)	NS
Diabetes, *n* (%)	68 (20)	39 (20)	29 (19)	NS
Smoking history, *n* (%)	166 (48)	94 (49)	72 (47)	NS
Previous MI, *n* (%)	38 (11)	16 (8)	22 (14)	NS
Previous PCI, *n* (%)	52 (15)	20 (10)	32 (21)	< 0.01
Previous CABG, *n* (%)	43 (12)	33 (17)	10 (7)	< 0.01
COPD, *n* (%)	58 (17)	34 (18)	24 (16)	NS
CVA/TIA, *n* (%)	29 (8)	14 (7)	15 (10)	NS
AF, *n* (%)	83 (24)	47 (24)	36 (23)	NS
PVD, *n* (%)	55 (16)	24 (12)	31 (20)	< 0.05
Creatinine (mean ± SD)	112 ± 97	114 ± 117	110 ± 65	NS
Elective admission, *n* (%)	271 (78)	149 (77)	122 (79)	NS

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular event; TIA: Transient ischaemic attack; AF: Atrial fibrillation; PVD: Peripheral vascular disease; NS: No significant difference. Obesity was defined as body mass index > 30 kg/m^2.

(21% *vs* 10%, *P* = 0.007), but less likely to have previous coronary artery bypass graft (7% *vs* 17%, *P* = 0.03). There were no reported complications with any of the cases that underwent coronary angiography.

Echocardiographic and procedural characteristics are presented in Table 2. There were no differences between the two groups in gradients, valve area, or left ventricle function. Transfemoral approach was performed in the majority of cases (89%). Patients who underwent CA were more likely to have undergone an alternative access TAVI *i.e.*, *via* subclavian, trans axillary, apical, or direct aortic. Similarly, general anaesthesia was more frequently used in CA *vs* no CA groups (12% *vs* 2%, *P* < 0.001)

The primary endpoint of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable between the two groups [22.6% *vs* 22.2%; hazard ratio (HR) 1.05, 95%CI: 0.67-1.64, *P* = 0.82] (Figure 1 and Table 3). All-cause mortality was comparable between the two groups (19% *vs* 17%; HR 1.18, 95%CI: 0.71-1.95, *P* = 0.52). Patients who had CA were less likely to be readmitted with heart failure (1.3% *vs* 6.2%, *P* = 0.022) but more likely to have repeat CA (5.8% *vs* 0.5%, *P* = 0.003). Likewise, patients in the CA group had higher rate of subsequent MI (3.9% *vs* 1.0%, *P* = 0.07), although this did not reach statistical significance.

We also assessed whether flow limiting lesions on CA before TAVI were associated with events post TAVI. One-third (54/154) of patients had flow limiting lesions on CA before TAVI. There were no differences in the incidence of the primary endpoint (29.6% *vs* 19.0%, *P* = 0.13), readmission with heart failure (3.7% *vs* 1.0%, *P* = 0.24), or spontaneous MI (7.4% *vs* 3.0%, *P* = 0.21) between patients with flow limiting *vs* those with no flow limiting lesions on CA, respectively (Figures 2 and 3). Repeat CA following TAVI was statistically more frequent in those with flow limiting lesions (9.3% *vs* 0%, *P* = 0.005) (Figure 3). Two patients had percutaneous coronary interventions at a median of 40 mo post TAVI. One patient with known flow limiting lesion which was not revascularised before TAVI while the second patient developed *de novo* flow limiting lesion.

Table 2 Echocardiographic and procedural characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (*n* = 348)	No coronary angiogram group (*n* = 194)	Coronary angiogram group (*n* = 154)	*P* value
Peak gradient (mean ± SD)	74 ± 23	73 ± 22	74 ± 24	NS
Mean gradient (mean ± SD)	43 ±15	44 ±15	43 ±15	NS
Valve area (mean ± SD)	0.70 ± 0.20	0.71 ± 0.18	0.69 ± 0.22	NS
Preserved LV function, *n* (%)	274 (79)	158 (81)	116 (75)	NS
Moderate MR, *n* (%)	35 (10)	20 (10)	15 (10)	NS
PA pressure (mean ± SD)	39 ± 20	40 ± 15	39 ± 25	NS
Indication for AR or mixed AoV disease, *n* (%)	19 (6)	9 (5)	10 (7)	NS
Bioprosthetic valve, *n* (%)	17 (5)	14 (7)	3 (2)	< 0.05
GA, *n* (%)	23 (7)	4 (2)	19 (12)	< 0.01
BAV, *n* (%)	34 (10)	15 (8)	19 (12)	NS
Transfemoral approach, *n* (%)	311 (89)	183 (94)	128 (83)	< 0.01
Balloon-expanding, *n* (%)	295 (85)	161 (83)	134 (87)	NS
Valve size (> 23 mm), *n* (%)	222 (64)	125 (64)	97 (63)	NS

LV: Left ventricle; MR: Mitral regurgitation; PA: Pulmonary pressure; AR: Aortic regurgitation, AoV: Aortic valve disease; GA: General anaesthesia; BAV: Balloon valvuloplasty performed for pre-dilatation; NS: No significant difference.

Table 3 Clinical endpoints following transcatheter aortic valve implantation procedure

	Whole group (*n* = 348)	No coronary angiogram group (*n* = 194)	Coronary angiogram group (*n* = 154)	*P* value
Primary endpoint, *n* (%)	78 (22.4)	44 (22.6)	33 (22.2)	NS
Death, *n* (%)	63 (18.1)	37 (19.0)	26 (17.0)	NS
Myocardial infarction, *n* (%)	8 (2.3)	2 (1.0)	6 (3.9)	NS
Readmission with heart failure, *n* (%)	14 (4)	12 (6.2)	2 (1.3)	< 0.05
Coronary angiogram post valve intervention, *n* (%)	10 (2.9)	1 (0.5)	9 (5.8)	< 0.01
Death & myocardial infarction, *n* (%)	69 (19.8)	38 (19.5)	31 (20.3)	NS
Death & readmission with heart failure, *n* (%)	70 (20.1)	43 (22.1)	27 (17.6)	NS
Myocardial infarction & readmission with heart failure, *n* (%)	21 (6)	13 (6.7)	8 (5.2)	NS

Primary endpoint was defined as a composite of death, myocardial infarction, revascularisation, and readmission with heart failure. NS: No significant difference.

DISCUSSION

The main finding of this study was that our devised approach of selective CA tailored to patient clinical characteristics was safe and feasible over a relatively short follow up. Second, a composite of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable irrespective of CA before TAVI procedure and importantly, there were no differences based on the obstructive nature of coronary lesions on CA before TAVI. Third, patients with flow limiting lesions pre-TAVI were more likely to have repeat CA following TAVI.

There is a strong association between CAD and aortic stenosis. In almost 16000 patients undergoing TAVI in the German Aortic Valve Registry, 50% of patients were

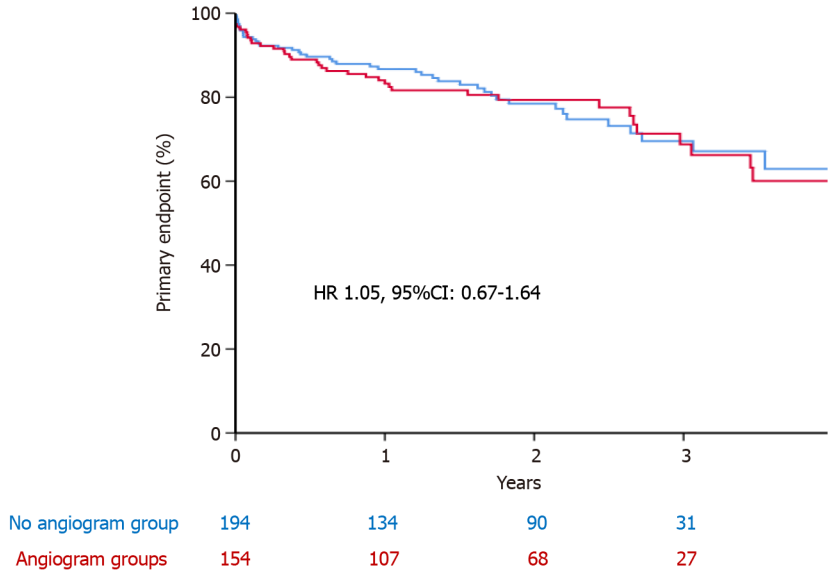


Figure 1 Primary endpoint of transcatheter aortic valve implantation patients stratified according to whether coronary angiogram was performed. Kaplan-Meier curves comparing cumulative incidence of all-cause mortality, myocardial infraction, repeat coronary angiogram, and re-admission to hospital with heart failure in patients with underwent coronary angiogram (in red) versus those who did not undergo coronary angiogram (blue). HR: Hazard ratio.

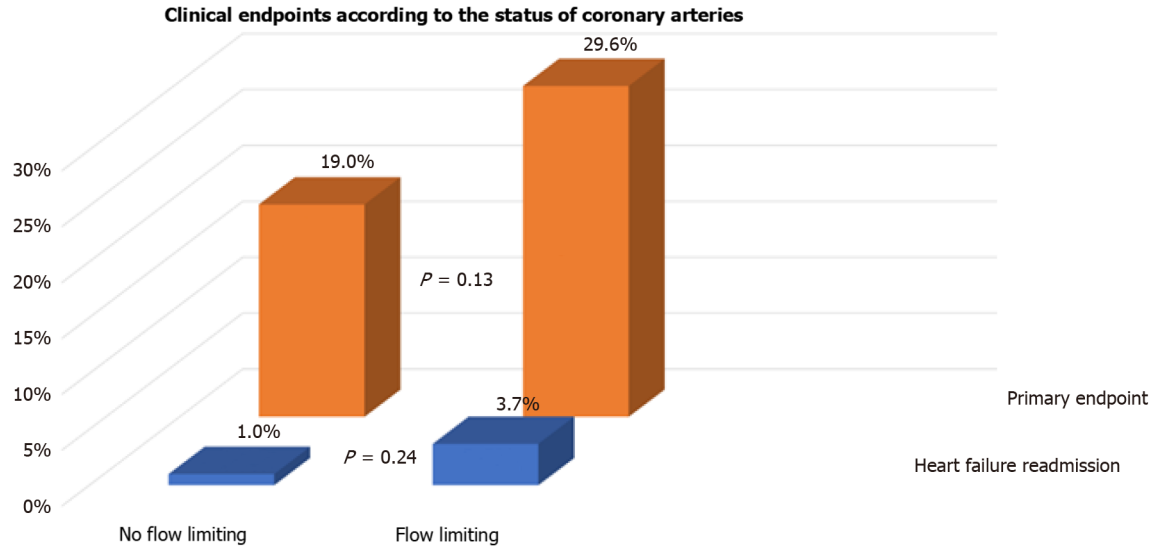


Figure 2 The incidence of the primary endpoint and heart failure readmission according to obstructive nature of coronary lesions. There was no difference in the incidence of the primary endpoint or readmission with heart failure between patients with obstructive versus non-obstructive coronary lesions.

reported to have concomitant coronary artery disease[13]. The management of CAD in this setting is controversial with previous studies highlighting the prognostic role of CAD in patients undergoing TAVI[14]. Moreover, observational data suggested a potential caveat when coronary arteries were not revascularised by demonstrating an association between rapid pacing and adverse outcomes in TAVI patients[15,16]. Coronary revascularisation was proposed to mitigate ventricular stunning and reduce prolong hypotension during rapid pacing, although this needs to be confirmed in randomised trials[17].

Nonetheless, percutaneous coronary intervention was not consistently associated with a reduction in adverse events following TAVI[10,18]. Recently, the percutaneous coronary intervention prior to TAVI (ACTIVATION) trial showed no difference in one-year survival or readmission to hospital according to whether coronary revascularisation was performed before TAVI[19,20]. This was the first randomised trial to test this hypothesis and challenges the current recommendation of performing routine coronary revascularisation for proximal CAD before TAVI[1,2]. Moreover, Snow *et al* [21] showed that the management of aortic stenosis and concomitant CAD can be

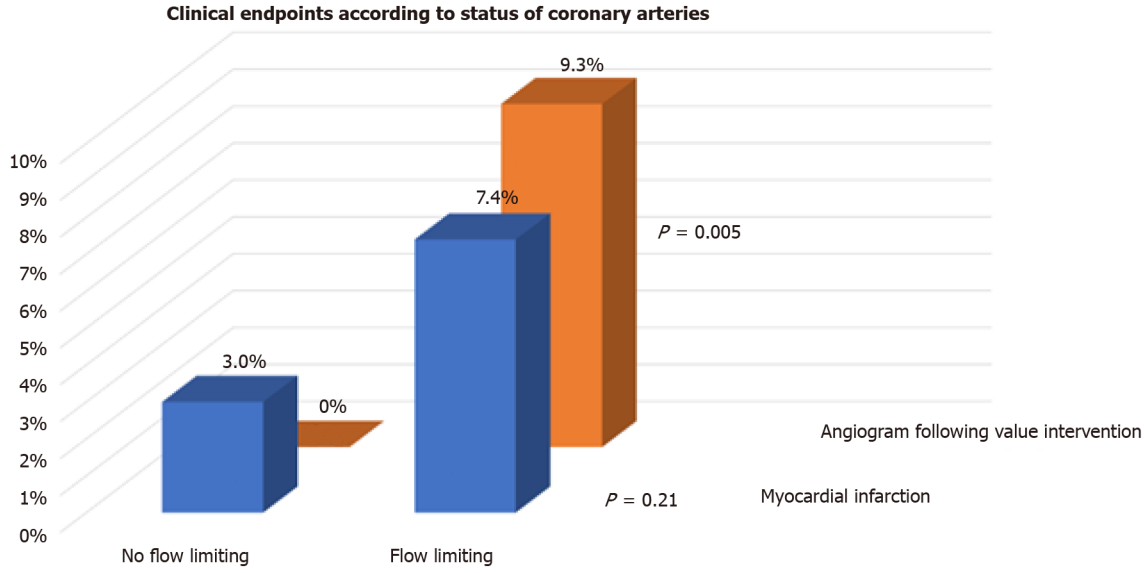


Figure 3 The incidence of the myocardial infarction and repeat coronary angiogram according to obstructive nature of coronary lesions. There was no difference in the incidence of myocardial infarction between patients with obstructive versus non-obstructive coronary lesions. Patients with flow limiting lesions were more likely to have repeat coronary angiograms following transcatheter aortic valve implantation procedure.

effectively managed by TAVI alone[21]. Importantly, our data are consistent with the results of these studies, and questions the need for CA, and revascularisation, before TAVI.

The current study suggests that the criteria for selective CA before TAVI is a safe and feasible. Patients with history of exertional chest pain suggestive of angina, left ventricle dysfunction, or extensive calcification on CT were deemed suitable for CA before TAVI. Up to 40% of patients with aortic stenosis may report angina symptoms and coronary revascularisation is indicated to relieve symptoms and improve quality of life. The presence of left ventricular dysfunction maybe related to CAD and suggests a second pathophysiological process, in addition to aortic stenosis, that needs to be addressed and managed. Advances in technology allowed CT-derived fractional flow reserve to assess CAD pre TAVI. This approach was illustrated to be safe and feasible in patients with severe aortic stenosis, and is currently assessed in the Functional Testing Underlying Coronary Revascularisation in aortic stenosis study[22].

Routine CA subjects patients to additional invasive procedure with associated risks, albeit small[23]. Contrast-induced nephropathy is a recognised risk with CA and is increased in the elderly and in patients with renal dysfunction[24,25]. These features are commonly observed in patients undergoing TAVI, and may exacerbate the renal risk associated following TAVI procedure itself[26]. Moreover, routine CA would add further delays to patients who are waiting for definitive valve intervention. There was an increase in mortality risk of almost 4% for each month delay while waiting for TAVI procedure[27].

Access to coronary arteries following TAVI has been reported to be challenging[28-30]. This was highlighted with self-expanding compared to balloon-expanding valves [31]. Therefore, it may be argued that upfront revascularisation of coronary lesions pre-TAVI would overcome the need to access the coronary arteries following TAVI. Nonetheless, these studies were of small sample size with success rate in engaging coronaries ranging from 50% to 100%[32]. Better understanding of the relationship between the bioprosthetic valve, particularly leaflets commissures, and coronary ostia would allow selective CA following TAVI[33].

Coronary events are relatively uncommon following TAVI. In our series, MI was reported in 2.3% of cases which was comparable to other contemporary studies[34]. Importantly, subsequent CAs did not always demonstrate culprit coronary lesions that required revascularisation. This should not be surprising since other mechanisms of MI were proposed such as coronary embolism secondary to subclinical leaflet thrombosis, late migration of the bioprosthetic valve, impaired coronary flow dynamic, and coronary hypo-perfusion related the valve bio-prosthesis[32]. Moreover, Faroux *et al*[30] showed that most coronary lesions were newly developed lesions that were not flow limiting prior to their valve procedure in patients presenting with acute coronary syndrome following TAVI[30]. This was reflected in our data whereby there

was no difference in events rates according to the presence of flow limiting lesions before TAVI. In other words, patients with non-obstructive CAD had similar incidence of ischaemic events to those with flow limiting lesions, and the use of CA did not identify a group of patients who were at a higher risk of future events. Interestingly, those with flow-limiting lesions were more likely to undergo repeat CA following TAVI. This is likely to reflect information bias as patients with known obstructive lesions will have a lower threshold to be brought back for CA compared to those with no flow limiting lesions.

Our study has several limitations. This was a retrospective single centre study associated with the inherent limitations of the design of the study. We had to exclude almost 25% of patients who underwent TAVI in our centre as their post procedural follow up could not be ascertained. Clinical endpoints were not adjudicated and were defined according to hospital discharge letters. This bias may have been mitigated by including hard events such as mortality and heart failure admissions.

CONCLUSION

Selective CA is a feasible and safe approach. It is not associated with high adverse outcomes. The role of CA before TAVI is increasingly undermined by the low ischaemic event rate. Additionally, the disconnect between CAD and subsequent cardiac events question the pre-emptive approach of coronary revascularisation in TAVI. Large randomised trials are required to test this hypothesis in the future.

ARTICLE HIGHLIGHTS

Research background

Routine coronary revascularisation pre-transcatheter aortic valve implantation (TAVI) was not associated with improved outcomes, yet, coronary angiogram (CA) is still performed as part of TAVI work up.

Research motivation

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram before TAVI procedure.

Research objectives

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

Research methods

Retrospective analysis of consecutive patients undergoing TAVI who underwent CA *vs* those who did not was performed. Decision to undergo CA pre-TAVI was tailored to patients clinical characteristics.

Research results

The primary endpoint was a composite of all-cause mortality, myocardial infraction, repeat CA, and re-admission with heart failure was comparable between the two groups.

Research conclusions

Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials.

Research perspectives

Future randomised clinical trials are required to test whether selective CA is safe.

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ORIGINAL ARTICLE

Observational Study

Associations of new-onset atrial fibrillation and severe visual impairment in type 2 diabetes: A multicenter nationwide study

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Abstract

BACKGROUND

Many studies have demonstrated an association between type 2 diabetes mellitus (T2DM) and atrial fibrillation (AF). However, the potential independent contributions of T2DM and AF to the prevalence of visual impairment have not been evaluated.

AIM

To determine whether such an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

METHODS

We conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools. This study had evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. T2DM patients were categorized into two groups: patients without and with incident AF. T2DM patients without AF were selected as the reference group. The association between incident AF and visual impairment among T2DM patients was assessed using multivariate logistic regression.

RESULTS

statement: This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand (IRB# S007h/54).

Informed consent statement: All patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment.

Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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A total of 27281 T2DM patients with available eye examination data were included in this analysis. The mean age was 60.7 ± 10.5 years, and 31.2% were male. The incident AF was 0.2%. The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. T2DM patients with incident AF were associated with an increased OR of 3.89 (95%CI: 1.17-13.38) for severe visual impairment compared with T2DM patients without AF.

CONCLUSION

T2DM patients with incident AF were independently associated with increased severe visual impairment. Therefore, early eye screening should be provided for these high-risk individuals.

Key Words: Type 2 diabetes mellitus; Atrial fibrillation; Visual impairment; Retinopathy; Blindness

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Core Tip: The independent contributions of diabetes mellitus and atrial fibrillation (AF) to the prevalence of visual impairments have not been evaluated. AF is relatively common in diabetic patients and should be regarded as a marker of adverse outcomes for cardiovascular diseases in type 2 diabetes mellitus (T2DM). In this study, we explored whether an association between T2DM with incident AF and visual impairment exists, and if so, the prevalence and magnitude of this association. We found a nearly three-fold higher prevalence of severe visual impairment in T2DM patients with incident AF compared to those without AF [OR of 3.89 (95%CI: 1.17-13.38)]. It may be useful to increase screening for visual impairments in T2DM patients with incident AF. The results of our study could encourage public health initiatives for the prevention of vision impairment by early eye screening in these high-risk individuals.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common chronic disease worldwide[1]. T2DM is associated with significant morbidity and mortality and has rapidly emerged as a global public health issue[2,3]. Diabetic retinopathy and visual impairment are among these common and severe complications of T2DM.

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in the world[4,5]. Its prevalence is predicted to more than double by 2050[6]. Previous studies found that AF may be relatively common in diabetic patients, and it should be regarded as a marker of increased adverse cardiovascular outcomes[7]. In addition, diabetes has long been recognized as a risk factor for AF[8,9]. The overlap of the pathophysiology of diabetes and AF concordantly increase the risk of thromboembolic events, and this has been well-established in the literature[10]. The potential independent contributions of diabetes and AF to the prevalence of visual impairment, however, has not been evaluated.

This study was thus aimed to determine whether such an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

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MATERIALS AND METHODS

Study design and population

This was an analysis of the DM/HT dataset from 2013[11]. This was a nationwide survey conducted annually in Thailand to evaluate the status of medical care in T2DM patients who visited the public hospitals of the Thai Ministry of Public Health and the clinics in the Thailand National Health Security Office's program. The inclusion criteria of this DM/HT survey consisted of T2DM patients aged ≥ 35 years who received regular medical care in the targeted hospital for at least 12 mo. Patients who received care at primary care units outside Bangkok and university hospitals were excluded from this study. A two-stage stratified cluster sampling method was utilized to select a nationally and provincially representative sample of T2DM patients in Thailand. The first stage of sample collection consisted of the provinces that constituted 77 strata. The second stage of sample collection was the hospitals' levels in each province, which were stratified into five strata according to the size of the hospital. These five strata were regional (> 500 beds), provincial (200-500 beds), large community (80-120 beds), medium community (60 beds), and small community (10-30 beds) hospitals. All regional (n = 25) and provincial (n = 70) hospitals were enrolled, but only 456 (62% out of 736) community hospitals were included. Of 456 community hospitals, 10%, 20%, and 70% were large, medium, and small community hospitals, respectively.

All patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment. This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects of the Ministry of Public Health of Thailand, due to the bureaucratic system regulations in Thailand. Well-trained research nurses reviewed medical records and collected data into a case record form. Data entry into this form was then transferred to the central data management of the Medical Research Network of the Consortium of Thai Medical Schools. This data management team adjudicated the process of data collection to ensure it was compiled according to the study protocol. This team was also responsible for inquiries to study sites to verify data. Site monitoring was randomly performed in approximately 10% of study sites. This study was conducted by the Strengthening the Reporting of Observational Studies in Epidemiology[12].

Data collection

Clinical characteristics, demographic information, medication, and laboratory data were collected using a manual data retrieval from the medical record as described above. The laboratory data included results from 12 mo prior to the consent process. Incident AF was identified by ICD10 code I48, and subsequently verified by medical record review during the 12 mo of the study period. This verification of AF consisted of electrocardiogram (ECG). The date of first ECG documenting the presence of AF was considered the onset of atrial fibrillation. We exclude patients who had prior history of AF before the start date. Estimated glomerular filtration rate (eGFR) was estimated based on age, sex, race, and most recent creatinine with calculation *via* the Chronic Kidney Disease Epidemiology Collaboration equation[13]. CHA2DS2VASc score was calculated by using clinical data from the medical record. Primary outcome was diagnosis of severe visual impairment within 12 mo of data collection. Binocular visual acuity (VA) was examined using a semi-qualitative assessment and documented by physicians. Severe visual impairment was based on the worst VA exam of both eyes that consisted of "counting fingers," "hand motions," "projection of light," "perception of light," and "no light perception."

Statistical analysis

Continuous variables were presented as mean ± SD. Categorical variables were presented as count with percentage. Clinical characteristics and outcomes were compared among the different groups using the independent t-test for continuous variables, and Chi-squared test, and Fisher's exact test for categorical variables. T2DM patients were categorized into two groups: (1) T2DM patients without AF; and (2) T2DM patients with incident AF. T2DM patients without AF were selected as the reference group. Univariate and then multivariate logistic regression analysis, adjusting for priori-defined variables, were performed to assess the independent association between AF onset and severe visual impairment. Odds ratio (OR) with 95% confidence interval (CI) was reported. The adjusted variables consisted of age, sex, duration of T2DM, body mass index (BMI), smoking, comorbidities, complications,

and medications. Comorbidities and complications were hypertension, ischemic heart disease, cerebrovascular disease, diabetic retinopathy, eGFR, and CHA2DS2VASc score. Medications were insulin, antiplatelets, and anticoagulants. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL, United States).

RESULTS

Clinical characteristics

A total of 27339 adult T2DM patients with eye examination data from 831 public hospitals in Thailand were included in this analysis. Clinical characteristics are summarized in Table 1. The mean age was 60.7 ± 10.5 years, and 31.2% were male. The mean diabetic duration was 7.1 ± 4.8 years. The mean BMI was 25.6 ± 4.5 kg/m^2. The mean eGFR was 66.9 ± 25.9 mL/min per 1.73 m^2. The mean CHA2DS2VASc was 2.9 ± 1.0. The prevalence of T2DM with incident AF was 0.2% (n = 48).

Association between of AF and severe visual impairment in T2DM

The prevalence of severe visual impairment in all T2DM was 1.4%. Severe visual impairment was documented in 1.4% of patients without AF and in 6.3% of patients with incident AF (Table 2).

In adjusted analysis, incident AF was associated with an increased OR of 3.89 (95%CI: 1.17-13.38) for severe visual impairment (Table 3).

DISCUSSION

An analysis of the baseline patient characteristics showed that T2DM with incident AF was associated with older age. Moreover, T2DM patients with AF had a higher prevalence of ischemic heart disease, cerebrovascular disease, and increased use of antiplatelet medications compared to patients without AF. These findings are consistent with a study performed by Nichols *et al*[14] and Benjamin *et al*[9], where AF was similarly found to be correlated with older age and ischemic heart disease. However, in their study, history of smoking was not associated with AF in T2DM patients. It is not surprisingly to find these associations, as it could be hypothesized that since these clinical characteristics are established risk factors for development of any cardiovascular diseases, it follows that they could also precipitate AF development in T2DM patients.

Prevalence of severe visual impairment in T2DM patients

The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. According to previous studies from the United Kingdom[15] and the United States[3], the overall prevalence of visual impairment in T2DM ranges between 0.75% to 3.80%. Etiologies of visual impairment in T2DM patients include retinopathy of any type (particularly diabetic retinopathy), glaucoma, and cataracts[16]. A recent meta-analysis found that diabetes was associated with an increased incidence of glaucoma[3].

Association between AF and severe visual impairment

This study showed that AF is independently associated with severe visual impairment in adult T2DM patients. No prior studies have investigated this association. The pathogenesis of poor vision in recently diagnosed AF may be multifactorial, including retinal emboli[17,18]. Retinal artery occlusion (RAO)[19] and retinal vein occlusion (RVO)[20] are increasingly common in older subjects. As age increases, the risk of AF also substantially increases. Previous studies from Hayreh *et al*[21] and Yen *et al*[19] draw a potential pathophysiologic association, as they have reported that patients with AF are at increased risk of developing RAO. A study by Christiansen *et al*[22] also found that RAO was associated with an increased risk of incident AF. O'Mahoney *et al*[23] and Christiansen *et al*[24] reported that RVO might be an important cause of blindness in populations with high atherosclerotic risk. These conditions share the same traditional risk factors as for cardiovascular diseases, possibly due to shared pathophysiologic mechanisms.

Table 1 Baseline characteristics

Characteristics	All	T2DM without AF	Incident AF	*P* value
N/*n* (%)	27339	27281 (99.8)	48 (0.2)	
Age (yr, mean ± SD)	60.7 ± 10.5	60.7 ± 10.5	65.9 ± 9.9	0.001
Male, *n* (%)	8518 (31.2)	8499 (31.1)	19 (39.6)	0.21
Duration of T2DM (yr, mean ± SD)	7.1 ± 4.8	7.1 ± 4.8	6.6 ± 3.4	0.46
Body mass index (kg/m^2, mean ± SD)	25.6 ± 4.5	25.6 ± 4.5	24.8 ± 4.5	0.24
Smoking, *n* (%)	1084 (4.0)	1080 (4.0)	4 (8.5)	0.12
Comorbidity and complication, *n* (%)				
Hypertension	19840 (72.6)	19801 (72.6)	39 (81.3)	0.18
Ischemic heart disease	947 (3.5)	939 (3.4)	8 (16.7)	< 0.001
Cerebrovascular disease	666 (2.4)	661 (2.4)	5 (10.4)	0.01
Diabetic retinopathy	2008 (7.4)	2005 (7.4)	3 (6.7)	1.00
Medication, *n* (%)				
Insulin use	5848 (21.4)	5840 (21.4)	8 (16.7)	0.42
Antiplatelets or anticoagulants	16321 (60.1)	16285 (60.1)	36 (75.0)	0.04
eGFR (mL/min/1.73 m^2, mean ± SD)	66.9 ± 25.9	66.9 ± 25.9	60.5 ± 25.7	0.09
CHA2DS2VASc score (mean ± SD)	2.9 ± 1.0	2.9 ± 1.0	3.7 ± 1.4	0.001

AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus; eGFR: Estimated glomerular filtration rate.

Table 2 Prevalence of severe visual impairments stratified by presence of incident atrial fibrillation in type 2 diabetes mellitus patients

Outcomes	All	T2DM without AF	Incident AF	*P* value
Severe visual impairment, *n* (%)	387 (1.4)	384 (1.4)	3 (6.3)	0.03
Counting finger, *n* (%)	181 (0.7)	181 (0.7)	0 (0)	1.00
Hand movement, *n* (%)	101 (0.4)	99 (0.4)	2 (4.2)	0.01
Projection of light, *n* (%)	18 (0.1)	18 (0.1)	0 (0)	1.00
Perception of light, *n* (%)	24 (0.1)	24 (0.1)	0 (0)	1.00
No light perception, *n* (%)	77 (0.3)	76 (0.3)	1 (2.1)	0.13

T2DM: Type 2 diabetes mellitus; AF: Atrial fibrillation.

Conditions like anterior ischemic optic neuropathy (AION)[25], age-related macular degeneration (AMD)[26,27], and cataracts may all be other potential etiologies for visual impairment in this population[28]. Callizo *et al*[25] found that AION may cause blindness in patients with AF. Clemons *et al*[26] and Topouzis *et al*[27] suggest an increased risk of AMD with diabetes mellitus. In a cohort study by Hahn *et al*[29], it was found that diabetic retinopathy might increase the risk of both dry and wet AMD. These studies support a potential similar pathophysiologic mechanism between diabetic retinopathy and AMD. Optimal diabetic control may reduce the development of AMD. Klein *et al*[28] found that T2DM is associated with an increased incidence and progression of cataracts, which may be worsened by suboptimal glycemic control. In summary, cardiovascular disease and its associated risk factors have an adverse effect on the incidence of age-related cataracts. These risk factors need to be promptly investigated in order to reduce ophthalmologic complications through early interventions.

Strengths

Our study consisted of a large-size sample from a multicenter and nationwide population-based design that provided detailed eye examination information while

Table 3 Association of incident atrial fibrillation and severe visual impairment in type 2 diabetes mellitus patients after multivariate logistic regression analysis

	Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1,2]	*P* value
T2DM without AF	1 (Reference)		1 (Reference)	
Incident AF	4.67 (1.45-15.10)	0.01	3.89 (1.17-13.38)	0.03

[1]Adjusted for age (continuous), gender (male or female), duration of T2DM (continuous), body mass index (continuous), smoking (yes or no), hypertension (yes or no), ischemic heart disease (yes or no), cerebrovascular disease (yes or no), diabetic retinopathy (yes or no), insulin (yes or no), antiplatelets or anticoagulants (yes or no), eGFR (continuous), and CHA2DS2Vasc score (continuous).

[2]Hosmer-Lemeshow test: Chi-square 13.31, *P* value 0.10.

AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus; eGFR: Estimated glomerular filtration rate.

accounting for potential confounders in order to allow an adequate estimate of severe visual impairment burden in T2DM patients with AF. Our analysis of the association between eGFR and DR utilized a multiple logistic regression model that accounted for several possible confounders, including age, sex, duration of T2DM, body mass index (BMI), smoking, other comorbidities, and medications. Comorbidities included hypertension, ischemic heart disease, cerebrovascular disease, and diabetic retinopathy. Medications that were adjusted for included insulin and antiplatelet medication. Lastly, visual impairment severity was measured using a semi- qualitative clinical scale composed of bedside testing items, which is an easy test to perform in the community setting.

Limitations

This study had several limitations. First, we identified AF using ICD 10 codes and then subsequently confirmed by medical record review for documented ECGs. As ECGs were usually performed when clinically indicated rather than universally, our study may have underdiagnosed asymptomatic AF. This may explain the low prevalence of AF in our study compared to previous reports[30-33]. Future studies utilizing advanced cardiac monitoring technology such as signal-averaged ECGs and Holter monitors would more accurately capture total prevalence of AF. In addition, AF could be paroxysmal, and periodic ECGs may not have detected these paroxysmal AF episodes. Thus, future studies are needed to better assess the associations of visual impairment with asymptomatic AF and AF subtypes among T2DM patients. Second, our study was cross-sectional in nature. A longitudinal study in the future may provide further details on the etiology of visual impairments in order to better confirm the association and elucidate the pathophysiology of new-onset AF and poor vision in T2DM patients. Third, information on prior eye surgeries, such as vitrectomy due to retinal hemorrhage, was scarce. These patients may have suffered a prior visual impairment rather than incorrectly associated with incident AF. Fourth, information on the etiology of visual impairment other than diabetic retinopathy was not available. Finally, although we performed multivariate analysis for further adjustment of potential confounders including CHA2DS2-VASC and anticoagulation, we did not have information on the specific type of AF, type of anticoagulation therapy used, international normalized ratio (INR) levels, previous AF medications for rate control, and outcomes of AF treatment. These are potential confounding factors that were unaccounted for. Therefore, this study was unable to determine the association between optimally treated AF and visual impairment in T2DM patients.

Implications

Our study found a nearly three-fold higher prevalence of poor vision in T2DM patients with incident AF. Several conditions such as glaucoma, cataracts, and retinopathy are potentially reversible causes of vision impairment, especially if treated early. It may be useful to screen for visual impairment and its etiologies in T2DM patients with recent-onset AF (less than 1-year). The results of our study could encourage public health initiatives to institute early eye screening in these high-risk individuals in order to prevent vision impairment. Further studies are needed to elucidate whether these interventions would translate into improved clinical outcomes.

CONCLUSION

The prevalence of severe visual impairment in T2DM patients with incident AF was nearly three times higher than the prevalence of impaired vision in all T2DM patients. Moreover, T2DM patients with incident AF were independently associated with severe visual impairment. Early eye screening should be performed in these high-risk individuals as it may provide an earlier diagnosis, allowing for prevention and treatment of potentially reversible causes of vision impairment.

ARTICLE HIGHLIGHTS

Research background

Previous studies have shown an association between type 2 diabetes mellitus (T2DM) and atrial fibrillation (AF). However, the independent contributions of T2DM and AF on the prevalence of visual impairment have not been evaluated.

Research motivation

Earlier studies have demonstrated that AF is relatively common in diabetic patients, and it should be regarded as a marker for adverse cardiovascular outcomes in T2DM.

Research objectives

To investigate whether an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

Research methods

This study evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. The association between T2DM with incident AF and visual impairment were assessed using multivariate logistic regression.

Research results

A total of 27281 T2DM patients with available eye examination data were included in this analysis. The prevalence of incident AF in T2DM patients was 0.2%. The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. T2DM patients with incident AF were associated with an increased OR of 3.89 (95%CI: 1.17-13.38) for severe visual impairment compared to those without AF.

Research conclusions

T2DM patients with incident AF were independently associated with severe visual impairment. Early eye screening should be provided for these high-risk individuals.

Research perspectives

Overlapping diabetes and AF leads to an increased risk of thromboembolic events. However, the independent contribution of T2DM and AF to the prevalence of visual impairments has not been evaluated. Therefore, it may be useful to screen for visual impairment and its etiologies in T2DM patients with incident AF.

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REVIEW

Quantifying tissue perfusion after peripheral endovascular procedures: Novel tissue perfusion endpoints to improve outcomes

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Abstract

Peripheral artery disease (PAD) is a flow-limiting condition caused by narrowing of the peripheral arteries typically due to atherosclerosis. It affects almost 200 million people globally with patients either being asymptomatic or presenting with claudication or critical or acute limb ischemia. PAD-affected patients display increased mortality rates, rendering their management critical. Endovascular interventions have proven crucial in PAD treatment and decreasing mortality and have significantly increased over the past years. However, for the functional assessment of the outcomes of revascularization procedures for the treatment of PAD, the same tests that have been used over the past decades are still being employed. Those only allow an indirect evaluation, while an objective quantification of limb perfusion is not feasible. Standard intraarterial angiography only demonstrates post-intervention vessel patency, hence is unable to accurately estimate actual limb perfusion and is incapable of quantifying treatment outcome. Therefore, there is a significant necessity for real-time objectively measurable procedural outcomes of limb perfusion that will allow vascular experts to intraop-

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eratively quantify and assess outcomes, thus optimizing treatment, obviating misinterpretation, and providing significantly improved clinical results. The purpose of this review is to familiarize readers with the currently available perfusion-assessment methods and to evaluate possible prospects.

Key Words: Peripheral arterial disease; Critical limb ischemia; Endovascular treatment; Peripheral angioplasty; Tissue perfusion; Quantification

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Core Tip: Endovascular interventions have been proven critical in the treatment and management of peripheral artery disease-affected patients, by decreasing mortality and improving quality of life. However, currently available methods only allow an indirect evaluation of the functional assessment of treatment outcomes, while an objective quantification of limb perfusion is not feasible. This review aims to familiarize readers with currently available perfusion-assessment techniques that will allow vascular experts to intraoperatively quantify and evaluate outcomes, hence optimizing treatment, obviating misinterpretation, and providing significantly improved clinical results.

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INTRODUCTION

Peripheral artery disease (PAD) is caused by narrowing of the peripheral arteries typically due to atherosclerosis, which instigates restriction of blood flow to the distal extremities. Risk factors for developing atherosclerosis include smoking, diabetes mellitus, obesity (body mass index > 30), increasing age, hypertension, high cholesterol levels, raised homocysteine levels, and family history of cardiovascular disease[1,2].

PAD affects almost 200 million people globally[3] with patients either being asymptomatic or presenting with claudication, critical limb ischemia (CLI), or acute limb ischemia (ALI)[4,5]. It has been shown that PAD-affected patients have an increased risk of coronary artery disease (CAD) mortality, cardiovascular mortality, and all-cause mortality[6]. Additionally, when compared to patients with symptomatic CAD, patients presenting with CLI can demonstrate higher mortality rates[7]. Diabetes mellitus is another recognized risk factor for CLI correlated with increased lower-limb major amputation and mortality rates. A recent large retrospective analysis of the 2002–2015 National Inpatient Sample database demonstrated a significant increase in hospitalization for CLI for subjects with diabetes in the United States but a decreased in-hospital mortality over time, correlated with revascularization[8]. As a result, PAD management is critical to improve patients' long-term survival and decrease mortality, with management varying depending on symptoms and severity of the disease. Aggressive risk factor modification is vital to improve cardiovascular risk. Lifestyle changes, pharmacotherapy, exercise therapy, endovascular, and/or surgical intervention are further available treatment options[9]. Notably, endovascular interventions for PAD treatment have significantly increased in recent years, significantly outnumbering surgical procedures[8,10]. Amongst other factors, this could be due to the high technical success, low complication rates, and shorter hospitalization stays observed with endovascular treatments but also because many PAD patients either do not have surgical options or are deemed unfit for surgery[11-13].

Over the past few years, several beneficial devices have been introduced in everyday clinical practice to improve outcomes of endovascular procedures used for the management of PAD. Yet, for the functional assessment of these outcomes, the same tests that have been used in the past decades [*e.g.*, intraprocedural morphological

assessment with digital subtraction angiography (DSA), ankle-brachial index (ABI), pressure measurements across the treated lesion] are still being employed. Nonetheless, these methods only allow an indirect evaluation of the outcomes of revascularization procedures for the treatment of PAD, while an objective quantification of limb perfusion is not feasible. For example, since angiography only demonstrates post-intervention vessel patency, it is unable to accurately estimate actual limb perfusion and hence is incapable of quantifying treatment outcome. Therefore, for the appropriate assessment of endovascular procedures in the management of PAD, there is a significant necessity for objectively measurable procedural outcomes of limb perfusion.

The purpose of this review is to familiarize readers with currently available perfusion-assessment methods and to evaluate possible prospects in quantifying and optimizing endovascular outcomes in the treatment of lower limb arterial ischemia.

STANDARD ARTERIAL PRESSURE MEASUREMENTS

Systolic blood pressure (SBP) measurements throughout the vascular tree offer valuable information in PAD diagnosis.

The ABI is a readily available, fast, inexpensive examination[14] that calculates the ratio produced by dividing the SBP measured at the ankle with the higher SBP measured at either arm. Ankle pressure and ABI should be calculated with the patient lying flat in the supine position after a 5 to 10-min rest[15]. Values most considered as indicative of PAD are those ≤ 0.90. More importantly, in patients with signs of ischemia, an ABI < 0.90 is considered diagnostic for PAD with sensitivity and specificity reaching 95% and 100% accordingly[16]. Furthermore, an ABI < 0.50 has been linked to more severe CAD and increased mortality[17]. On the other hand, values between 1.0 and 1.4 are considered normal, while values > 1.4 are attributed to non-compressible arteries and are therefore considered non-diagnostic[15,18]. As heavily calcified, non-compressible vessels are very common in patients with diabetes mellitus and chronic kidney disease; ankle pressures and ABI values are often untrustworthy and rendered non-diagnostic in such patients because they can be falsely increased[18,19].

Toe-brachial index - Toe systolic pressure

Great toe pressures and measurements of the toe-brachial index (TBI) can prove superior to non-diagnostic, high-value ABIs in these patient groups demonstrating severely calcified vessels, because the digital arteries are typically spared, thus being able to more accurately determine vascular disease[19,20]. A TBI ≤ 0.70 is abnormal and considered diagnostic of PAD[21], and a TBI < 0.11 is related to ischemic rest pain [22]. However, since toe pressure evaluation between studies demonstrates variable diagnostic accuracy, there has not yet been a widely accepted TBI or toe pressure threshold that can confirm the diagnosis of CLI[23].

Limitations

The ABI may not prove useful in the setting of severely calcified, non-compressible vessels. Moreover, false-negative ABI measurement can occur in up to 17% of diabetic patients and 24% of hemodialysis patients[24,25]. Nonetheless, there are several additional significant limitations to the employment of arterial pressure measurements. Amongst other considerations, some of the technical factors that should be thought through when calculating the ABI include correct cuff placement (2 cm above the medial malleolus)[26], use of the appropriate pressure cuff size (width should be at least 40% of the limb circumference)[27,28], use of a suitable Doppler probe (8-10 MHz), and correct probe-to-skin surface angle (45-60°)[15]. Additionally, the potential risk of thrombosis does not allow segmental pressure measurements over formerly placed stents or bypass grafts. Moreover, the utilization of arterial pressure measurements can be limited in patients with CLI since placing the cuff over an affected limb will often prove intolerable and painful. Nevertheless, in the presence of open wounds and ulcers, cuff placement may also pose the risk of contamination, rendering ankle or toe pressure measurements inapplicable depending on wound/ulcer location. In the same setting, arterial pressure measurements will not be applicable in cases of prior amputation.

Reed *et al*[29] showed that a post interventional ABI increase of ≥ 0.23 can augment wound healing and potentially reduce the necessity for a subsequent angioplasty, while a post endovascular revascularization TBI increase of ≥ 0.21 is correlated with

reduced major adverse limb events and with improved wound healing. Also, Decrinis *et al*[30] found that a post-angioplasty ABI increase of 0.10 and 0.15 can predict no residual > 50% stenosis, with sensitivities of 79% and 67% and specificities of 92% and 100%, respectively. However, other studies show that ABI correlates poorly with Rutherford classification and the angiographic vessel runoff and that it may not adequately predict wound healing[31,32].

Notably, the ABI can only imply the approximate site of stenosis or occlusion, but it cannot determine its exact location since it could also reflect changes elsewhere in the arterial tree[33]. Due to this fact it cannot accurately differentiate graft failure from PAD progression, hence rendering its accuracy in predicting revascularization failure poor. Considering the above, ABI alone is not a dependable method of post-revascularization follow-up. Lastly, arterial pressure measurements such as ABI and TBI can only assess tibial or toe pressure, respectively, but are not able to quantify oxygenation and tissue perfusion. Hence, they only indirectly evaluate treatment outcomes.

Overall, post-procedural foot perfusion outcomes cannot be accurately quantified using ABI, as the existing data does not consider ABI a sufficient predictor of post-procedural results and relegate it a poor predictor of wound healing.

LASER DOPPLER SKIN PERFUSION PRESSURE MEASUREMENTS AND TRANSCUTANEOUS OXYGEN MONITORING

The first attempt to non-invasively assess post-revascularization limb perfusion was made using laser Doppler skin perfusion pressure (SPP) measurements and transcutaneous oxygen ($TcPO_2$) monitoring.

Laser doppler skin perfusion pressure measurements

Laser Doppler measurement of SPP is a non-invasive technique that (by using a laser Doppler sensor) detects the movement of red blood cells (RBCs) following the slow release of the pressure occlusion cuff. In this way, SPP measurements calculate the capillary opening pressure and provide an indirect estimation of the microcirculatory flow status within the artery at skin level[34]. SPP is advantageous in that it is not altered by vascular calcifications[35]. Notably, SPP values > 30 mmHg after successful endovascular treatment with balloon angioplasty and/or stenting have been correlated with improved wound healing in a retrospective study of 113 consecutive CLI patients, with a sensitivity and a specificity of 81.4% and 69.2%, respectively[34]. On the other hand, if SPP values are < 30 mmHg, wound healing is doubtful[36]. More recently, in a large sub-analysis of 156 CLI patients included in a prospective multicenter registry, postprocedural SPP was significantly correlated with amputation-free survival, major adverse limb events, and wound healing at 1-year follow-up. Additionally, the authors reported that ABI did not correlate with clinical outcomes[37].

Transcutaneous oxygen monitoring

Transcutaneous oxygen ($TcPO_2$) is a non-invasive test measuring oxygen concentration in the subcutaneous tissue 1 to 2 mm below the skin that can be performed at the bedside and does not use ionizing radiation. First, a conductive gel is applied over the area under examination, and subsequently, an electrode that can sense oxygen is placed on the affected limb. The electrodes heat the area beneath the skin, dilating the capillaries and allowing oxygen to readily flow to the skin, thus providing an optimal reading. The test serves as an indicator of oxygen and nutrients reaching the tissues through microcirculation[38], and since these are carried to tissues through the arteries, it can indirectly measure blood flow. Therefore, it can provide direct information about the endpoint of limb perfusion, which is tissue oxygenation. Normal $TcPO_2$ values are between 50-70 mmHg.

Over the past years, several authors have investigated the role of $TcPO_2$ in PAD patients, and sufficient data support its use both for PAD screening and post-revascularization success evaluation. Patients with CLI (ABI < 0.4) will almost always have $TcPO_2$ values < 30 mmHg[39]. Moreover, it is a highly accurate and particularly valuable test in predicting wound/ulcer and amputation healing[40]. Specifically, values over 30 mmHg have been correlated with improved wound healing rates[41, 42], while values < 30 mmHg have been associated with a reduced chance of wound healing[43,44]. Likewise, Andrews *et al*[45] found that a cut-off $TcPO_2$ value of 38 mmHg had a sensitivity and specificity of 71% in predicting wound healing or failure.

When compared to the ABI, Pardo *et al*[38] found that an increase in $TcPO_2$ measurements following endovascular procedures has more specificity and sensitivity compared to ABI, and hence may be a better alternative in the evaluation of angioplasty results.

In the setting of open wounds or prior amputations, where arterial pressure measurements are not applicable, $TcPO_2$ and SPP measurements can be adequate alternatives. Additionally, since arterial pressure measurements cannot accurately identify the exact arterial disease location, these local perfusion tests may prove advantageous in angiosome-based revascularization[46,47].

Limitations

Despite published evidence suggesting the clinical utility of SPP and $TcPO_2$, these techniques are not widely available and present several limitations. $TcPO_2$ is only a skin perfusion marker, whose measurements are performed in a small area. $TcPO_2$ results can be affected by numerous physiological, methodological, and technical issues. Perfusion assessment measures should be attained in a warm room to avoid cold-induced vessel constriction that could alter $TcPO_2$ and SPP values[39]. Similarly, in patients exhibiting abnormal involuntary movements, reliable measurements will also not be feasible[48]. Other factors such as site selection, electrode equilibration, patient age, patient positioning, patient status before examination, pain, smoking and caffeine consumption, skin temperature changes, sympathetic tone, tissue edema, hyperkeratosis, cellulitis, and local skin integrity[35,39] may affect the accuracy of measurements, hence decreasing overall reliability. In addition, bony prominences, larger veins, or varicose veins should be avoided during cuff placement for SPP measurements, since they may produce artifacts[48].

Also, $TcPO_2$ can calculate the partial pressure of oxygen adjacently to the wound but cannot determine actual measurements within the wound itself[49]. In the same manner, since measurements are relatively localized, values may not accurately represent total limb ischemia[39].

MATTERS THAT NEED TO BE ADDRESSED

The above-mentioned non-invasive techniques that are being employed in the assessment of limb perfusion estimate different perfusion characteristics, and each one of them has its advantages and disadvantages. For instance, ABI/TBI measures arterial pressures and hence cannot quantify tissue oxygenation and cannot provide sufficient information regarding wound healing and patient outcome. $TcPO_2$ measures oxygen tension, while SPP measures capillary opening pressure. Although the latter methods are more reliable predictors of outcomes and offer a quantifiable outcome indicative of tissue perfusion, accurate tissue perfusion values cannot be obtained. Moreover, despite optimistic initial results, data regarding the role of SPP and $TcPO_2$ in guiding or predicting endovascular treatment outcomes in PAD patients remain limited, and large prospective controlled studies are awaited.

NON-INVASIVE IMAGING STUDIES

Examples of non-invasive imaging studies include duplex ultrasound (DUS), computed tomography (CT) angiography (CTA), and magnetic resonance imaging angiography (MRA). DUS uses two modes of ultrasound, the B-mode that assesses vessel structure, and Doppler that evaluates blood flow velocity and direction. CTA/MRA provide information regarding the vessel's anatomic relationship with other organs and provide information regarding vessel structure and morphology of stenosis. As a result, these methods can only measure lower extremity blood flow, and thus, are only surrogate tissue perfusion markers. Techniques that enable more accurate quantification of tissue perfusion include perfusion CT and arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI). However, these techniques are not employed regularly in the clinical evaluation of PAD.

CT perfusion

CT perfusion (CTP) has been readily employed in cerebral imaging, with its most well-known application being the non-invasive diagnosis of cerebral infarction/ischemia

[50]. Similarly, Hur *et al*[51] demonstrated that CTP could be used to measure blood flow in lower limbs and also in the diagnosis of PAD by providing quantitative information regarding foot perfusion, while in the same study, color-coded perfusion map readings correlated well with both clinical and angiographic findings in PAD patients undergoing revascularization. Additionally, Sah *et al*[51] showed that CTP is feasible in PAD assessment and demonstrated a positive correlation between CTP blood flow, blood volume, and lesion length, and an inverse correlation between blood volume and ABI, suggesting that CTP may serve as a non-invasive technique, supplementing the diagnostic workup of PAD[52]. CTP examinations can be performed by contemporary CT scanners, as a supplement to CTA. Although CTP has the potential to quantify perfusion and monitor treatment response, it is a costly examination that necessitates the use of iodinated contrast and exposes patients to radiation.

Arterial spin labeling MRI

Arterial spin labeling (ASL) MRI is a non-invasive and non-ionizing perfusion measurement technique that allows measurements at the tissue level by exploiting the ability of MRI to magnetically label inflowing arterial blood before it enters the tissue under investigation (below the imaging slab)[53]. T1 signal differences between control and tag images are proportionate to blood flow and are used to produce perfusion maps[54]. With this technique, blood serves as an endogenous tracer, obviating the need for contrast agents.

Although initially developed and used to measure brain perfusion[55], ASL has found several clinical applications since. Notably, it is a reproducible, radiation-free technique that can successfully quantify peak exercise blood flow in calf muscles in patients experiencing claudication[56].

Limitations of ASL include low signal-to-noise ratio, relatively long scan acquisition times, patient movement artifacts, and errors owing to potentially slow blood flow, often seen in PAD/CLI patients.

Blood oxygen level–dependent MRI

BOLD MRI has been used for many years in functional MRI (fMRI) of the brain. This technique exploits the ability of fMRI to detect changes in the concentration of oxygenated and deoxygenated hemoglobin (Hb) due to a fundamental difference in their paramagnetic properties (deoxy Hb is paramagnetic while oxyHb is not). As a result, it uses the Hb saturation state as an endogenous tracer, hence also eliminating the need for contrast agents. Heavily T2* weighted sequences are used to detect such changes[57]. Even though BOLD imaging has been mostly used in fMRI to detect which parts of the brain demonstrate most activity, Bajwa *et al*[58] evaluated BOLD MRI as a clinical tool for the measurements of calf muscle perfusion in CLI patients. This study demonstrated statistically significant interuser and interscan reproducibility and found a significant correlation between MRI measurements and tissue vascularity found in muscle biopsy samples obtained in the scanned region.

Limitations of BOLD imaging include erroneous measurements potentially related to slow blood flow (as mentioned with ASL) often seen in PAD patients and susceptibility of T2* sequences to artifacts. However, when compared to ASL MRI, BOLD MRI seems to have a higher signal-to-noise ratio, faster acquisition times, and reduced motion artifacts[58].

Nonetheless, for the purposes of this review, the most important limitation of ASL and BOLD imaging is the fact that although they can be used to quantify post-procedural perfusion outcomes, they are impractical when physicians require real-time feedback during endovascular interventions.

INTRA-OPERATIVE TWO-DIMENSIONAL PERFUSION ANGIOGRAPHY

Neuro-interventional procedures associated with acute stroke treatment have effectively employed two-dimensional perfusion angiography (2D-PA) by using flat detector technology[59]. This application has improved acute stroke patient management by allowing cerebral blood volume (CBV) assessment and by predicting final infarct volume.

When applied in peripheral vessels, standard DSA is used, with a rate of three frames per second. The images that are attained are reconstructed with a post-processing software that calculates the changes in density per pixel before and after the endovascular intervention, and the results are then viewed on a dedicated workstation[60]. In a study conducted by Jens *et al*[60], the DSA data obtained during

this technique were used to produce a time–density curve, which represented foot perfusion concerning time. Successful endovascular interventions performed on below the knee arteries in this study showcased improved perfusion curves, hence making functional imaging in CLI patients a more feasible goal. Moreover, another study conducted by Kagadis *et al*[61], using a custom-made, 2D perfusion DSA algorithm (Figure 1) demonstrated a post angioplasty mean transit time decrease that indicated increased tissue perfusion following successful revascularization. However, this study was limited mainly by the very small number of patients investigated.

Overall, advantages of 2DPA include the fact that it does not require additional radiation exposure or additional contrast administration[62] and that it can be used instantly, while the procedure is being conducted to evaluate the interventional results [60]. This will allow physicians to make more informative and objective decisions on whether the undertaken treatment is sufficient or further improvements are required [62], while it could also aid in determining a meaningful, functional revascularization endpoint, beyond the anatomical endpoint assessed with standard intraprocedural DSA (less than 30% residual stenosis)[60]. However, acquisition of the appropriate software is required while obtained images are very susceptible to patient/limb movement-induced artifacts[60-62]. The fact that such perfusion software is currently incorporated in new Angiography systems (Siemens, Toshiba, Phillips) indicates that there is a recognized need to overcome standard anatomical imaging and progress to the era of real-time, functional, quantifiable imaging.

Nonetheless, additional studies are necessary to further validate this technique and determine its role in PAD/CLI-related interventions by comparing it to other available methods and correlating it with clinical outcomes.

IMPLANTABLE DEVICES - O_2 MICRO-SENSORS

Implantable devices such as O_2 micro biosensors may be advantageous because they can measure oxygen concentrations in tissues instead of vascular oxygenation. They can calculate tissue oxygenation in multiple areas and can potentially be utilized in monitoring tissues at risk, wounds, and reconstructive surgery. These phosphorescence devices are as small as 0.5 mm × 0.5 mm × 5 mm and can be integrated within the area/tissue of interest *via* a 16G or 18G needle[63]. Once positioned, these biocompatible hydrogel sensors remain in the body permanently, surpassing the foreign body response[64]. Subsequently, a reader is fixed on the skin above the microdevice, and then a LED source emits light into the skin above the sensor. Local tissue O_2 levels will then be calculated by an external photodetector in the reader and can be continuously tracked. The first-in-man prospective, single-arm, observational study included 10 patients with CLI (four micro-oxygen sensors injected in the foot of each patient). The study demonstrated that injectable micro-oxygen sensors could effectively and safely calculate tissue O2 concentrations in CLI patients during their endovascular intervention and post-operatively for 28 days[63]. Moreover, a statistically significant postoperative increase in the concentration of oxygen was noted. Nonetheless, additional and larger studies are required to confirm the utility and applications of these devices.

MICROWAVE RADIOMETRY THERMOMETRY

Microwave radiometry (MWR) is a non-invasive technique allowing accurate temperature measurements of internal tissues. Based on the principle that radiation intensity is proportional to tissue temperature, this method detects internal tissue temperatures at microwave frequencies by using contrasting dielectric qualities of different tissues[65]. This technique uses an antenna containing a microwave and an infrared sensor, which is applied at a 90 angle over the tissue surface being examined, for an approximate duration of 8-10 s. To obtain measurements, the microwave emissions are converted into temperature by using a data processing unit and suitable software.

Tissue temperature measurements have previously been applied in the diagnosis of numerous entities[66] including the characterization of neoplastic tissue or inflammation of atherosclerotic plaques[67-69]. Guidelines for diabetic foot management suggest that pedal perfusion is evaluated by the combination of ABI, TBI, Doppler arterial waveforms, and $TcPO_2$[70,71]. However, detecting the concomitant presence of vascular disease in diabetic foot ulcers remains a difficult and challenging task.

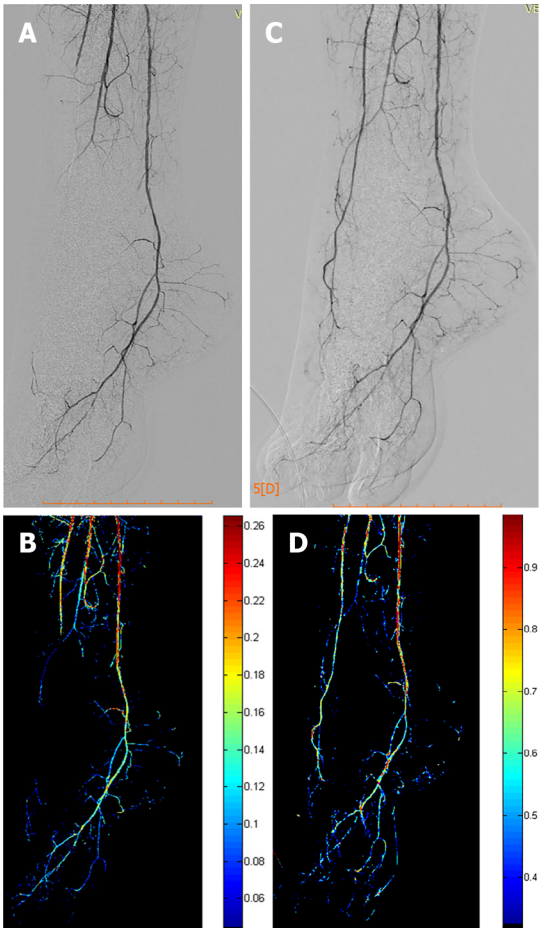


Figure 1 Two-dimensional perfusion digital subtraction angiography algorithm. A and B: Pre-procedural digital subtraction angiography (DSA) depicting a chronic total occlusion of the distal anterior tibial and pedal arteries with the respective perfusion blood volume (PBV) map; C and D: Post-procedural DSA after balloon angioplasty of the occlusion and corresponding post-procedural PBV map.

Spiliopoulos *et al*[72] conducted a study to investigate the ability of MWR thermometry to non-invasively differentiate CLI in patients with diabetic foot ulcers. This multicenter study including 80 patients demonstrated that the temperatures measured near ulcers were significantly lower in patients with CLI (either with or without diabetes) than in non-ischemic controls. Importantly, it showed that a cut-off temperature less than 31.8 °C was diagnostic of CLI with a sensitivity and specificity of 100.0% and 88.37%, respectively.

The above findings indicate that MWR thermometry could be employed in the differentiation of arterial ischemia in patients with diabetic foot ulcers. This thermometric technology is currently being studied for the quantifiable assessment of post revascularization foot perfusion to predict successful wound healing and initial data are awaited. Limitations of this modality include the fact that it needs to be performed in standard room temperatures and that in cases of overlying infection/inflammation, false-negative results may be obtained.

PERIPHERAL FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) is an invasive method frequently employed in coronary artery revascularization to calculate pressure variations across a stenotic lesion[73,74]. It is a pressure ratio produced by dividing the mean pressure distal to the lesion with that proximal to the lesion. The cutoff FFR value is 0.80, with an FFR above 0.80 indicating non-significant stenosis and an FFR below 0.80 indicating a significant lesion[75]. Measurements are obtained *via* a small sensor/ transducer on the tip of the angiographic wire during pharmacologically induced hyperemia, which is achieved by injecting vasodilating agents. FFR allows the determination of whether certain stenosis is oxygen depriving, hence rendering it a valuable indicator of the stenosis's functional severity and the necessity for coronary intervention[73].

Notably, according to a meta-analysis from Christou *et al*[76], the concordance of FFR when compared with non-invasive imaging conveyed a sensitivity and specificity of 76%, concluding that FFR results usually agree with non-invasive imaging studies, although their correlation can be deficient.

The use of FFR in PAD (peripheral FFR-pFFR) uses the same principles as the FFR in CAD. It has been recently employed in the evaluation of the physiological implications of iliac and superficial femoral artery stenosis[77,78] and also in CLI patients with severe below-the-knee arterial disease[79]. Hioki *et al*[77] found a significant association between pFFR and post-exercise ABI and noted a substantial pFFR improvement after endovascular procedures, while Banerjee *et al*[80] demonstrated an important correlation between walking impairment, pFFR, and rest and exercise ABI. Potential applications of pFFR include its intraoperative evaluation after apparently successful revascularization. Although FFR has been thoroughly investigated in CAD and is considered to be a valuable tool (particularly in the management of intermediate lesions), the use of pFFR has been limited, with available evidence-based data being sparse, and clinical efficacy remaining questionable warranting further investigation.

An advantage of FFR is that it is unaffected by heart rate and SBP changes and that it considers collateral flow[73]. The latter means that it could potentially render morphologically severe stenosis functionally insignificant. Moreover, FFR allows for simultaneous intraprocedural diagnosis and treatment with angioplasty and stenting. Importantly, FFR can have significant value in vessels with multiple stenotic lesions [81]. The pFFR can be obtained by 2D perfusion DSA and therefore implemented in real-time decision-making during peripheral angioplasty procedures. Nevertheless, its drawbacks include its invasive, time-consuming nature and the requirement for drug administration (vasodilating agents), which could cause important side effects[82].

INDOCYANINE GREEN FLUORESCENCE ANGIOGRAPHY

Indocyanine green (ICG) fluorescence angiography was initially used in retinal vessel imaging[83] and subsequently in the evaluation of tissue perfusion in various medical fields[84,85]. Following intravenous injection of the fluorescent ICG dye, the latter is activated by the use of near-infrared laser (approximately 780 nm)[84]. This procedure produces fluorescence that is subsequently detected and measured.

There is currently an insufficient number of studies that have applied this method in PAD patients. ICG fluorescence angiography perfusion measurements have been shown to predict the possibility of amputation healing[86] and have the potential to detect PAD patients with lower limb arterial occlusions who have developed extensive collaterals[87]. Additionally, it may permit real-time evaluation of flow in peripheral bypass and endovascular procedures[88]. In a retrospective study of 11 patients (13 peripheral bypass grafts), Yamamoto *et al*[89] performed quantitative near-infrared fluorescence angiography (NIR) using the fluorescence ICG to visualize blood perfusion and predict the patency of peripheral arterial bypass graft patency by measuring their fluorescence luminance intensities. Time-intensity curves of ICG opacification through the graft (Q graft) and distal host artery (Q distal) were assessed. Interestingly, increased Δ(Qgraft − Qdistal) and integral(Qgraft − Qdistal) quantitatively analyzed using NIR could predict anastomotic stenosis.

Igari *et al*[90] enabled peripheral blood circulation assessment during DSA in a retrospective study of ICG intraarterial DSA in 16 patients, (22 limbs) with PAD. The authors concluded that ICG evaluation during DSA might be used to assess peripheral blood flow during endovascular procedures.

ICG fluorescence angiography has the limitation of only being able to evaluate tissues up to 3 mm beneath the surface of the skin, hence only allowing microcirculation evaluation in the aforementioned regions. As a result, this technique may demonstrate inadequate efficacy in early PAD patients, because in this patient category microcirculation perfusion alterations will initially occur in deeper muscular tissue than at the skin, as seen in advanced CLI patients[84].

NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) is a non-invasive method that employs near-infrared light to determine tissue oxygenation. It comprises a light source emitting near-infrared wavelengths and a detector that measures the reflected light after the

latter has been absorbed and scattered by illuminated tissue being examined. According to the device being used, NIRS can illuminate tissue at depths between 1-3 cm. Variations in wavelength absorption reflect the concentration of oxygenated and deoxygenated hemoglobin, thus providing information regarding tissue oxygen saturation and, as a result, tissue perfusion (Figure 2)[91].

NIRS applications vary widely, including several utilizations in the field of medicine[92]. Amongst these, it has also been investigated in PAD where it appears to have the ability to be used as a complementary method in its diagnosis and evaluation of severity[93]. Importantly, studies from Mesquita *et al*[94] and Kagaya *et al*[95] revealed significantly lower tissue oxygen saturation values in PAD patients when compared to healthy patients, while a comparative study from Boezeman *et al*[96] found that using NIRS to monitor foot oxygenation (tissue oxygen saturation; StO_2 in muscle tissue) in 14 CLI patients being subjected to EVT is a safe and feasible technique that can detect and record hemodynamic changes.

Limitations of NIRS include overlying infection/inflammation and the strong possibility of erroneous measurements when examining tissues with an abundance of overlaying fat[97]. Moreover, NIRS measurement results can be sensitive to oxygen delivery and extraction[98].

Nonetheless, additional studies are necessary to further clarify the role of NIRS in PAD, its intraprocedural applications, and its potential in predicting wound healing.

LASER-BASED IMAGING

Laser doppler imaging

Laser doppler imaging (LDI) is a non-invasive, non-ionizing, bedside-performed technique measuring blood cell speed and concentration. Similar to other methods, it also employs laser light, but in this instance, it is reflected and scattered by flowing blood cells, and then detected and converted into an electrical signal[99]. Subsequently, a color-coded perfusion image can be generated that may allow for a more accurate evaluation of the angiosome(s) associated with the disease[99]. Applied from a distance, LDI evaluates a larger area of skin by implementing a scanning motion that includes the whole leg[100]. Laser wavelength, scanning speed, and distance between scanner and area under examination can alter tissue penetration and hence should be unchanged to permit reproducibility of measurements and reliability in their comparison[101].

LDI has already found several clinical applications, including rheumatologic disorders, burn and dermal inflammation assessment, and assessment of wound healing and cutaneous ulceration[101]. The prospect of wound healing and cutaneous ulcer evaluation could prove valuable in PAD patients. Moreover, in the setting of PAD, quantifiable real-time increases in microcirculatory perfusion following EVT have been reported[102]. As a result, when using LDI, the operator can obtain real-time quantitative data regarding changes in target angiosome perfusion during the endovascular procedure, while it also has the potential to be proven valuable in the perioperative assessment.

Disadvantages of this technique include the low-depth penetration of laser light, the fact that measurements can be altered by temperature and vasoactive substance consumption, and the fact that measurements can be inconstant, rendering their serial comparison problematic[84].

Laser speckle contrast imaging

Laser speckle contrast imaging (LSCI) is a fast, inexpensive, and relatively simple imaging technique with the ability to produce 2D perfusion maps of large areas under investigation[103]. A typical LSCI comprises a laser light emitter and its diffuser, a camera with its lens, and appropriate processing software. When the tissue under investigation is illuminated with coherent laser light, it serves as a scattering medium and the backscatter produced causes a random interference pattern, which is called a speckle. This technique is based on the variations of backscattered light caused by the interaction of light with flowing RBCs[104]. LSCI is similar to laser Doppler in many ways, but it is still unclear if it measures flow or velocity[104]. Although originally used to measure retinal blood flow, LSCI has been employed in cerebral and skin perfusion assessment[105] and can generally be used in perfusion assessment of various tissues with many additional clinical applications (*e.g.*, burn wound assessment and rheumatological disorders, to name a few)[104]. Moreover, LSCI has been shown useful in assessing diabetic foot ulcers owning to local ischemia[106],

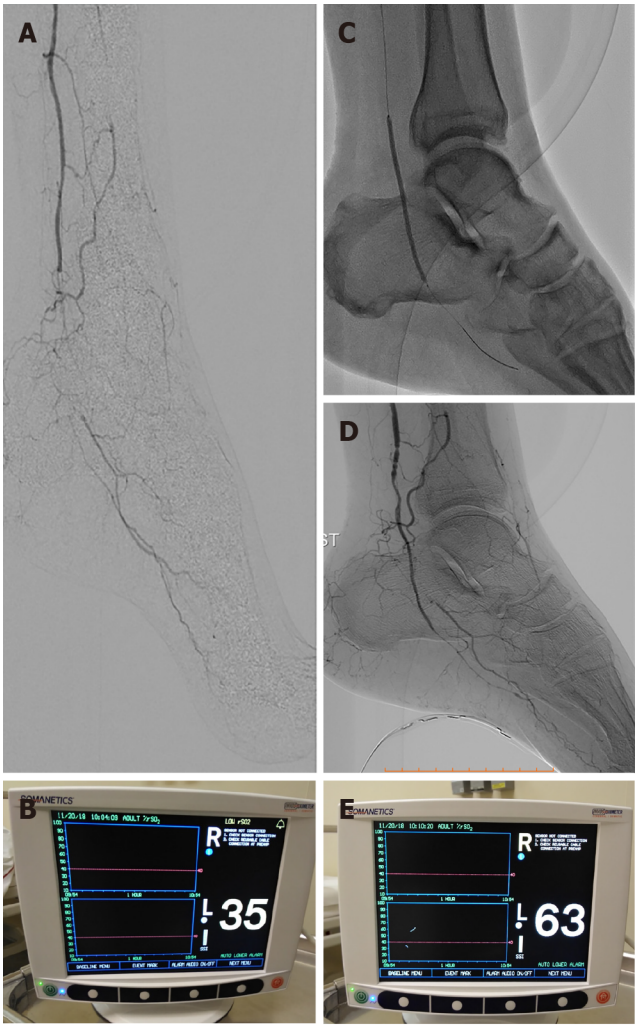


Figure 2 A case of 68-year-old male patient with insulin-dependent diabetes mellitus and advanced Rutherford-Becker class 6 gangrene of the left foot. A and B: Digital subtraction angiography depicting a total occlusion of the distal posterior tibial artery and very low percentage value (35%) of regional hemoglobin oxygen saturation according to real-time near-infrared spectroscopy (NIRS) assessment of foot perfusion; C and D: Balloon angioplasty and final angiographic result demonstrating revascularization of the target occlusion. Note the NIRS electrode attached to the plantar surface of the treated foot; E: Immediately after revascularization, the percentage value of regional hemoglobin oxygen saturation was increased to 63%, demonstrating an 80% increase in foot tissue perfusion.

while - along with $TcPO_2$ – it has also proven beneficial in the diagnosis of severe foot ischemia[107].

LSCI allows microvascular blood flow assessment owning to its high spatial resolution, while it has an added advantage of not necessitating direct contact with the tissue being examined to measure blood flow[105,107]. LSCI is mainly limited by its susceptibility to motion artifacts either due to patient breathing or movement[108]. As a result, addressing this issue is crucial in order to increase the usage of this technique in PAD/CLI patient management, where involuntary limb movements are often present.

Diffuse contrast speckle analysis

Diffuse contrast speckle analysis (DSCA) is a new non-invasive, non-ionizing optical modality that combines LSCI and diffuse correlation spectroscopy (DCS) in order to measure deep tissue blood flow by exploiting the sensitivity of the speckle contrast signal to RBCs movement[109]. DCS can probe deep tissue blood flow by monitoring light intensity fluctuations of the reflected diffuse speckle from tissue and can offer continuous blood flow monitoring, while LSCI (which has been analyzed above) is more suitable for shallow depths[109]. As a result, DSCA employs the deep tissue probing applications of DCS and the simple instrumentation and analysis of LSCI. The difference between DCS and DSCA is that with DSCA a specific region is imaged using a charge-couple device camera so that speckle contrast can be attained for a specific exposure time[110].

DSCA has found several applications in many fields since its development. Clinical applications include cerebral blood flow assessment[111], peripheral vascular health assessment for the evaluation of burns[112], and monitoring of foot tissue blood perfusion in diabetic patients with non-healing wound lesions undergoing vascular interventions[113].

Similar to other optical modalities, this technique has a limited depth penetration and, just as previously mentioned with LSCI, is susceptible to motion artifacts[111].

EMERGING DEVICES

Based on these latter technologies, novel perfusion devices have been available in the market, and others are currently under development. Recently, a real-time tissue perfusion device (PEDRA™ Xauron™ Perfusion System) has received Food and Drug Administration Breakthrough Device Designation for intraprocedural use during CLI treatment. It is a portable laser-based tissue monitoring system currently undergoing its first-in-man study. It provides real-time intraprocedural feedback on whether microcirculation has been improved post-intervention. As blood flows through the skin, the RBCs scatter the laser light, the amount of which is reflected on the monitor, hence quantifying perfusion. Data achieved with this system are claimed to be highly reproducible, however, further research on its clinical utility is required.

Additionally, the HyperView monitor (HyperMed Imaging; Memphis, TN, United States), which enables hyperspectral imaging for superficial tissue oximetry by measuring oxyhemoglobin, deoxyhemoglobin, and oxyhemoglobin saturation in superficial limb tissue, has recently received CE-Mark.

CONCLUSION

Current research validates the prospect of real-time, intraoperative, perfusion-guided revascularization techniques that will allow vascular experts to intraoperatively quantify and assess outcomes optimizing treatment. Such modalities have the potential to obviate misinterpretation of treatment outcomes and provide significantly improved clinical results. Also, novel four-dimensional angiography systems are expected to introduce state-of-the-art fusion imaging and real-time foot perfusion monitoring in everyday clinical practice soon. This will enable the use of novel tissue perfusion endpoints that could improve outcomes of endovascular treatment of arterial ischemia.

Therefore, the development of real-time tissue perfusion imaging and monitoring modalities that allow objective measurements and accurate quantification should be further investigated and validated by large, randomized trials.

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REVIEW

Exercise-mediated adaptations in vascular function and structure: Beneficial effects in coronary artery disease

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Abstract

Exercise exerts direct effects on the vasculature *via* the impact of hemodynamic forces on the endothelium, thereby leading to functional and structural adaptations that lower cardiovascular risk. The patterns of blood flow and endothelial shear stress during exercise lead to atheroprotective hemodynamic stimuli on the endothelium and contribute to adaptations in vascular function and structure. The structural adaptations observed in arterial lumen dimensions after prolonged exercise supplant the need for acute functional vasodilatation in case of an increase in endothelial shear stress due to repeated exercise bouts. In contrast, wall thickness is affected by rather systemic factors, such as transmural pressure modulated during exercise by generalized changes in blood pressure. Several mechanisms have been proposed to explain the exercise-induced benefits in patients with coronary artery disease (CAD). They include decreased progression of coronary plaques in CAD, recruitment of collaterals, enhanced blood rheological properties, improvement of vascular smooth muscle cell and endothelial function, and coronary blood flow. This review describes how exercise *via* alterations in hemodynamic factors influences vascular function and structure which contributes to cardiovascular risk reduction, and highlights which mechanisms are involved in the positive effects of exercise on CAD.

Key Words: Exercise; Endothelium; Flow-mediated dilation; Endothelial shear stress; Coronary artery disease; Hemodynamics

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Core Tip: Exercise has beneficial effects on the function and structure of the vasculature, thereby leading to a reduction of the cardiovascular risk. Hemodynamic forces, in particular endothelial shear stress, play a critical role in modulating the endothelial cell phenotype towards atherogenesis or atheroprotection. Exercise improves clinical outcomes in patients with coronary artery disease (CAD). We herein discuss the alterations induced by exercise on vascular function and structure, and the mechanisms involved in the benefits of exercise regarding patients with CAD.

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INTRODUCTION

Cardiovascular disease is the main cause of morbidity and mortality in western societies. Although traditional risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking) have a systemic atherogenic effect on the entire vasculature, local hemodynamic factors determine the distribution of atherosclerotic lesions. Endothelial shear stress (ESS), the frictional force acting on the endothelium as the result of blood flow, represents a continuous stimulus eliciting structural and functional effects on the endothelium and plays a critical role in the development of atherosclerosis. Atherosclerotic lesions develop preferentially at areas with disturbed local hemodynamic factors, mainly in regions with low ESS, such as the inner curvature of coronary arteries or in the outer waist of a coronary bifurcation and downstream from a luminal obstruction where ESS is oscillatory. In contrast, arterial regions with physiologic/increased local flow and ESS are thought to be protected from atherosclerosis[1-3].

Multiple studies suggest that exercise decreases the risk of coronary artery disease (CAD) with the positive impact on both primary and secondary prevention being greater than 30%[4,5]. Exercise-based cardiac rehabilitation has been associated with reduced both all-cause and cardiac mortality as well as hospital admissions[6,7]. Exercise also decreases the risk of cardiovascular events and, in patients with CAD, increases exercise capacity, decreases myocardial ischemia, and delays the onset or inhibits angina pectoris[8,9].

The effects of exercise on traditional risk factors do not fully explain the tremendous impact of exercise on cardiovascular risk: differences in known traditional and novel risk factors explain approximately 60% of exercise-mediated cardiovascular disease risk reduction and only 35% of the heart disease risk reduction[10]. Exercise exerts direct effects on the vasculature through the impact of ESS on the endothelium, which leads to functional and structural adaptations that decrease atherosclerotic risk[9,11]. In addition, exercise-induced changes in flow-mediated dilation (FMD), an index of vascular function, do not correlate well with changes in traditional cardiovascular risk factors[12]. Therefore, it is possible that the cardioprotective effect of exercise is, at least in part, independent of changes in traditional risk factors and is mediated by functional and structural adaptations.

The purpose of this review is to describe how exercise *via* alterations in hemodynamic factors influences vascular function and structure contributing to cardiovascular risk reduction, and to highlight which mechanisms are involved in the positive effects of exercise on CAD.

EXERCISE AND MECHANISMS OF ACTION: ROLE OF HEMODYNAMIC FACTORS

Exercise-induced hemodynamic alterations have been reported to play a major role in cardiovascular disease risk reduction, leading to direct effects on the vasculature that

are atheroprotective. These vascular adaptations concern mainly the endothelium and the cross-talk between the endothelium and smooth muscle cells (Figure 1)[11,13,14].

The normal endothelial phenotype is of utmost importance in artery health, and thus, changes in endothelial cell phenotype are related to the development and progression of atherosclerosis. Endothelial dysfunction precedes and is present during the evolution of atherosclerosis, indicating that a proatherogenic endothelial phenotype plays an important role in both the initiation and progression of atherosclerosis[13,15,16]. Furthermore, latest evidence suggests that physical activity exerts beneficial effects by maintaining a normal phenotype of arterial endothelial cells[17-19].

Exercise has beneficial effects in the primary and secondary prevention of CAD, which are closely related to changes in the endothelial cell phenotype[17,20,21]. Exercise augments nitric oxide (NO) bioavailability through a variety of mechanisms; data from cell-culture and animal experiments suggest that NO bioavailability can be affected by many different alterations in the following steps of the NO pathway. Exercise acts as a stimulus for the endothelium to (1) increase the availability of L-arginine (the precursor molecule for NO); (2) promote NO synthase (NOS) activity and expression; and (3) augment the production of extracellular superoxide dismutase, which prevents premature breakdown of NO. These effects likely contribute to amplified exercise capacity and, ultimately, cardiovascular protection. Cardiovascular risk factors, as well as established atherosclerotic disease, are associated with profound impairment of the NO pathway and systems, which may lead to limitations in exercise capacity. Exercise in populations with coronary artery disease can increase NO bioavailability and contribute to secondary prevention[17,22,23]. In addition, the beneficial effects of exercise on preventing atherosclerosis progression and the improvement of endothelial function and phenotype are associated with decreased expression of adhesion molecules as well as inflammatory cell infiltration[24].

The beneficial effects of physical activity on vascular health result from exercise-induced changes in hemodynamic factors. Exercise produces increases in blood flow to the heart and active skeletal muscle, generating shear forces that have been suggested to differentiate gene expression in endothelial and vascular smooth muscle cells[13,25]. Increases in mean ESS positively modify the expression of atheroprotective genes; the beneficial effect of exercise also extends to arteries that do not directly present increased mean ESS during exercise (Figure 1)[14,26]. Accumulating data suggest that elevated ESS is a signal for increased endothelial NOS, decreased endothelin-1 and decreased vascular cell adhesion molecule 1 (VCAM-1) expression. Several intracellular signaling mechanisms have been identified, including G proteins, calcium, and proto-oncogene tyrosine-protein kinase Src (c-Src)[27-30]. Investigation of gene expression patterns of cultured endothelium exposed to different flow waveforms has shown that mean ESS significantly influences the expression of approximately 3000 genes[31]. Data from *in vivo* models provide a correlation between increases in mean ESS and antiatherogenic effects. Chronic increases in blood flow are associated with upregulation of endothelial NOS mRNA, protein and activity, as well as with decreased endothelin-1 bioavailability[13]. Furthermore, during chronic exercise training, improvement of endothelial and mitochondrial function is found to be mediated by adenosine monophosphate-activated protein kinase alpha-2 (AMPKα 2) in studies with *AMPKα2* knockout mice[32-34].

Elevated blood flow during exercise is also related to increases in pulse pressure leading to an increase in cyclic strain across the vasculature. However, data obtained from cell culture demonstrated controversial results regarding the effect of cyclic strain. Although some studies reported that cyclic strain produced an antiatherogenic endothelial cell phenotype, other experiments suggested that cyclic strain had the opposite effect leading to a proatherogenic phenotype in cultured endothelial cells[35-38]. A more recent experiment using a whole vessel preparation reported that the decrease of cyclic strain stimulus leads to lower levels of phosphorylation of the endothelial NOS while it increases the production of reactive oxygen species[39].

EFFECTS OF EXERCISE ON VASCULAR FUNCTION AND STRUCTURE

Exercise and vascular function

Exercise has well-documented positive effects on endothelium-dependent vasodilator capacity, and ESS plays a major role in transducing these changes since enhancement in endothelial function is induced by increased endothelium-derived NOS shear-related protein expression[17]. Many studies have been conducted to investigate not

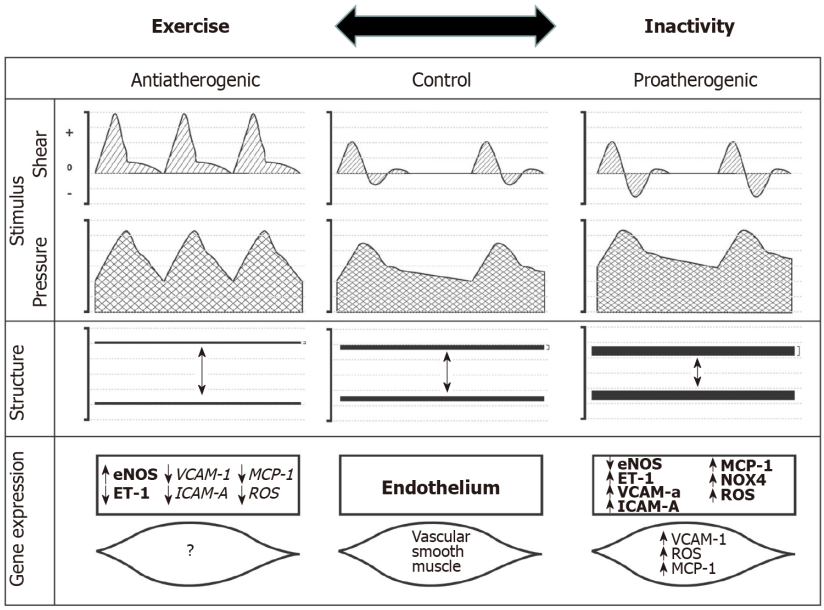


Figure 1 Schematic and hypothetical representation of how hemodynamics during exercise may impact vascular phenotype. The middle panel (Control) represents an artery being exposed to a "typical" hemodynamic stimulus [*i.e.* shear stress pattern (upper signal) and blood pressure (lower signal)]. No abnormalities are observed in artery structure [*i.e.* diameter (arrow) or wall thickness (bracket) or gene expression in the endothelial or smooth muscle cells. The left panel represents hemodynamic stimuli that may be associated with antiatherogenic effects, which include a predominant antegrade shear pattern and cyclic, intermittent elevations in arterial blood pressure (or pulse pressure). These hemodynamic stimuli are related to outward remodeling and a smaller arterial wall thickness, while some observed (in TextTitleface) antiatherogenic genes have been shown to be upregulated, and proatherogenic genes are hypothesized (in italics) to be downregulated under these conditions. On the right panel, proatherogenic shear (dominant retrograde shear component) and pressure (chronic elevation in systolic and diastolic pressure) hemodynamic stimuli are presented. These stimuli are believed to contribute to inward remodeling, thickening of the artery wall and increased expression of proatherogenic genes and downregulation of genes involved on the NO pathway. Adapted from Newcomer *et al*[14] with permission from the American Physiological Society. Citation: Newcomer SC, Thijssen DH, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. *J Appl Physiol (1985)* 2011; 111: 311-320. Copyright ©The American Physiological Society (APS).

only the impact of different patterns of exercise-related ESS on NO-mediated endothelial function, but also the manipulation of the shear stress stimulus during exercise. The modality by which vascular response to exercise training can be influenced in hypertensive individuals has been studied by the SEFRET study, while in spontaneous hypertensive mice the lack of a positive effect of high intensity exercise on endothelial function was found to be related to NO availability imbalance[40,41]. Kim *et al*[42] enrolled middle-aged marathoners with exercise-induced hypertension and reported increased angiotensin II with a reduction in NO levels. These findings may explain the deterioration of arteries vasodilator capacity and elevated blood pressure during exercise in this group of long-distance runners, as well as the therapeutic effect of angiotensin II inhibitors in patients with exercise-induced hypertension. Experimental data also support the hypothesis that physical exercise combined with the administration of renin-angiotensin-aldosterone system blockers could have beneficial effects in order to prevent hypertensive cardiac alterations (*e.g.*, left ventricular hypertrophy)[43].

Exercise effect on the vasculature has also been investigated in respect to other conditions, considering a load of high fat meal in healthy subjects, or in a different study considering glucose ingestion in adults with pre-diabetes. Both studies concluded *via* FMD measurements that exercise produces beneficial effects by attenuating the susceptibility to oxidative damage[44,45]. In patients with type 2 diabetes, acute (2 h after exercise) improvement of endothelial function was observed by FMD measurements after a bout of seven 1-minute cycling intervals using leg resistance exercises, while without leg resistance the beneficial effects were observed at 1 h post exercise[46]. No long-term study on patients with diabetes is available yet.

The acute impact of different exercise modalities, and as a consequence different patterns of blood velocity and flow on the upper limb vasculature function, has also been investigated. FMD, a largely NO-mediated vasodilator response, has been simultaneously studied in both brachial arteries of healthy young men before and after 30-min interventions consisting of bilateral forearm heating, recumbent leg cycling, and bilateral handgrip exercise. During each intervention, a cuff was inflated on 1 arm to unilaterally manipulate the shear rate stimulus. These studies revealed a significant

difference in the pattern of ESS between the 3 interventions. Post-intervention FMD was significantly increased compared with pre-intervention in response to each intervention[47,48]. Beneficial effects have also been reported in women[49]. Taken these results into account, we speculate that increases in anterograde blood flow and ESS lead to enhanced endothelial function.

Observations that predominantly lower limb exercise induces upper limb vascular adaptation have indicated that a generalized or systemic impact of exercise on endothelial function occurs in vascular beds other than those where the exercise stimulus is focused[50-52]. Therefore, exercise induces both localized improvements in vascular function in the active regions through repetitive increases in ESS and systemic vascular adaptations in case of large muscle group exercise.

Based on the above studies one can speculate that different patterns of blood flow and ESS during exercise lead to different hemodynamic and ESS stimuli to which the endothelium is exposed and as a consequence to different vascular adaptations, including the production and bioavailability of NO (Figure 1)[14].

Flow-mediated dilation in response to reactive hyperemia is, surprisingly, manifested only after blood flow drops back to baseline levels. It remains a puzzle whether this discrepancy (*i.e.* dissociation of flow and diameter) could be explained by a reduction in transmural pressure produced by high flow. Dedicated studies have shown that blood pressure and transmural pressure fall after cuff release at the time of peak hyperemic flow. Flow interruption 20 s after cuff release (during high flow but no dilation) leads to an immediate increase in artery diameter. These observations suggest that flow-dependent dilation may be offset by a flow-induced fall in local arterial pressure, and thus, in transmural pressure. This observation indicates that the combination of systemic pressure and local ESS may determine the ultimate vasoactive arterial response following acute exercise[53]. The critical role of these parameters is further confirmed by showing that during a single handgrip exercise, the response (measured by FMD 15 minutes after exercise) was blunted by the addition of an inflated pneumatic cuff to the exercising arm, clearly by abruptly influencing the local ESS[54]. Finally, improvement of the endothelial function was the conclusion of a recent systematic review meta-analysis, where the overall effect of exercise training on the endothelial function in heart failure patients was assessed by FMD in a total of 16 studies[55].

Adaptations that occur in human vasculature following acute exercise, as mentioned above, are useful to understand the impact of repeated episodic exposure to exercise. Previous studies conducted in healthy, asymptomatic subjects have reported that there was no adaptation in endothelial function following exercise and, interestingly, this observation was independent of whether exercise involved localized or large muscle systemic exercise[4]. Therefore, it may be difficult to enhance normal endothelial function in healthy subjects. However, there is evidence suggesting that a moderate-to-higher load (intensity, frequency, duration) of exercise may be necessary for improving endothelial function in healthy asymptomatic humans[56]. Campbell *et al*[57] examined the impact of long-term aerobic exercise during advancing age. They highlighted the importance of remaining active throughout a lifetime, since enhancement of endothelial vascular function is apparent only in athletic older persons, and not in otherwise healthy sedentary individuals following only a period of exercise training. Despite this beneficial effect, it is not clear which exercise load is most appropriate since exercise of high intensity may also cause oxidative stress[58, 59]. Qiu *et al*[60] revealed that chronic aerobic and combined aerobic and resistance exercise training programs improved endothelial function even in patients with type 2 diabetes, whose endothelium is characterized by impaired nitric oxide bioavailability following exercise training. Limited data are available regarding the endothelial function of coronary microcirculation, which suggest that coronary microvascular vasodilator response is enhanced following high-intensity exercise in humans[23]. Finally, we should consider that exercise may induce a transient increase in vascular function in healthy humans, which also influences conduit coronary arteries. FMD may be initially enhanced, but subsequently declined to pre-training levels, as exercise induces changes in arterial structure[52,61,62].

Exercise and vascular structure

Remodeling of luminal dimension: Exercise induces adaptations in the cross-sectional size of arteries, and athletes are characterized by augmented peak vasodilator capacity, which is associated with luminal expansion of resistance arteries[63,64]. Peak vasodilator capacity is significantly greater in the dominant limb of athletes compared to both their non-dominant limb and non-athletic control subjects[65,66]. These data suggest that resistance artery luminal adaptation is apparent in athletes and can occur

as a result of localized and intrinsic vascular stimuli. However, there are some studies in which lower limb exercise induced enhanced peak vasodilator capacity of the upper limb, thereby suggesting a generalized effect of exercise on arterial lumen adaptations [67].

As far as structural adaptations of resistance vessels in the normal heart are concerned, exercise increases arteriolar densities and diameters as suggested by experimental studies in animals[68]. An increase of total cross-sectional area of arterioles in the diameter range of 20-120 μm has been reported, with a higher increase in arterioles of 20-40 μm than in arterioles of 40-120 μm[69]. The impact of aerobic training on the growth of the capillaries of the coronary circulation is also well established. Capillary proliferation is a fundamental response to exercise but is accompanied by concurrent transformation of capillaries into arterioles[70]. Although some experimental studies suggested that exercise causes an increase in myocardial capillary density in prepubescent rats, it seems to have no effect on capillary density in postpubescent ones[71,72]. Exercise-induced angiogenesis may temporarily exceed the increase in left ventricular mass, but with prolonged exercise, angiogenesis matches the left ventricular hypertrophic response[69].

Various methodological approaches suggest that exercise induces growth of epicardial arteries which is in proportion to exercise-induced cardiac hypertrophy (left ventricular mass)[73-75]. Angiographic studies suggest that exercise significantly induces enhanced coronary artery dilating capacity in more active subjects, whereas there is no difference at rest between runners and control subjects[76,77]. For this reason, it is important to elicit dilator responses in order to uncover differences between athletes and control subjects; of note, basal arterial tone in athletes may be enhanced because of alpha-adrenergic and NOS inhibition-induced vasoconstriction, as well as increased resting plasma norepinephrine concentration[78]. Finally, transthoracic echocardiographic assessment has shown similar results since coronary flow reserve, an index of conduit artery vasodilator capacity, is greater in humans undergoing regular exercise[79].

Remodeling of arterial wall: Arterial wall thickness may have implications for cardiovascular risk since common carotid and femoral artery intima-media thickness have been found to be independent predictors of future clinical cardiovascular adverse events[80,81]. Furthermore, arterial wall remodeling may differentiate vascular functional responses since a larger wall-to-lumen ratio is correlated with greater responses to vasoactive stimuli[82].

Studies on the exercise-mediated responses of brachial, carotid, and superficial femoral arteries have shown that arterial wall thickness may be influenced by systemic factors, such as arterial pressure in contrast to shear-mediated impacts on arterial lumen size, which are more localized[64]. A decreased wall thickness is observed in all arteries (carotid, brachial and superficial femoral) of able-bodied athletes compared with control subjects. In contrast to the effects on lumen diameter, a decreased wall thickness was found in both limbs and was not related to exercise type[64,83]. Another study examined bilateral brachial artery wall thickness across an 8-wk period of bilateral handgrip training. ESS was attenuated by cuff inflation around one forearm, but brachial artery pressure responses during exercise were not affected. Handgrip exercise had no effect on baseline brachial artery diameter, blood flow, or shear rate, but significantly decreased brachial artery wall thickness after 6 and 8 wk (similar in cuffed and non-cuffed arm) and wall-to-lumen ratio after 8 wk (also similar in cuffed and non-cuffed arm)[84].

These findings suggest that in contrast to exercise-induced adaptations of arterial luminal dimensions, which are modified by more local mechanisms and mainly by ESS, wall thickness is affected by rather systemic factors, such as transmural pressure, which is modulated during exercise as a result of generalized changes in blood pressure. The interest in wall remodeling has been due to its use as an index of pre-clinical atherosclerosis and estimation of cardiovascular risk. Regarding the time period required for these adaptations, studies have reported that the effects of exercise on atherosclerosis of the carotid artery may require intensive or prolonged exercise, whereas aerobic exercise decreases femoral, popliteal, and brachial artery intima-media thickness in a relatively shorter period[85]. Therefore, a decrease in arterial wall thickness in athletes and healthy young subjects should not necessarily be considered synonymous with a decrease in cardiovascular risk, but as a physiological impact on wall remodeling with yet unknown long-term health implications (Figure 1)[14,86].

EXERCISE AND CORONARY ARTERY DISEASE

Exercise is well known to have a major role in both primary and secondary prevention of CAD, while regular physical activity of 150 min/wk reduces the risk of numerous chronic diseases and decreases cardiovascular mortality[4,9,10,22,87]. In patients with symptomatic CAD, exercise augments physical performance and raises the angina threshold. Endurance exercise has also been shown to attenuate the extent of ischemic ST-segment depression during exercise and decrease perfusion defects on scintigraphy, indicating a possible enhancement in myocardial perfusion[88,89]. The great benefits of exercise are also demonstrated by the fact that physical exercise in selected patients with CAD leads to higher event-free survival and exercise capacity at lower costs compared with percutaneous coronary angioplasty, reflecting the impact of exercise on the whole arterial tree and not only a single location[90].

Several mechanisms have been proposed to explain the exercise-induced benefits in patients with CAD. These include decreased progression (or regression) of coronary plaques/lesions in CAD, recruitment of collaterals, enhanced blood rheological properties, and improvement of endothelial function and coronary blood flow, as well as enhancement of vascular smooth muscle cell function[22,23,91].

Decreased progression or regression of atherosclerotic lesions

Early investigations indicated that the extent of myocardial perfusion was associated with the magnitude of coronary stenosis depicted by angiography. There is evidence that exercise induces enlargement of conduit coronary arteries in normal subjects, and reduces the development or even causes regression of atherosclerotic lesions in coronary arteries in animal CAD models[74,76,77]. Many studies have been conducted to document the regression or decreased progression of atherosclerotic lesions[92,93].

Experimental studies provided controversial results regarding the effect of exercise on reducing the development of coronary artery atherosclerosis or decreasing lesion progression. However, more recent experiments suggest that although exercise has cardio-protective effects and reduces the risk for cardiovascular disease, it may not inhibit progression or reverse coronary artery disease according to angiographic measures of lesion area[91,94,95]. In addition, Kim *et al*[96] studied veteran marathon runners and reported increased prevalence of coronary artery plaques among those with exercise-induced hypertension, thereby suggesting that exercise-induced hypertension could be a novel risk factor for coronary artery plaque formation.

Several randomized trials in humans evaluated angiographically the impact of exercise and investigated whether exercise has a direct effect on the extent of CAD[97-99]. However, findings derived from these studies need to be carefully interpreted since exercise is only one component of lifestyle and medical interventions.

In the Stanford Coronary Risk Intervention Project, the main angiographic outcome was the rate of change in the minimal diameter of diseased segment. Multifactor risk reduction slowed down the progression of CAD; the rate of narrowing of coronary lesion was 47% less than for subjects in the usual-care group[98]. Studies on the impact of exercise and low-fat diet on coronary morphology and myocardial perfusion found that despite the progression of CAD, patients participating in physical exercise and low-fat diet were characterized by lower stress-induced myocardial ischemia and improvement of myocardial perfusion[100]. In the long-term, when patients were reevaluated 6 years later, in the intervention group, the progression of coronary stenoses had a significantly slower rate than in the control group, and that effect was mediated by chronic physical exercise[97].

The Lifestyle Heart Trial demonstrated that lifestyle changes may induce regression of coronary artery atherosclerosis after only 1 year according to the average percentage diameter stenosis, whereas in the control group there was progression of coronary lesions[101]. After 5 years, these lifestyle changes continued to have impacts on CAD in the experimental group, since further regression of coronary lesions was documented, whereas progression of coronary atherosclerosis continued in the control group[99]. In addition, it appears that physical inactivity is considered as a significant atherosclerotic risk factor and accelerates atherosclerosis development[102]. Additionally, there have also been reports on the potential of different levels of regular–leisure time–exercise to enhance cardio-respiratory fitness and retard progression of (or reverse) CAD. Patients in the exercise intervention group have exhibited an increase in oxygen uptake and in peak exercise while a decrease in the respective parameters was observed in the control group. Decreased progression or regression of CAD lesions was observed, only when CAD patients could sustain a high level of leisure time physical activity for 1 year[103]. Nytrøen *et al*[104] investigated the effect of high-intensity interval training on cardiac allograft vasculopathy in heart

transplant recipients. They demonstrated that 1 year of exercise training resulted in significantly lower atheroma volume (assessed by intravascular ultrasound) compared with the control group. A recent review provides recommendations to physicians regarding high-intensity interval training (*i.e.* short bouts of high-intensity submaximal exercise interspersed with rest periods) which has become very popular among patients following cardiac rehabilitation programs[105]. In addition, low-volume high-intensity interval training (typically involving less than 15 minutes of high-intensity exercise per session) is a time and energy efficient way of exercise and leads to similar or even greater cardiorespiratory fitness and cardiac function enhancement when compared to traditional ways of aerobic exercise[106].

Exercise may have a greater impact on CAD progression or regression following treatment with percutaneous coronary intervention (PCI) and stent implantation. Diameter restenosis after PCI was significantly higher in untrained compared with trained patients. In addition, myocardial perfusion of patients with angiographic restenosis was enhanced only in the exercise group[107]. Studies in a porcine PCI model suggest that exercise significantly decreases the extent of neointimal hyperplasia lesion and restenosis[108]. A recent meta-analysis demonstrated that rehabilitation exercise programs (including cycle ergometer, jogging, climbing, swimming and treadmill) reduced the incidence of coronary artery restenosis following PCI in patients with CAD[109]. A possible explanation for this beneficial impact of exercise is that coronary hemodynamics are altered by interventional procedures and exercise bouts generate more beneficial "mechanical" signals in the walls of these arteries[91].

Atherosclerotic lesion composition

Experimental studies have shown that moderate physical exercise reduces the bulk of coronary lesions and spontaneous atherosclerotic plaque rupture leading to prolonged survival[110]. Exercise alters the extracellular matrix composition of the neointima in animal PCI models and decreases neointimal proliferation, which may have a significant impact on preventing restenosis following coronary angioplasty[108]. Differences in the intima/media ratio were observed after exercise, as well as higher collagen and elastin contents of atherosclerotic plaques were detected in exercise groups. Lower macrophage concentration in the atherosclerotic plaques has also been found in the exercise group. Furthermore, a significant decrease in MMP-9/TIMP-1 (matrix metalloproteinases to tissue inhibitor of matrix metalloproteinases) ratio, which has an important role in the atherosclerotic plaque vulnerability, has been reported after exercise[111]. The latest studies support the idea that physical exercise may convert a vulnerable thin-cap atheroma to a more stable lesion, less prone to rupture, which can reduce cardiac mortality[91].

Collaterals recruitment

Studies in animals suggest that exercise stimulates coronary collateral development [112-114]. Endothelial progenitor cells are considered to initiate neovascularization in response to ischemia after myocardial infarction; a significant increase of endothelial progenitor cell proliferation and function has been observed in mice both with and without myocardial infarction in the exercise group[111,115]. However, there are some contradictory data that report no development of coronary collaterals in dogs with normal coronary arteries[116,117]. The effect of physical exercise on collateral vessel growth in humans is also disputable. Patients with ischemic heart disease and left ventricular systolic dysfunction who have been randomized to exercise and control groups demonstrated that there is enhanced perfusion and contractile response to dobutamine, which were correlated with an increase in coronary collateralization in the exercise group[118]. Zbinden *et al*[119] demonstrated that a 3-month endurance exercise training program enhanced coronary collateral supply to normal vessels, as well as to previously stenotic arteries with percutaneous intervention in patients referred for diagnostic coronary angiography due to chest pain or positive treadmill exercise test. However, there are many angiographic studies conducted at rest in patients with CAD that did not confirm this hypothesis[120,121]. A randomized trial including patients with CAD did not show any significant effect of exercise on collateral formation after 1 year, although progression of CAD was significantly slowed in the intervention group[122].

Blood rheological properties

Abnormalities of blood rheological properties are an independent risk factor for cardiovascular disease, and may contribute to athero-thrombogenesis. However, there

are limited literature data about the effect of exercise on blood rheological properties. Recent studies suggest that blood becomes more dilute because of expansion of blood volume as a result of exercise training. It has been reported that this hypervolemia and blood dilutional effect may contribute to enhanced cardiac stroke volume during exercise[123]. Blood rheology may be enhanced after regular physical exercise since different experimental approaches, including regular exercise, demonstrate a decrease of blood viscosity[124]. However, blood rheology may also remain unaffected in patients with CAD and heart failure[125]. Further studies are necessary to determine the possible association between exercise and blood rheological profiles, especially since the improvement of blood viscosity remains an interesting therapeutic option for symptoms relief in patients with CAD; enhanced fluidity may facilitate oxygen delivery to the exercising muscles because of a reduced resistance to blood flow within the microcirculation.

Enhancement of endothelial function and coronary blood flow

None of the above-mentioned mechanisms fully explain the beneficial effect of exercise on cardiovascular mortality and myocardial perfusion, as well as the major role that exercise has gained in cardiac rehabilitation. During the last two decades, endothelial dysfunction has been correlated with major risk factors for CAD, and identified even before coronary stenoses are visible. Endothelial dysfunction is considered a significant predictor of coronary adverse events and has a great role in myocardial ischemia. Coronary endothelial function depends on NO bioavailability, the balance of which is disrupted in CAD. The impairment of NO production, in addition with an increase in oxidative stress, induces the loss of endothelial cells by apoptosis and the deterioration of endothelial function, leading to paradoxical vasoconstriction and myocardial ischemia[18,22,126]. Exercise attenuates paradoxical vasoconstriction in patients with CAD and leads to improvement of endothelial function as it restores the disrupted NO balance.

Patients with CAD are characterized by functional alteration of circulating progenitor cells, which maintain the integrity of the vasculature. Exercise restores the regenerative capacity of circulating progenitor cells in cardiovascular disease and prevents further impairment of vessels vasomotion. A recent meta-analysis demonstrated increased levels of endothelial progenitor cells into the peripheral blood of patients with cardiovascular disease following exercise training protocols[127]. As a consequence, exercise enhances vasodilator capacity in different vascular beds and improves myocardial perfusion in the absence of changes in baseline coronary artery diameter[18,126,128].

Exercise in patients with CAD may enhance coronary endothelial function. To investigate this hypothesis, patients with coronary endothelial dysfunction (according to abnormal acetylcholine-induced vasoconstriction) were randomized to an exercise or a control group. Coronary vasoconstriction in response to acetylcholine was significantly attenuated and adenosine-induced flow-dependent vasodilation was improved after physical exercise, which indicates that exercise had beneficial impacts on the endothelium of epicardial conduit vessels[23]. In addition, exercise induces increases in coronary blood flow reserve, as assessed by adenosine infusion, indicating augmentation in vasodilator capacity of resistance coronary vessels. A recent meta-analysis studied the long-term effects of aerobic exercise in patients with coronary artery disease, suggesting a significant enhancement of vascular vasomotor function and coronary flow velocity reserve[129]. Patients with CAD following a 6-month aerobic exercise training program had higher peak response to acetylcholine when they performed high-frequency exercise compared with low frequency cardiac rehabilitation programs[130]. In addition, a 2-wk twice daily aquatic endurance plus calisthenics exercise training program in patients with a recent myocardial infarction or revascularization intervention improved both aerobic exercise capacity and vascular endothelial function[131]. Kollet *et al*[132] conducted a randomized pilot study and enrolled post-myocardial infarction patients undergoing PCI who performed a 30-min moderate-intensity aerobic training program. This group of patients demonstrated enhanced endothelial function as determined by improved FMD of the brachial artery after each exercise period. On the contrary, prolonged sitting leads to significant deterioration of vascular function in the lower limbs. However, this deleterious effect on FMD may be reversed by "sitting interruption" strategies including simple resistance and aerobic activities[133]. All these observations suggest that exercise reduces stress-induced myocardial ischemia and improves endothelium-dependent coronary vasodilation in patients with CAD[23]. Patients with newly diagnosed CAD and improved FMD after 6 mo of optimized therapy for reducing cardiovascular risk factors had a lower rate of adverse cardiac events (10% *vs* 26%, $P < 0.01$) during 3 years

of follow-up, while persistent impairment of endothelial vasomotor function was an independent predictor of adverse outcomes[134].

Exercise does not quickly restore endothelial function to normal levels; restoration of normal endothelial function may require more extended exercise[23]. Improvement of vascular endothelial function of conduit and resistance coronary vessels may occur shortly after the beginning of exercise in patients with CAD; however, augmentation of the capillary bed needs a period of few weeks and collateral formation and regression of coronary lesions requires a much more extended exercise period[22].

The vasodilator response of epicardial arteries to nitroglycerine-induced endothelium-independent coronary vasodilation is not significantly affected following exercise. However, there is evidence that epicardial coronary arteries of highly trained middle-aged endurance runners demonstrate greater dilating capacity to nitroglycerin compared with inactive individuals. Thus, it is possible that high intensity endurance training over a long period may be necessary to enhance endothelium-independent dilation capacity of coronary vessels in patients with CAD[76].

In the majority of cases, the positive impact of exercise is limited to the function of the endothelium, whereas smooth muscle function stays unaltered. However, some studies report that enhancement of smooth muscle function is possible to occur but in more severe disease. Thus, one can speculate that there is a stepwise process of dysfunction and amelioration which begins with the endothelium and migrates to the remaining layers of the vessel wall[135].

CONCLUSION

Cardiovascular disease is closely related to local hemodynamic factors. Exercise has direct effects on the vasculature *via* the impact of ESS on the endothelium, leading to decreased atherosclerotic risk. Exercise contributes to maintaining a normal phenotype of arterial endothelial cells which is the result of changes in hemodynamic factors, ultimately leading to beneficial effects. Different patterns of blood flow and ESS exert variable stimuli on the endothelium and result in improved NO bioavailability and adaptations in vascular function and structure. Regarding arterial structure, wall thickness may also be influenced by systemic factors. In patients with CAD, exercise has multiple beneficial effects beyond endothelial function since it contributes to the conversion of vulnerable atherosclerotic plaques to a more stable phenotype, may enhance the recruitment of collaterals, and improves the blood rheological properties. These effects translate to reduced cardiac mortality indicating the value of exercise in cardiac rehabilitation programs. Further research is required to investigate and clarify the molecular mechanisms underlying the structural and vascular adaptations. Finally, it is a great challenge to study the different vascular adaptations which are induced by each type of exercise as well as which training program is most effective for each population group.

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REVIEW

Stent visualization methods to guide percutaneous coronary interventions and assess long-term patency

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Abstract

Evaluation of acute percutaneous coronary intervention (PCI) results and long-term follow-up remains challenging with ongoing stent designs. Several imaging tools have been developed to assess native vessel atherosclerosis and stent expansion, improving overall PCI results and reducing adverse cardiac events. Quantitative coronary analysis has played a crucial role in quantifying the extent of coronary artery disease and stent results. Digital stent enhancement methods have been well validated and improved stent strut visualization. Intravascular imaging remains the gold standard in PCI guidance but adds costs and time to the procedure. With a recent shift towards non-invasive imaging assessment and coronary computed tomography angiography imaging have shown promising results. We hereby review novel stent visualization techniques used to guide PCI and assess stent patency in the modern PCI era.

Key Words: Percutaneous coronary intervention; Stent visualization; Stent underexpansion; Quantitative coronary analysis; Digital stent enhancement; Intravascular ultrasound; Optical coherence tomography; Coronary computed tomography angiography

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Core Tip: Evaluation of acute and long-term percutaneous coronary intervention (PCI) results remains challenging. We hereby review current available tools for guiding and assessing PCI results.

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INTRODUCTION

Atherosclerosis is a slow-progressing multifocal immunoinflammatory disease of medium and large-sized arteries[1]. Exposure to established risk factors triggers an oxidative response leading to the formation of fatty streaks within the vessel wall. Phagocytosis of these lipid rich proteins by macrophages induces cell apoptosis leading to cellular debris which, along with necrotic endothelial and smooth muscle cells, form the principal constituent of the lipid-rich plaque core. The deposit of calcium and phosphate-rich hydroxyapatite crystals occurs as a macrophage-mediated response to oxidation and endothelial dysfunction[2]. Coronary artery disease (CAD) secondary to atherosclerosis remains the most common cause of death across the globe, imposing a major health and economic burden on nations[3,4]. Despite major technological and therapeutic advances, the prevalence of CAD is expected to continue to rise secondary to an increase in the aging population[5]. Coronary artery angiography (CAG), despite being invasive, remains the gold standard technique to assess significant coronary artery disease and to guide percutaneous coronary intervention (PCI). PCI reduces major cardiac events in acute coronary syndrome events[6] and improves the quality of life in chronic coronary syndrome[7]. The first human cardiac catheterization dates back to 1929 when Dr. Forssmann[8] auto-measured the pressure in his cardiac chambers using a urinary catheter. Cournand *et al*[9] and Nossaman *et al*[10] later developed right heart catheterization with a standard diagnostic tool, and in 1956, along with Dr. Forssmann[8], were awarded the Nobel Prize in Medicine for their work. Dr. Seldinger[11] developed his safe percutaneous catheterization technique in 1953 followed by Dr. Sones[12] who performed the first selective coronary angiogram in 1958. In 1964 the first peripheral angioplasty was performed by Drs. Dotter and Judkins[13]. Since then, PCI has undergone a rapid technological evolution, beginning with Turina *et al*[14] in 1979 who developed the initial coronary balloon angioplasty, later referred to as plain old balloon angioplasty (POBA). POBA was the first step for modern coronary intervention and was limited by the risk of acute thrombosis (3%-8%)[15,16] and early vessel recoil (5%-10%), along with a high rate of restenosis (33%)[17-22]. Nevertheless, POBA paved the way to the first coronary stents that were implanted in 1986 by Sigwart *et al*[23]. Although the recent ISCHEMIA trial did not show evidence of a reduced risk of ischemic cardiovascular events or death for an initial invasive strategy as compared with optimal medical treatment among patients with stable angina and moderate or severe ischemia[7], only 4% of contemporary real-world patients would be eligible for the trial[24]. Using coronary physiology guidance, PCI also decreases cardiac death and myocardial infarction in chronic coronary symptoms[25]. Several trials (BENESTENT, STRESS, CAVEAT) have laid the cornerstone upon which angiographic guidelines have been proposed, and coronary stent implantation after PCI has been shown to improve short- and long-term clinical outcomes[26-28]. However, a coronary stent should meet numerous design criteria in order to fulfill its function, including the fact that the stent platform must be radio-opaque enough to provide the required visibility for correct placement and proper expansion in order to ensure successful stent deployment[29,30]. In addition, a stent must have a narrow profile when collapsed for easy deliverability[31,32]. Strut thickness has been a key element of stent design, with thinner struts associated with greater deliverability. Several studies have also shown a lower rate of restenosis associated with thinner stent' struts[31,33,34]. Consequently, a move towards thinner struts stents has been made, with current stent strut thickness being between 60-100 μm. Initial stents were made of nitinol and were self-expandable. These were later replaced by balloon expandable stents.

Atherosclerosis is an intimal focal disease-causing connective tissue proliferation and lipid accumulation. In order to preserve their lumen, atherosclerotic vessels dilate in a remodeling response and only after reaching the capacity of this response does stenosis occur. These facts imply that an accurate assessment of coronary artery stenosis and reference diameter is of major importance. Lesion severity evaluation by visual estimation remains subjective and has been shown to be inadequate secondary to a high degree of intra-observer and inter-observer variability[35]. In fact, the lumen in eccentric plaques alters in shape and size, and the reference segment (deemed as normal) may be either narrowed or dilated. For decades, PCI guidance and results have been evaluated by visual assessment, nevertheless, angiography alone does not provide sufficient information in several scenarios presenting a major risk factors of stent thrombosis, such as stent fracture, stent malapposition or stent overlap[29,36,37]. To study PCI efficacy and results, several carefully acquired coronary angiographic films need to be interpreted in detail pre- and post-intervention, as well as at follow-up. Alternative imaging techniques have been developed to overcome these

limitations. We hereby review the coronary stent visualization methods currently used for the assessment of PCI results.

QUANTITATIVE CORONARY ANALYSIS

Since visual assessment of lumen diameter and stenosis is scarcely sensitive, quantitative coronary analysis (QCA) was first described for a theoretical objective evaluation of coronary artery stenosis and lumen diameter in clinical settings. Since then, the field has grown substantially, with several methods and algorithms being developed since the late 1970s[38]. The European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions Task Force on the Evaluation of Coronary Stents in Europe recommended a mandatory assessment by offline QCA core lab analysis in case of comparative studies[39], and QCA was endorsed by the Academic Research Consortium 2[40]. QCA relies on coronary angiography in order to obtain objective parameters and can also be used to assess immediate and long-term PCI results[38]. It is based on the use of dedicated software allowing the precise determination of specific parameters in an operator-independent manner and can serve either a clinical purpose (on-line during a procedure) or a research one (off-line)[41]. With ongoing research, X-ray imaging has significantly progressed, leading to many available computer-integrated applications that allow the quantification of coronary stenosis leading to QCA validation and incorporation in various systems[42]. Multiple validated software are currently available on the market, among which the most widely used are CAAS II (PIE Medical, Maastricht, The Netherlands) and QAngio XA (Medis, Leiden, The Netherlands)[43-45].

QCA requires an optical magnification of the angiographic image. A digital cineangiogram is generated on an image processor after image acquisition. Using an integrated software and analysis system, digital quantification of selected frames can be easily performed with or without magnification. After digitalization, and prior to computer analysis, the images are stored in a specifically designed image processing system.

The real challenge of QCA is the selection of the coronary angiography sequence with a minimal foreshortening and minimal overlap with nearby structures after intracoronary nitroglycerine administration in order to reduce any vasospasm. In addition, the accuracy and reliability of the analysis is improved by increasing the distinction between the contrast-filled coronary artery and the background (best achieved while the patient is in deep inspiration). A frame including a completely contrast-filled catheter is first selected and a central line is hand-drawn along the tip of catheter. Once the image has been acquired and processed, boundary delineation within the area of interest is performed by the computer. QCA usually focuses on one or more coronary segments and is generally carried out in the case of an ambiguous coronary lesion. The area of interest can be identified automatically by the computer software or manually. The operator indicates the window of interest, an approximation of the borders or points along the vessel's central line[46,47]. The software automatically recognizes its margins and performs calibration. In order to derive quantitative information from the analysis, a calibration converts measured pixels to *in vivo* millimeters by using the contrast-filled known catheter diameter as a reference standard or using an automatic calibration obtained from recent systems[48]. By assuming a homogeneous distribution of contrast within the vessel lumen, the errors within the edge definition are minimized in eccentric lesions by densitometry[38]. Then, an appropriate frame that includes the segment of interest is selected during end-diastole when coronaries are least subjected to myocardial contractions. Similar to the calibration procedure, a central line is drawn in order for the software to generate automatic contours. The frames are then automatically transferred to a digital lossless compression file that generates a series of diameters and parameters along the vessel line expressed in millimeters and percentages. This also allows an automatic reconstruction of the vessel lumen and interpolates the diseased segment to the proximal and distal references considered disease-free using an algorithm based on the calculation of mean diameter values at different points along the segment of interest (Figure 1). Edge definition, although more important than quantification, is harder to accomplish[48]. The difference in luminal cross-sectional area can then be compared between normal and diseased segments in addition to the assessment of PCI results. The analysis can also be performed after stent implantation in order to compare several parameters pre- and post-stent implantation. Hence, QCA permits the evaluation of the minimal lumen diameter (MLD, the smallest diameter within the

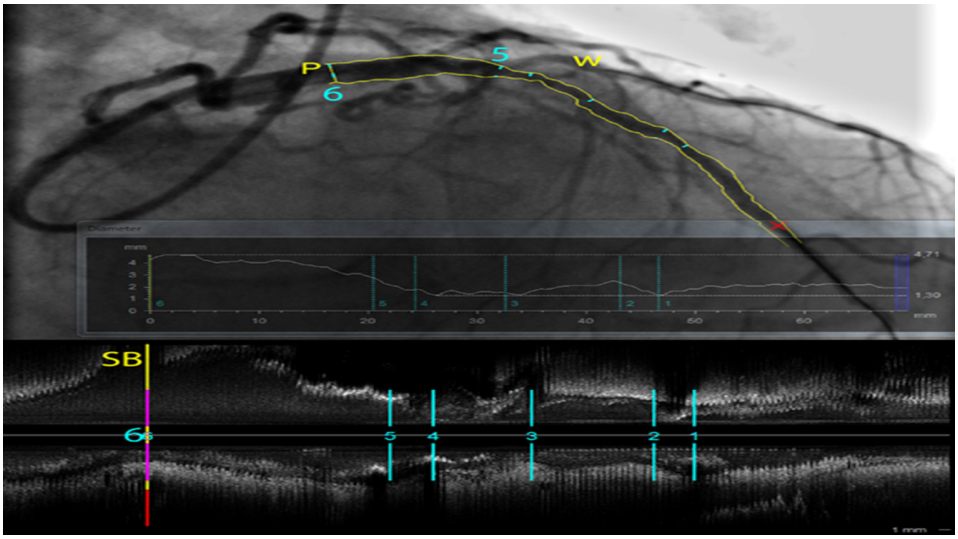


Figure 1 Quantitative coronary analysis analysis (CAAS software, Pie Medical Imaging) of a long stenosis in a left anterior descending artery. The vessel borders are automatically detected and diameters are plotted along the vessel centerline. Different measurements (1-6) are shown on a co-registered intravascular ultrasound (IVUS) pull-back longitudinal view at the bottom. At P (6), the ostium free of disease of a large side branch (first diagonal artery) is better characterized in the 3D volume data from the IVUS pull-back than on the overlapping structures of the angiogram. (W) shows a wire in the second diagonal branch, illustrating the inherent limitations in the interpretation of a coronary angiography that is only a 2D shadow projection of a complex 3D coronary tree filled with contrast that requires multiple views in different projections.

segment studied), the reference vessel diameter (RVD, averaged diameter of the coronary assumed disease-free), the diameter stenosis percentage, the lesion length (LL, measured by two points where the margins change direction), the acute gain (post-procedural MLD-pre-procedural MLD), and late loss (post-procedural MLD-follow-up MLD for example at 6 mo). On-line digital systems and off-line computer processing systems have become widely available. These systems facilitate the accurate clinical analysis of vessel diameter, percent stenosis, stent deployment, and other endovascular interventions. One of the major coronary angiography drawbacks is its two-dimensional luminogram of a three-dimensional structure, as well as vessel overlap and foreshortening during acquisition. Furthermore, QCA is influenced by the frame selection, vessel movement, end-diastolic phase and calibration[49,50].

THREE-DIMENSIONAL QCA

Currently, 2-dimensional QCA remains the most commonly used and validated technique despite its drawbacks. However, as more complex lesions are treated more frequently, 3-dimensional QCA analysis software is a valuable tool. Three-dimensional QCA is based on standard 2-dimensional angiography images obtained in two views at least 30 degrees apart and with as much minimal vessel overlap. Several 3D QCA programs are currently available, among which, the most commonly employed and validated are CAAS 5 (Pie medical Imaging, Maastricht, The Netherlands) and CardiOp-B (Paieon Medical Ltd. Park Afek, Israel)[51-53]. Although these applications defer in their respective calibration methods, nevertheless they allow a better understanding and visualization of coronary anatomy and help the operator find the optimal working angle[54,55]. Three-dimensional QCA software also allows the assessment of bifurcating lesions and helps choose the appropriate treatment strategy [56].

Although 3-dimensional QCA programs are readily available and have already been validated[55,57,58], they fail to improve accuracy by resolving the problem of vessel foreshortening. Several comparative studies between 2-dimensional and 3-dimensional QCA have led to mixed results with regards to the accuracy of this technology[55,57,59-61].

Visual assessment of coronary lesions tends to underestimate < 50% stenoses and to overestimate those > 50%[62,63], while QCA tends more to overestimate lesions < 50% than those between 50% and 75% and underestimate stenoses > 75%[41,64]. QCA may be easily and rapidly employed in everyday clinical practice to objectively, precisely and independently assess coronary lesion severity. Hence, QCA may direct treatment

of a stenosis if a functional assessment is not available. Additionally, QCA instantly assesses objective parameters, such as RVD and lesion length, allowing for a more precise choice of treatment material as well as PCI result assessment. QCA has also played a pivotal role in clinical research through its reproducibility and independence. It has become a fundamental core laboratory tool for the off-line assessment of devices and/or the progression of atherosclerosis following pharmacological therapies[65].

Although QCA has been around for more than 30 years now, it still presents multiple limitations. Nevertheless, it remains an easy-to-use tool, both when used in clinical research and as a complementary tool in practice alongside angiography.

DIGITAL STENT ENHANCEMENT

Stent positioning and deployment is carried out under angiography guidance and hence relies on the radiopaque nature of the material used for visualization. Long-term safety concerns of implanted coronary stents have led to increased research on the improvement of stent technology. It has been stipulated that thinner struts are associated with a better outcome in drug-eluting stents (DES). The ISAR STEREO trials have identified thicker struts thickness to be an independent predictor of in-stent restenosis[33,34,66]. Furthermore, the use of thinner-strut stents has been associated with a significant reduction in myocardial infarction[67]. In addition, inadequate stent deployment and underexpansion has been shown to be a major factor for stent thrombosis associated with a high death rate and non-fatal myocardial infarction[29,68]. With recent advancements in stent design technology, DES has become the standard-of-care for patients with acute and chronic coronary syndromes. The first DES consisted of a stainless-steel backbone rendering them radiopaque with good visibility on angiography. However, given the inverse relationship between strut thickness and fibrous hyperplasia, newer second-generation DES have switched to cobalt chromium or platinum chromium, along with a trend towards thinner struts decreasing stent radiopacity, all while preserving radial strength. Although the incidence of stent thrombosis has decreased during the first year after implantation as compared to BMS, its rate remains high[69]. Stent architecture assessment is also important in order to assess PCI results and complications. With the trend toward the use of lower X-ray power during procedures at 7.5 frames per second, and despite the use of radiopaque materials in stent construction, the visualization of stents remains challenging and insufficient for stent expansion assessment. Stent visibility is further altered with stent motion within the sequence as well as in larger patients due to X-ray scattering.

Since the early 2000s, a new image processing technique called digital stent enhancement (DSE) has been developed, specifically tailored for stent visualization. In order to produce an enhanced image of an implanted stent, DSE uses a motion-corrected X-ray image sequence making it reliable during the normal workflow during coronary angioplasties[70]. Due to the ease of use of this technique, several manufacturers have become interested in developing and validating new systems.

Although they cannot bring direct information regarding stent apposition onto the vessel wall, DSE systems can provide relevant images for assessing deployment irregularities, lesion treatment, and potentially measuring stent expansion[71]. Several case reports and case series have validated the use of the different DSE systems in different clinical settings. Additionally, a decrease in late loss and binary restenosis, along with a lower incidence of target lesion revascularization at 6 and 12 mo respectively, were found in patients where DSE was used as compared to patients treated without DSE[72].

StentBoost Subtract System® (Philips Healthcare, Best, The Netherlands) is currently the most used technique and is extensively validated[73-77]. StentBoost Subtract System has also been shown to have high enough specificity as compared to intravascular imaging[73,78]. StentViz (GE Healthcare, Milwaukee, WI, United States), StentOptimizer (Paieon, Rosh Haayin, Israel) and ClearStent (Siemens Healthcare, Munich, Germany) have also been studied and validated[79-81]. Nevertheless, these systems all depend on the X-ray angiographic system vendor. StentEnhancer (Pie Medical, Maastricht, The Netherlands) is a recently added DSE with the advantage of being vendor independent.

DSE improves the fluoroscopic image quality by reducing the influence of background noise. It consists of a short X-ray sequence where the stent is moving with each heartbeat and during breathing. This is based on the fact that over a whole sequence, the sum of the images of the stent is displayed with a much higher contrast

to noise ratio. Hence, the DSE algorithm "tracks" the stent motion along the sequence and automatically integrates the value of the stent' pixels along their trajectories. As a result, the overall sum of the pixels is displayed in an enhanced still-image.

After stent deployment, the stent delivery balloon is kept in place deflated and cineacquisition of the stented segment is performed without contrast injection. Stent-motion is detected using the two balloon radiopaque markers[70,82]. Forty-five frames are acquired and automatically transferred to a workstation where software corrects for motion-compensated temporal averaging[83,84]. Immediately after, an enhanced image of the stent is displayed with an improved resolution and a superior signal-to-noise ratio (Figure 2). These steps may be repeated with a post-dilation balloon. A modified DSE technique, aimed at visualizing the stent in relation to the vessel, is also available. This differs from the abovementioned technique by the contrast injection [84]. The resulting image can be used for stent expansion assessment, visually and quantitatively, much like during QCA analysis[85-87]. Its ease-of-use and availability, along with the high-quality stent images delivered, have led to DSE being an important alternative or complement to stent visualization techniques during PCI. DSE systems are rapid, cost-effective, do not require contrast injection and can be used during complex PCI cases, such as ostial or bifurcating lesions[74,88]. However, an increase in radiation exposure has been reported, but this had no significant impact on patient radiation dose[89].

INTRAVASCULAR IMAGING

Coronary angiography only provides a planar, 2-dimensional evaluation of the contrast-filled coronary lumen and fails to evaluate the atherosclerotic plaque located within the arterial wall, hence often underestimating the degree of intraluminal stenosis[35]. The addition of quantitative digital assessment (QCA and DSE) improves the overall coronary assessment but still presents pitfalls. In fact, extensive coronary disease with positive remodeling may appear "normal", leading to a false feeling of reassurance. This is especially apparent with patients presenting with extensive disease on computed tomography angiography but found to have minimal disease on angiography. In order to bypass these limitations, the idea of intravascular imaging emerged in 1971, thanks to Bom *et al*[90] in Rotterdam, and Yock *et al*[91] later recorded the first greyscale transluminal ultrasound images of human arteries. Since then, major breakthroughs have been achieved including intravascular ultrasound (IVUS) radiofrequency tissue characterization and optical coherence tomography (OCT). Intravascular imaging has the advantage of capturing plaques from close proximity. These techniques have been a valuable tool in everyday practice shedding light on whether the plaque is at risk of progression, vessel diameter size, acute PCI results and reasons behind target lesion failure and revascularization.

IVUS

IVUS imaging relies on the properties of ultrasound waves which are produced by the oscillatory movement of a transducer[92]. A piezoelectric crystal inside a transducer, attached to a catheter, produces high frequency sound waves which penetrate tissue, reflect off vascular structures and return to the transducer, which then transmits the information to a dedicated system for processing. These catheters are 3.2 to 3.5 French in size and compatible with 5 French guiding catheters over 0.014 in guidewires.

The first ultrasound imaging catheters, designed by Bom and colleagues, were used for cardiac chamber and valve assessment. It was not until 1988 that the first intracoronary images were recorded[93]. Since then, IVUS has been extensively used and developed, and has been the cornerstone of major interventional trials, from the bare metal stents era to the newer bio-absorbable stents (BVS). In addition, IVUS has allowed a better understanding of CAD progression, vessel reaction to PCI, as well as long- and short-term vessel remodeling after stent implantation.

In order to increase radial resolution, IVUS catheters use higher frequencies than non-invasive echocardiography, typically between 20 and 60 MHz. Resolution increases with increased frequency, however penetration decreases. Currently, 2 types of IVUS catheter designs exist on the market: a solid-state, phased array one and a rotational, mechanical one. Solid-state catheters (Volcano, Philips Healthcare, Best, The Netherlands) consist of multiple transducer elements mounted circumferentially at the tip of the catheter. The phased-array transducers are activated in groups in a rotational

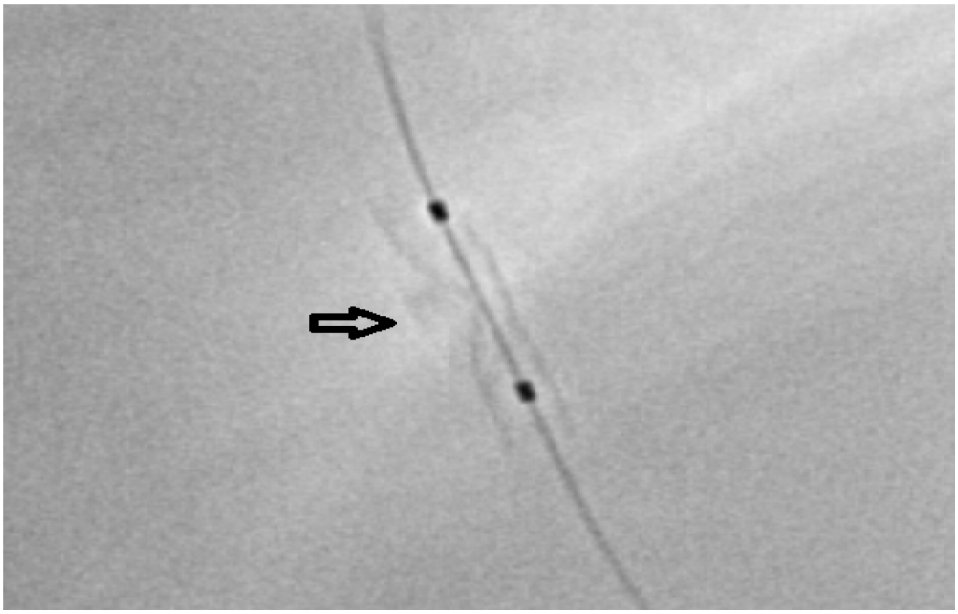


Figure 2 Digital stent enhancement image using StentBoost Subtract System (Philips Healthcare, Best, The Netherlands) showing stent underexpansion. The two balloon markers are visible (two black dots). The calcifications responsible for the underexpansion are clearly visible (arrow).

manner. The collected information is then transferred to a computer system which computes a cross sectional image of the vessel. Volcano catheters also offer kind of virtual histology, (VH-IVUS). The advantage of a solid-state system is its prepackaged ease of setup along with the lack of guidewire artefacts. This is because the catheter is advanced on the wire itself, meaning that there are no non-uniform rotational distortion (NURD) artefacts, which usually result from mechanical binding, as in this case there is no friction on the catheter. On the other hand, solid-state catheters have a low resolution, running at 20 MHz, and a blind spot all around the imaging ring, with a need for masking this "ring down" zone by digital subtraction before acquiring images. Rotational systems (Boston Scientific, Santa Clara, CA, United States; Terumo Corporation, Tokyo, Japan; Philips Healthcare, Best, The Netherlands; Acist Medical Systems Inc., Eden Prairie, MN, United States) use a single transducer element at the tip of the catheter rotated by an external motor drive attached to the catheter. Similar to solid-state systems, a cross sectional image is displayed after gathering echoes while the catheter rotates. Rotational systems have the advantage of having a significantly higher axial resolution with transducers up to 60 MHz with a large bandwidth. Nevertheless, rotational system setup is somewhat more cumbersome with the need to flush the catheter. They use a short monorail with, consequently, an artefact of the wire running along the imaging crystal. However, this offers a more stable automated pull-back of the imaging tip inside a sheath for length measurements of vessel structures. In order to perform imaging, the catheter is advanced beyond the area of interest over a 0.014 in. guidewire after a 100-200 mcg intracoronary nitroglycerin injection in order to minimize vasospasm and to have maximal vasodilation. The catheter is then pulled back in order to obtain the desired images either manually or automatically (motorized) at a standardized speed (up to 10 mm/s). Motorized pull-back has the advantage of providing longitudinal information of the area of interest in order to assess lesion length, while manual pull-back provides a more detailed and prolonged view of the area of interest. Regardless of the system used, proper identification of the three histologic vessel layers is critical for an accurate interpretation (Figure 3). The major advantage of IVUS imaging is its ability to see both intraluminal and extra-luminal elements in the vessel (coronary thrombus, edge dissection after stenting, *etc.*). It also allows for accurate and reproducible measurements of several segments of the vessel. In fact, the proximal and distal reference vessel segments can be identified and measured, along with the minimal lumen area (MLA), minimal and maximal lumen diameter, lumen eccentricity, area stenosis, cross section area (CSA), plaque area and burden, and the remodeling index can be computed. IVUS can also guide PCI, evaluate stent expansion, assess side branch compromise, determine the underlying mechanism of stent thrombosis/underexpansion and evaluate tears of the vessel from coronary dissections[94]. Although IVUS presents many advantages, several pitfalls remain. The displayed image relies on the absorption and reflection of

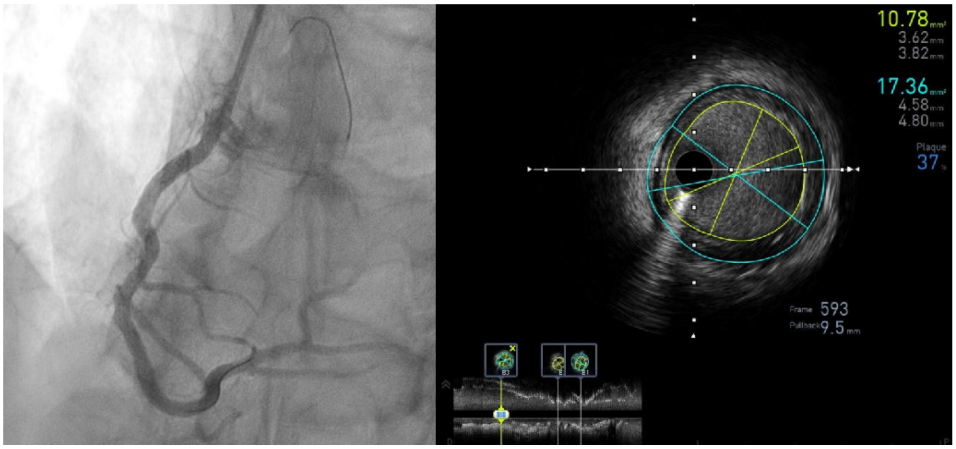


Figure 3 Intravascular ultrasound pull-back of a right coronary artery post stent implantation. Stent expansion is assessed and the minimal lumen area measured in different cross-sections (bottom longitudinal view) while the plaque burden at the distal reference (B3) is shown on the cross sectional frame 593 (lumen area 10.78 mm², vessel area 17.36 mm², plaque burden 37%).

ultrasound waves from tissues and, in the presence of calcium, which is a high reflector, all the ultrasound waves are reflected and do not penetrate beyond the underlying tissue. This reveals reverberation artefacts and shadowing behind the calcium with no possibility to analyze the extent of plaque and vessel structure behind the calcium. A wire artefact during IVUS images analysis may result in shadowing and difficulty seeing beyond the wire. Accurate analysis, especially with longitudinal measurements, can be hindered between systole and diastole secondary to the catheter movement[95]. In addition, blood speckle artefacts increase as blood flow decreases or the transducer frequency increases, hampering the ability to differentiate lumen from tissue, especially in the case of soft plaques and thrombus.

IVUS guided PCI has been shown to increase the choice of balloon and stent size by the PCI operator, increase the length of the stented segment, and increase the minimal lumen diameter and stent CSA at the end of the procedure as compared to angiography alone. Mixed results were found in multiple prospective studies during the bare metal stent era as to whether this increase improved clinical outcome[96-99]. In a meta-analysis, Parise *et al*[100] found a reduced 6-month angiographic binary restenosis with a significant reduction in revascularization rate and major adverse cardiac events in IVUS-guided PCI patients. Several retrospective and prospective studies were conducted during the DES era showing a net benefit of IVUS on overall clinical outcomes[101,102]. Several meta-analyses highlighted the net benefit of IVUS-guided PCI using DES with a significant reduction in major adverse cardiac events, myocardial infarction, target vessel revascularization, target lesion revascularization and stent thrombosis as compared to angiography guided PCI[103-105]. Recently, the 3-year follow-up of the ULTIMATE trial showed a reduction in cardiovascular death, target vessel failure and stent thrombosis in patients who underwent IVUS-guided PCI as compared to patients who underwent angiography-guided PCI alone[106,107]. With the treatment of more complex lesions, IVUS has been shown to improve mortality in left main stenting, probably due to a better stent apposition and lower rate of underexpansion[108-110], as well as in bifurcating lesions in order to predict side branch closure[111]. Moreover, IVUS is currently recommended for evaluating and guiding chronic total occlusion procedures[112,113].

VH-IVUS uses advanced backscatter signal analysis in order to try to characterize plaque composition. VH-IVUS limitations are the lack of thrombus detection and plaque characterization in the presence of calcium shadowing, and a limited resolution.

Despite the introduction of high definition IVUS catheters, the major limitation of IVUS imaging remains its limited spatial resolution, making the assessment of stent-strut tissue coverage challenging.

OCT

OCT is a light-based intravascular imaging technique that provides a high-resolution image of the tissue microstructure by using backscattering and near-infrared light

reflections from a fiber optic wire coupled with an imaging lens while simultaneously being pulled back and rotated. The first OCT clinical application on coronary arteries was reported in 1991 after the addition of transverse scanning[114]. The rapidly evolving technique was named by James Fujimoto and made way to contemporary OCT catheters that use a central light wavelength range of 1300 nm, which limits tissue penetration to 1-3 mm as compared to IVUS. With an axial resolution of 10-15 μm, OCT offers a very detailed picture of the vessel while the imaging optics of the catheter allow for a lateral resolution of 20-40 μm.

The first available OCT systems from LightLab Imaging (Westford, Massachusetts, United States) used an old OCT technology, called time-domain (TD) OCT, based on a broadband light source emitting through a fiberoptic coupler. The main disadvantage of this system was the slow speed of acquisition, which resulted in the need of total vessel flush for a long period. Newer generation OCT systems, termed Fourier-domain OCT (FD-OCT), use a fixed mirror and light is emitted by a "swept laser" source with a variable frequency. This allows for a faster frame acquisition rate (up to 100 frames/s) with only a short vessel flush duration. Continuous flush of contrast fluid is required in order to clear intraluminal blood since blood causes significant signal attenuation. The first FD-OCT was developed by St. Jude Medical (St Jude Medical, St. Paul, Minnesota; United States). It is a 2.5 Fr catheter compatible with 5 Fr guiding catheters. Currently a 2.4 Fr catheter is also available from Terumo (Terumo Corporation, Tokyo, Japan). The OCT catheter is advanced over a 0.014 inch wire to the distal vessel and an automated pull-back is then performed at a rate of up to 20-40 mm/s during short iodinated contrast injection (4 cc/s) in order to clear blood. During pull-back, a long spiral scan is created within less than 3 s in order to map the vessel and create the required frames. The emitted light splits into 2 parts: the first sample arm travels to the patient while the second reference arm travels a predefined distance. The two arms are then collected and an interferometer is used to measure the light reflected (back-scattered) from tissues in order to determine the depth of the tissue (A line). The system then processes the reflected light and computes a very high-resolution image due to the shorter wavelength of light and 3D tissue morphology.

Each image is made up of lines and pixels; the higher the lines/frames ratio is, the finer the image, and the higher the frame rate, the higher the longitudinal resolution. Artefacts associated with OCT include light attenuation from incomplete blood flushing, artefacts secondary to the guidewire, distortion of stent reflections from eccentric wire position (sunflower effect), air bubble artefacts, and stitch artefacts secondary to rapid catheter or wire movements (sew-up effect). These can be minimized through a proper positioning of the guidewire and appropriate contrast injection[115]. Even macrophage accumulation in thin-cap fibroatheroma or small intraluminal thrombi can be seen[116]. Plaque characterization can be achieved by OCT combining backscattering and attenuation measurements[117].

Currently, limited data for OCT-guided vs. angiography-guided interventions are available, while ongoing randomized clinical trials are running. A reduced rate of cardiac death and major adverse cardiac events has been reported in patients who underwent OCT-guided stenting[118], as well as larger final in-stent minimal lumen diameter[119] and a reduction in the number of stents implanted[120]. OCT-guided PCI has also been associated with better clinical outcomes in acute coronary syndrome patients[121,122]. In addition, a better stent coverage at 3 mo was found in OCT-guided PCI chronic CAD patients[123].

OCT delivers high-resolution intravascular images which are used in clinical practice, but mainly in the research field[124,125]. As compared to IVUS, OCT showed comparable stent expansions and comparative efficacy in the ILLUMIEN II and III studies respectively[126,127]. OCT was also shown to have non-inferior clinical outcomes as compared to IVUS in the OPINION[128] study. The latest European Society of Cardiology guidelines have included IVUS and OCT imaging as a class IIa recommendation[129]. Although both imaging modalities share multiple similarities, some controversy remains regarding which modality is to be used in specific cases. The need of contrast injection during OCT imaging tends to be a trigger towards IVUS use in patients with renal failure. The very high resolution of OCT images enables a more detailed evaluation at the endoluminal level and superficial plaques, and better stent implantation short- and long-term results[130]. However, OCT has lower penetration depth as compared to IVUS, which makes larger vessel visualization more challenging, in addition to the external elastic membrane-based approach for vessel sizing. IVUS images are significantly altered by the presence of calcium whereas OCT recognizes calcium plaques as well-demarcated low-intensity structures. The relatively smaller size of OCT may reduce the incidence of coronary spasm, and can identify coronary thrombosis and dissection easily. However, OCT fails to assess aorto-ostial

lesions. Several clinical studies have demonstrated the non-inferiority of OCT imaging as compared to IVUS (OPINION, ILLUMEN III)[127,131].

Co-registration of both OCT and IVUS with angiography has been developed[132] adding to the precision during PCI and reducing the risks of geographic miss[94,115]. An OCT/IVUS hybrid technology (Novasight) has been recently introduced, and further developed by Conavi Medical Inc. (Toronto, Canada), and this was reported in 2018[133]. A second hybrid system is currently under development by Terumo (Terumo, Tokyo, Japan) and is yet to be released.

Intravascular imaging has marked its place during PCI offering multiple benefits over angiography alone. Multiple meta-analyses and registries have proven its improved procedural and clinical outcome. However, intravascular usage rate remains low probably due to the increased cost, time and unfamiliarity of the operators[134]. With increasing PCI complexity, intravascular imaging adds a clinically proven indispensable benefit for successful intervention.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Coronary computed tomography angiography (CCTA) has recently emerged as a precise non-invasive tool for the detection and evaluation of CAD[135,136]. Computed tomography (CT) technology has advanced significantly since its first use, by Sir Godfrey Hounsfield in 1970, followed by the introduction of electron beam computed tomography by Douglas Boyd improving temporal resolution. A major breakthrough came in the 1990s with the introduction of multidetector computed tomography that has the ability of improving a 360° spatial resolution. CT images depict tissue densities and are the product of X-ray attenuation as they pass through tissue. A CT detector measures and converts the X-ray photons exiting the patient into light. This light is then transformed into an electrical signal by a photodiode and converted into a digital signal by a computer system. The image is an overall estimation of the attenuation of X-rays as they pass through tissues of different densities represented by Hounsfield units.

Currently, multidetector computed tomography scanners include 320-detector rings and two X-ray sources, allowing for the acquisition of submillimeter resolution over large volumes in milliseconds. Improvements in detector characteristics have increased the x, y and z axis spatial resolution, which allows for successful imaging of the coronary arteries while reducing radiation dose[137]. Three steps are required to successfully create a CCTA image: data acquisition, reconstruction and image display. Data acquisition involves scanning portions of the heart with each gantry rotation and requires proper patient selection, preparation, appropriate imaging protocols and contrast injection techniques. Effective heart rate control, proper timing of the scan after contrast injection and minimizing patient movement are all crucial during data acquisition. It is therefore advisable for patients known to have arrhythmias to be deferred from CCTA. CCTA has the advantage of visualizing the entire vessel, and can accurately evaluate stenoses severity and plaque morphology.

Along with CCTA already being established for the detection of CAD and confirming the ability of calcium score in providing a prognostic value in multiple large studies[137-139], it is an excellent diagnostic tool for bypass graft imaging. Moreover, CCTA has been validated and used for the assessment of coronary artery stent with recent technical refinements showing negative predictive values >90% for the exclusion of in-stent restenosis[138,140-142]. However, a blooming effect secondary to the stent struts and beam-hardening artefacts remain a challenge for proper evaluation[143,144]. This is also true for patients known to have excessive coronary calcium, as calcifications may interfere with the accurate interpretation of CCTA. Since coronary stenosis alone does not predict the risk of future cardiovascular events, the coronary artery calcium (CAC) score estimates the overall calcification burden and predicts future ischemic events without contrast use. With the introduction of bioresorbable stents (Figures 4 and 5), this set-back has been overcome[145,146]. Contrary to magnetic resonance imaging (MRI), pacemakers and defibrillators do not preclude the use of CCTA, however it should be noted that their leads may create artefacts.

CCTA has been shown to be a better predictor of obstructive CAD compared to traditional functional testing. The EVINCI study showed the superior accuracy of CCTA for the detection of CAD as compared to single photon emission CT (SPECT), position emission tomography (PET), echocardiography and cardiac MRI[147]. The prognostic value of CCTA was also demonstrated in the PROMISE and SCOT-HEART

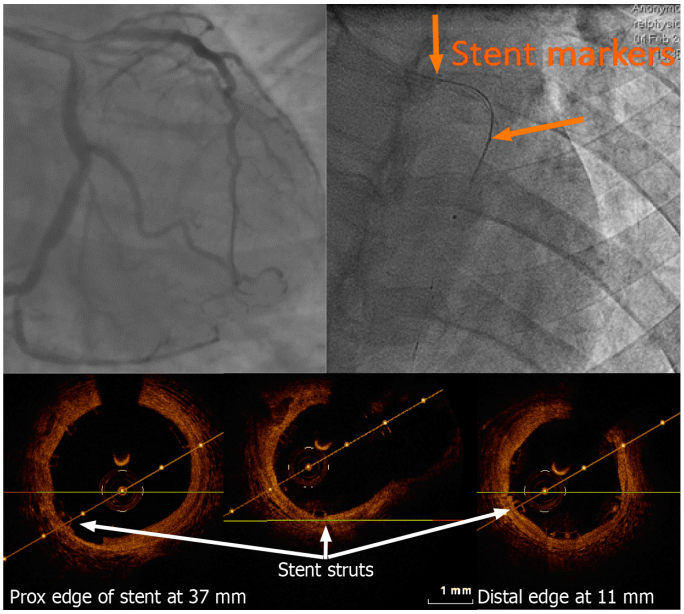


Figure 4 Left anterior descending artery optical coherence tomography pull-back post bioresorbable stent implantation carried out using a 2.7 French imaging catheter with a dedicated workstation (C7 Dragonfly and C7-XR, Lightlab Imaging [Westford, Massachusetts, United States)]. Of note, only the proximal and distal markers are visible. On optical coherence tomography (OCT), the thickness of the stent struts and its good apposition can be assessed without artefact as seen with conventional metallic struts. Stent length could be measured on the OCT pullback with a good agreement with the known stent length.

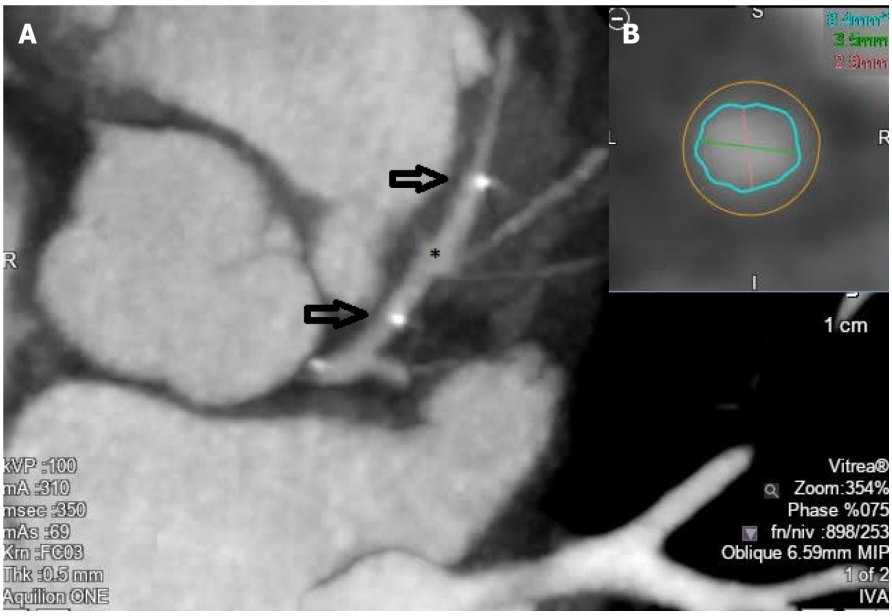


Figure 5 Coronary computed tomography angiography image of a bioresorbable stent (asterisk) implanted at the level of the proximal left anterior descending artery (A) (the two arrows represent the two radiopaque stent markers), and cross sectional cut allowing for lumen measurements (B).

studies which showed high CCTA prediction of cardiovascular events as compared to functional testing and standard care[139,148]. A meta-analysis showed a significant reduction of myocardial infarction as well as an increased incidence of coronary revascularization with no effect on all-cause mortality using CCTA in patients with chronic coronary syndrome as compared to usual care[149].

Observer variability and expertise remain a challenge for CCTA interpretation. Dedicated software programs for increasing automation and identifying high-risk plaques have been validated as well as newer technologies, including fractional flow reserve (FFR) derived from CCTA (FFR_{CT}), perivascular fat attenuation index (FAI) and wall shear stress (WSS)[136]. Advances in imaging modalities permitted a 3-

dimensional reconstruction of the coronary artery tree and a decrease in radiation exposure[150]. Myocardial perfusion by CCTA is also possible and allows for the assessment of the physiologic consequences of stenoses[136]. It has evolved as a valuable tool in guiding PCI and assessing lesion characteristics, especially in chronic total occlusion (CTO) lesions using co-registration with angiography[151]. In the acute disease setting, CCTA fails to differentiate between a thrombus and acute plaque hemorrhage.

CCTA technology still has a lot to offer in the future. It has been a useful and promising tool in the assessment and tracking of atheromatous plaques, improving understanding of early atherosclerosis.

CONCLUSION

The success of stent implantation during PCI procedures depends on proper positioning of the stent, expansion and apposition, all of which reduce the rate of major adverse cardiac events. Traditional two-dimensional angiography alone fails to fully assess the result of stent implantation. Pre-procedural measurement of the vessel diameter along with post-procedural evaluation of the strut-level and minimal lumen area and diameter improve clinical outcomes. Despite the substantial technological advances, a growing need for newer and more accurate tools for PCI guidance and assessment has emerged with the increasing number of complex procedures performed worldwide and ongoing stent technology advances.

Quantitative coronary analysis has developed substantially since its early beginnings due to its research and clinical uses both on-line and off-line. Recent 3-dimensional QCA systems have also emerged, providing more reliable assessment of lumen dimensions[152]. The ease-of-use and reproducibility of QCA analysis has made it widely available within PCI centers worldwide. However, several limitations persist and QCA measurements are lower compared with other imaging modalities [153]. Furthermore, QCA measurements are limited for diffuse lesions, as the reference diameter tends to be underestimated[50].

Digital stent enhancement imaging has been thoroughly validated for stent underexpansion. It allows for easy visualization of areas of stent underdeployment for positioning of post-dilation balloons. DSE has been reported to be associated with better angiographic and clinical outcomes[72] as well as stent fracture identification. DSE adds little additional time to the procedure, provides a better image resolution as compared to angiography with no risk of mechanical complications while using less contrast. It has been found to be particularly useful for obese patients, long lesions, in-stent restenosis and bifurcating lesions[77,86,154]. Although the accuracy and resolution of DSE is lower than intravascular imaging, measurement of stent diameters correlated well[71,73,87,153,155]. Its main drawback could be the increased radiation dose, however this does not have a significant impact on the patient[86]. DSE remains a useful and rapid tool that can be used in conjunction with intravascular imaging during PCI.

Intravascular imaging remains the gold standard during PCI and has demonstrated low complication rates. Several randomized controlled trials and observational studies have established the role of intravascular imaging-guided stent implantation during PCI with a reduction in major cardiac events and target vessel revascularization[105]. Compared to angiography, intravascular imaging-guided PCI has been shown to have a relative reduction of cardiovascular death, a lower risk of myocardial infarction, a decreased risk of target vessel revascularization and a reduction in the rate of stent thrombosis[105]. In addition, the greatest benefit of intravascular imaging guidance may be in complex lesions and stent failure patients. The non-inferiority of OCT as compared to IVUS in guiding PCI has been demonstrated in several clinical trials and meta-analyses[128,131,137,153,156]. Clear differences exist between the two technologies. OCT offers a higher resolution along with finer details, whereas IVUS has a better penetration and does not require flushing the lumen with contrast. IVUS and angiography co-registration systems have been tested and validated and provide valuable information. Furthermore, more recently, a 3-dimensional reconstruction of the coronary tree using IVUS co-registration allowed for further detailed information about vessel size, plaque size, shear stress and hemodynamic studies at every position along the vessel[152].

Thus, intracoronary imaging provides an accurate evaluation of coronary anatomy and plaque evaluation during PCI allowing for optimized stent sizing while avoiding stent malaposition, underexpansion and stent edge dissection, all in addition to an

accurate assessment of the stent result. However, its routine use in clinical practice remains low and highly variable, mainly due to the added procedure cost and time. Progress is still ongoing within the field, with further advances on the way using OCT/IVUS hybrid console systems.

With the ongoing paradigm shift towards non-invasive imaging, new reconstruction techniques have significantly improved coronary artery stent imaging by CCTA. The European Society of Cardiology recommends the use of CCTA for the evaluation of CAD for low to intermediate risk patients in the setting of chronic and acute coronary syndromes[157,158]. With its high specificity (97%), CCTA could be used to exclude in-stent restenosis[159]. The CAC score used during CCTA remains an important tool for future cardiovascular ischemic events. Artefacts secondary to the stent struts hinder the accurate evaluation of the stent lumen, however, with higher scan-detector row systems and thinner stent struts, an improved image quality can be achieved using CCTA. In addition, in the PLATFORM trial[160], the introduction of FFR_{CT} reduced the number of patients referred for invasive angiography by 61%. CMR allows the reduction of the contrast dose without compromising image quality. Both CCTA and CMR can easily and accurately assess coronary bypass grafts along with performing myocardial perfusion and a 3-dimensional reconstruction of the vessels. Furthermore, the introduction and on-going progress of newer generation bioresorbable stents have made CCTA an attractive tool for the evaluation of PCI results, as artefacts are greatly decreased[149,161].

In conclusion, invasive angiography remains the gold standard tool for the treatment of CAD and the visual guidance and evaluation of PCI results however, the conjunction and advances of several readily available alternative and complementary tools improve its sensitivity and accuracy.

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MINIREVIEWS

Interpersonal violence: Serious sequelae for heart disease in women

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Abstract

Experiencing various forms of violence in either childhood or adulthood has been associated with cardiovascular disease, both shortly after the event and during follow-up, particularly in women. The coronavirus disease 2019 pandemic has heightened the risk of domestic violence with serious sequelae for mental and cardiovascular health in women, possibly due to several contributing factors, ranging from lockdown, stay at home regulations, job losses, anxiety, and stress. Accordingly, it remains paramount to enforce proactive preventive strategies, at both the family and individual level, maintain a high level of attention to recognize all forms of violence or abuse, and guarantee a multidisciplinary team approach for victims of interpersonal or domestic violence in order to address physical, sexual, and emotional domains and offer a personalized care.

Key Words: Violence; Women; Depression; Cardiovascular disease; COVID-19; Personalized medicine

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Core Tip: Interpersonal violence has been associated with cardiovascular disease, particularly in women. The coronavirus disease 2019 pandemic has heightened the risk of domestic violence with serious sequelae for mental and cardiovascular health in women. There is a need of research aimed to better understanding the impact of intimate partner violence on cardiovascular risk in women, both shortly after the event and during follow-up. It is important to prevent violence and to guarantee a multidisciplinary team approach for patients who have experienced interpersonal violence in order to address physical, sexual, and emotional domains.

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INTRODUCTION

Interpersonal violence: A public health issue

Interpersonal violence represents a serious public health issue. It is defined as physical or sexual violence, emotional abuse, and stalking, and is experienced by more than 30% of women in United States. It is globally recognized as the leading cause of homicide death for women. Psychological violence has been recognized as a traumatic event equal to other types of abuse (*e.g.*, physical or sexual violence). It causes severe consequences, not only for the victims and families involved, but also to the whole society.

It is well known that intimate partner violence has short-term and long-term effects on the physical and mental health of victims and their children[1]. Epidemiological studies have highlighted an increased risk of chronic medical conditions (including asthma, arthritis, autoimmune disorders, cancer, stroke, diabetes mellitus, hypertension, sexually transmitted infections, and traumatic brain injury) among persons who have experienced partner violence[2]. Proposed mechanisms for the link between interpersonal violence and poor health are the activation of neuroendocrine and immune system pathways (including chronic inflammation and endothelial dysfunction) or epigenetic changes (telomere shortening) occurring in the context of acute and chronic stress. Situations of chronic stress associated with partner violence may also increase detrimental behavioral coping strategies (such as smoking, substance abuse, eating habits, sedentariety, disrupted sleep, scarce adherence to therapy, and failure to follow-up with their doctors) that produce a deterioration in the state of health[1], or an exasperation of other psychological and economic factors (low socio-economic status).

It has been recently suggested that intimate partner violence might increase the risk of cardiovascular disease in women. Chandan *et al*[3] conducted a retrospective study in a cohort of 18547 women from a United Kingdom primary care registry that found that women with a history of intimate partner violence had a 31% increased risk for later cardiovascular disease (in particular a 50% increased risk for ischemic heart disease), a 51% increased risk for diabetes mellitus, and a 44% increased risk for total mortality[3]. In general, chronic diseases, including cardiovascular disease and hypertension, cancer, sexually transmitted infections, drug and alcohol abuse, smoking, diabetes, and elevated cortisol, have been ascertained at greater rates in women who have been victims of intimate partner violence[4].

Scott-Storey[5] developed a conceptual model to portray direct and indirect pathways by which severity of lifetime abuse (physical, sexual, and/or psychological) may affect women's cardiovascular risk. According to this model, there are three pathways through which lifetime abuse may increase cardiovascular disease risk among women. First, lifetime abuse as a chronic stressor contributes to creating a state of vulnerability, potentially causing significant neuroendocrine, metabolic, hemostatic, and immunologic changes within the body (for example, elevated blood pressure, a

clinically important early indicator of cardiovascular risk)[6]. It is probable that chronic upregulation of the so-called fight-or-flight hormones, chronic inflammation, or dysregulation of the hypothalamic pituitary axis may contribute to poor heart health. Second, coping strategies used by victims of abuse to deal with stress, such as smoking and overeating, represent cardiovascular risk behaviors, and tend to persist long after the experience of abuse situation has ended. Third, it has been largely demonstrated that women with histories of abuse have higher incidence of depressive disorders and depressive symptoms, and depression strictly correlates to chronically elevated levels of cortisol, catecholamines, and inflammatory markers, all of which promote the development and progression of cardiovascular disease[7]. Recently it has been highlighted that women suffering from high levels of depressive symptoms in the immediate period after leaving an abusive partner may be most at risk for persistent mental illness after the separation: this reinforces the need for early depression intervention and treatment. It has been also hypothesized that women who experience less change in their depressive symptoms over time may have higher cardiovascular risk, and therefore, may be considered a potential target group for primary and secondary prevention of cardiovascular disease[5].

Biological mechanisms underlying physical health sequelae of interpersonal violence are very poorly understood: it can be hypothesized that intimate partner violence induces a chronic inflammatory state, but further studies are needed focusing on biomarkers of inflammation and specific markers of disease in abused women, including C-reactive protein, cortisol, erythrocyte sedimentation rate, and cardiac biomarkers (troponin, creatine kinase myocardial band, brain-natriuretic-peptide)[4]. There is evidence for a link between intimate partner violence and the development of endocrine diseases, including diabetes. Additionally, interpersonal violence has been associated with lowered cortisol awakening response, flattened diurnal cortisol patterns, and higher midday cortisol. Given that cortisol is considered a biomarker of physical and psychological stress states and is involved in endocrine disease states, the effect of interpersonal violence on cortisol levels may be a promising area of future research[8].

INTERPERSONAL VIOLENCE AND RISK OF CARDIOVASCULAR DISEASE IN WOMEN

There is a bi-directional relationship between mental health disorders (including depression, anxiety, and/or cognitive dysfunction) and cardiovascular diseases. Autonomic dysfunction and inflammation may contribute to the increased cardiovascular mortality risk associated with depression, and a mutation of the ryanodine receptor sarcoplasmic reticulum calcium release channel can result in cardiac arrhythmias and seizures[9]. Complex interrelated disease mechanisms also regard specific syndromes in which pre-existing neurological or psychiatric illnesses may predispose and contribute to cardiovascular involvement (as in Takotsubo syndrome), or in which psycho-physical stress, dysregulation of the interplay between innate immune and central nervous systems, and/or pre-existing cardiovascular disease lead to secondary mental health disorders and brain damage (as in peripartum cardiomyopathy and atrial fibrillation).

Many studies have shown a mutual bond between the cardiovascular system and depression. Patients with cardiovascular disease who are also depressed have a worse outcome than those patients who are not depressed. A graded relationship can be described: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events[10].

Depression is considered an independent risk factor for the development of cardiovascular diseases and contributes to a worse prognosis, further increasing the risk of mortality or subsequent major adverse cardiovascular events, such as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. After a stroke, women present poorer quality of life than men due to different risk factors among which one of the most frequent is depression[11-14]. This association between depression and cardiovascular diseases has been confirmed for both men and women, for different age groups, and in various cultures; furthermore, the strength of this link is similar to that of other risk factors, such as smoking and high cholesterol[15]. The relationship between depression and cardiovascular disease has been analyzed through etiological and prognostic studies. The possibility has been ascertained that depression exerts a direct influence on psychophysiological mechanisms, whose alterations result in the development of atherosclerosis, and thus, lead to coronary

events. Additionally, psychobiological models have identified different mechanisms of connection between depression and coronary artery disease. Other studies have shown that indirect mechanisms are based on the possibility that depression can favor cardiovascular disorders by modulating some coronary risk factors. This hypothesis has given rise to a line of research aimed at identifying various behavioral and psychosocial mediators that can explain the association between depression and coronary heart disease[11,12]. It has been also outlined that mind-body interventions, such as meditation, mindfulness and yoga can promote beneficial effects on stress reduction acting through modulation on cortisol secretion, blood pressure, heart rate variability, and immune reactions, and thus positively preserving women's cardiovascular health [15].

A growing body of research suggests that experiencing violence in either childhood or adulthood is associated with cardiovascular disease. The effects of violence may differ by life course stage. For example, violence exposure in childhood deserves a special attention, as biological mechanisms used to compensate for chronic stress exposure may be detrimental to health, leading to an early development of cardiovascular diseases. Furthermore, unhealthy habits used to cope with stress (lifestyle factors and substance use behaviors) can be formed during these early years, and could contribute to greater cardiovascular risk in childhood that may persist into adulthood. In addition, physiological development of the brain and other organ systems can be derailed under chronic exposure to stress, disrupting emerging brain architecture, as well as cognitive and behavioral functioning, and making children particularly vulnerable to the effects of violence and abuse with long-term consequences on the development of chronic disease, including cardiovascular disease [16]. Children who are exposed to threats to themselves, their family, or their community have an increased risk of subsequent myocardial infarction, stroke, ischemic heart disease, coronary heart disease, and/or death from one of these conditions. It should be noted that children from racial and ethnic minority groups or lower economic backgrounds face higher rates of such experiences, and may therefore be considered at higher risk for cardiovascular disease[17].

Long-term effects of violence exposure have been noted in relation to depression, aggression, substance use, and risk-taking behaviors. Many children and adults exposed to violence may develop post-traumatic stress disorder and depression, frequently associated with obesity, hypertension, and adverse cardiac outcomes[18]. Additionally, studies have documented an association of interpersonal violence exposure with tobacco use, alcohol use, poor dietary habits, and sedentary lifestyle, all of which potentially linked to cardiovascular health[19-21].

INCREASED CONCERNS ABOUT DOMESTIC VIOLENCE DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

The coronavirus disease 2019 (COVID-19) pandemic has produced in a few weeks a substantial disruption worldwide. In the COVID era, affectivity and sexuality are remodeled: social distancing slows down the spread of the Coronavirus but represses or changes the need for relationships. A high global prevalence of depression and anxiety during the COVID-19 pandemic has been described, with a wide variance based on the region and country, as a direct effect of physical distancing measures imposed by national governments[22].

It has been shown that physical distancing (mostly referred to as social distancing) may deteriorate physical and mental health. In particular, reduced social connection is associated with chronic physical symptoms, including cardiovascular disease, reduced nutrition, higher probability of hospital readmissions, reduced vaccine uptake, early mortality, depression with suicidal ideation, social anxiety, psychotic symptoms, and cognitive impairment[23]. In general, psychosocial risk factors such as stress, social isolation, low socioeconomic status, hostility, anger, and stress-related psychiatric disorders are known to have negative impacts on health outcomes, but their effects on ischemic heart disease, particularly in women, have not yet been fully demonstrated [24].

A heightened risk of domestic violence has been associated with the restriction of travels imposed by many governments to prevent the spread of COVID-19 and other infection-reducing measures. The reasons for this include social isolation, exposure to economic and psychological stressors, increase in negative coping mechanisms (such as alcohol or drugs misuse), and inability to access usual health and social services [25]. During quarantine due to COVID-19, home became a dangerous place for victims

of domestic violence because they are bound to stay the whole day with abusing partners and isolated from the others who could potentially give support. Present vulnerabilities can exacerbate family violence perpetration and prey victimization, and can aggravate maladaptive or dysfunctional relationships, directly impacting on cardiovascular system. It has been observed that women during quarantine report significant post-traumatic stress symptoms, and may show depression or anxiety, risk factors for the development or worsening of cardiovascular disease[26]. Currently, the pandemic has brought direct cardiac complications of infection and a potential impact on the standard acute and chronic management of cardiovascular disorders, compromising cardioprotective medications and health behavior regimens[27]. In addition, physical and social isolation can exacerbate maladaptive thought processes (such as anger, loneliness, pessimism, obsessive-compulsive behaviors, hopelessness, helplessness, and/or frustration) or extreme response to stress (such as hypervigilance or alcohol or drugs abuse) that may have consequences on population cardiovascular health[28]. Anxieties and fears related to risk of infection could result in missed cardiovascular or psychiatric medication scripts or delayed referral to psychologists or other specialists, and non-adherence or self-management of dietary, smoking, or physical activity recommendations.

Particularly in COVID, it should be mandatory to provide funding sources to provide telephone or remote counseling services to manage and prevent crisis situations[29]. As the global health community faces up to the spread of COVID-19, the ongoing epidemic wave of violence against women should be addressed.

A NEED TO IMPROVE TREATMENT AND PREVENTION OF INTERPERSONAL VIOLENCE AND CARDIOVASCULAR OUTCOMES

Cardiovascular disease is the leading cause of death in women worldwide; for women living with cardiovascular problems, the chronicity of the disease translates into substantial disability. There are sex and gender-related disparities in cardiovascular disease (including delayed onset and atypical clinical characteristics in women, non-traditional gender-specific risk factors, unconscious gender biases, underrepresentation of women in research trials, and a lack of disease awareness in racial and ethnic minorities), and significant healthcare disparities and gaps still exist in the care of female patients. For example, women are less likely to receive an early diagnosis and timely interventions for a cardiovascular disease and often have worse outcomes than men after acute coronary syndromes). Recognizing nontraditional cardiovascular disease risk factors represents an important opportunity to improve healthcare quality in women[30]. Doing so would help guarantee a multidisciplinary team approach for patients who have experienced interpersonal violence to address physical, sexual, and emotional domains of abuse and their several sequelae. Because it has been stressed that there are multiple pathways through which an experience of violence can affect cardiovascular risk, the best approach to the patients seems to be a multimodal intervention focusing concurrently on chronic stress, depressive symptoms, and cardiovascular risk behaviors[31]. Screening for psychiatric and psychological symptoms in cardiological clinical practice might necessitate increased downstream support from mental health providers, including immediate evaluation of suspected suicidality, and clinicians should be aware that treatments that improve cardiovascular function should also benefit coexisting mood disorders[32].

A routine screening with standardized instruments and trained staffs in clinical settings should be recommended, including social services and behavioral health providers. Hospitals should develop violence intervention programs in collaboration with community-based services addressing mental health and other risk factors. Specific home visitation programs should help support children and families exposed to violence. Intervention strategies should focus on traditional gender role transformation to minimize the relationship power-gap and prevent violence against women. There should be strict implementation of the legislation to penalize and possibly rehabilitate the perpetrators, and there should be widespread diffusion of digital platforms for seeking help.

It is important to disseminate as widely as possible the knowledge and tools related to prevention and to improve the empowerment of women subjected to interpersonal violence[33].

Research has a pivotal role in understanding the impact of interpersonal violence on cardiovascular risk in women, with a special focus on the mechanisms underlying biological, psychological and psychosocial underpinnings. The investigation of

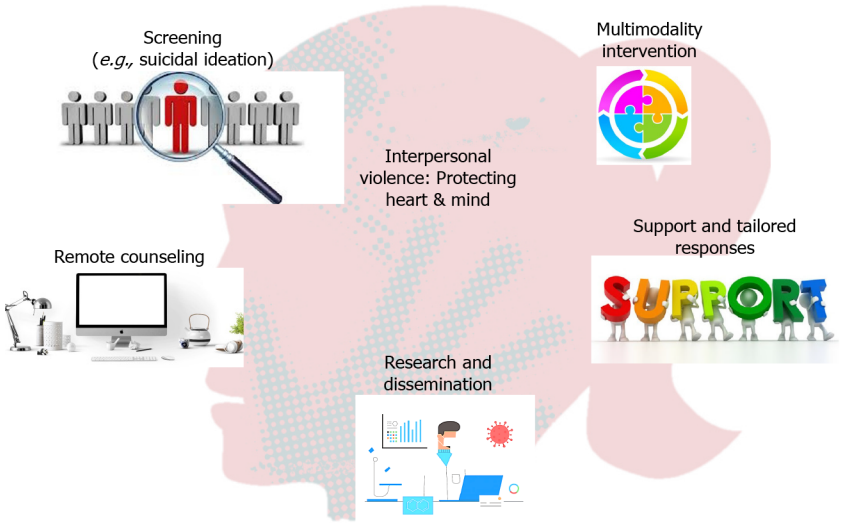


Figure 1 Recommendations to protect heart and mind of women who are victims of interpersonal violence.

potential epigenetic mechanisms by which violence exposure may contribute to heart disease by changing gene expression should not be overlooked, and other ways that the effects of violence exposure on the heart may be translated from generation to generation should be investigated[16]. Further studies designed to explore the chronicity and severity of violence exposure are needed to elucidate the relation between long-term effects of abuse and cardiovascular outcomes.

Intimate partner violence is a very complex issue, and is often difficult to identify because patients may present nonspecific sign and symptoms. Clinicians across all health care settings must be prepared to provide emotional and practical support, and to tailor personalized care to individual needs. Mental and physical health consequences related to interpersonal violence may persist long after the abusive situation has ended[34-36], and there is an urgent need to prevent long-term adverse effects and to extend periods of follow-up (Figure 1).

CONCLUSION

Prevention of violence against women of all ages, and interpersonal violence in general, is mandatory around the world. Cardiovascular disease and gender violence undoubtedly represent a key priority and a significant physical and mental health challenge facing women and clinicians today.

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MINIREVIEWS

Coronary artery aneurysm: A review

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Abstract

Coronary artery aneurysm (CAA) is a clinical entity defined by a focal enlargement of the coronary artery exceeding the 1.5-fold diameter of the adjacent normal segment. Atherosclerosis is the main cause in adults and Kawasaki disease in children. CAA is a silent progressive disorder incidentally detected by coronary angiography, but it may end with fatal complications such as rupture, compression of adjacent cardiopulmonary structures, thrombus formation and distal embolization. The pathophysiological mechanisms are not well understood. Atherosclerosis, proteolytic imbalance and inflammatory reaction are involved in aneurysmal formation. Data from previously published studies are scarce and controversial, thereby the management of CAA is individualized depending on clinical presentation, CAA characteristics, patient profile and physician experience. Multiple therapeutic approaches including medical treatment, covered stent angioplasty, coil insertion and surgery were described. Herein, we provide an up-to-date systematic review on the pathophysiology, complications and management of CAA.

Key Words: Coronary artery aneurysm; Complications; Atherosclerosis; Coronary artery ectasia

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Core Tip: Most patients with coronary artery aneurysm remain asymptomatic until the development of complications or the occurrence of obstructive coronary disease-related clinical manifestations. The underlying pathophysiology is miscellaneous. The ideal management of coronary artery aneurysm has not yet been defined, but computed tomography angiography is the recommended non-invasive test for long-term follow-up. Future prospective comparative trials targeted to define the appropriate strategy and the optimal time to intervene are required.

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INTRODUCTION

Coronary artery aneurysm (CAA) is a rare clinical entity defined by an abnormal focal dilation of the coronary artery exceeding the 1.5-fold diameter of the adjacent normal segment, whereas coronary artery ectasia describes similar but diffuse lesions involving ≥ 50% of the coronary artery length[1]. Thus, aneurysmal coronary disease is seen as focal aneurysm (*e.g.*, Kawasaki) but also in more diffuse forms (diffuse ectasia). In general, CAAs are divided into two types: saccular when the longitudinal diameter is less than the transverse diameter; and fusiform in the opposite condition[2-4] (Figure 1). Fusiform CAAs are commonly found in the left anterior descending artery [2-4]. Aneurysmal dilation ≥ 8 mm in diameter or four times higher than reference coronary diameter characterized a giant CAA[5-7]. The incidence of true CAA varies from 0.3% to 5.3%[8,9] knowing that most recent studies reported an incidence rate below 1%[10-13]. The right coronary artery is most commonly involved followed by left anterior descending artery, circumflex and left main[8,9]. A predilection to male gender and proximal coronary segment was described[14].

CAA is usually a silent disorder incidentally detected by coronary angiography or computed tomography (CT) angiography. The wide spectrum of clinical presentations ranging from chest pain to sudden cardiac death results from the development of complications and/or the coexistence of obstructive coronary artery disease[8,15-20]. Until now, the management of CAA is individualized depending on clinical manifestations, patient conditions, CAA characteristics, physician experience and preference. A poor long-term prognosis has been attributed to the presence of CAA[21,22]. Herein, we provide an up-to-date systematic review on the pathogenesis, complications and management of CAA.

PATHOPHYSIOLOGY

The pathophysiological mechanisms of CAA are not well understood, but atherosclerosis is the main identified etiology in adults and Kawasaki disease in children[5]. Atherosclerosis is a chronic progressive transmural inflammatory disease affecting the different vascular layers from the tunica intima to the external elastic lamina, thereby contributing to a weakened vascular wall[23-27]. It is worthy to mention that stenotic coronary atherosclerosis and CAA commonly coexist. They share in common several histological patterns like hyalinization, lipid deposition, destruction of coronary layers, focal calcification and fibrosis[23-27]. All of these arteriosclerotic modifications on top of the liberation of nitric oxide, which enhances vasodilation, reduce the coronary resistance to intraluminal pressure predisposing it to dilatation and CAA formation. Kawasaki disease is an acute inflammatory syndrome that may infiltrate the arterial wall resulting in acute vasculitis and subsequent aneurysmal dilation[28]. Indeed, a high level of tumor necrosis factor-alpha, which is an inflammatory cytokine, was linked to the breakdown of elastin and the development of CAA[29]. Currently, coronavirus disease 2019 markedly increased the incidence of Kawasaki disease with cardiovascular involvement in children and young adults[30]. Other vasculitic disorders like Takayasu arteritis, polyarteritis nodosa, systemic lupus erythematosus and rheumatoid arthritis may lead to CAA[31,32].

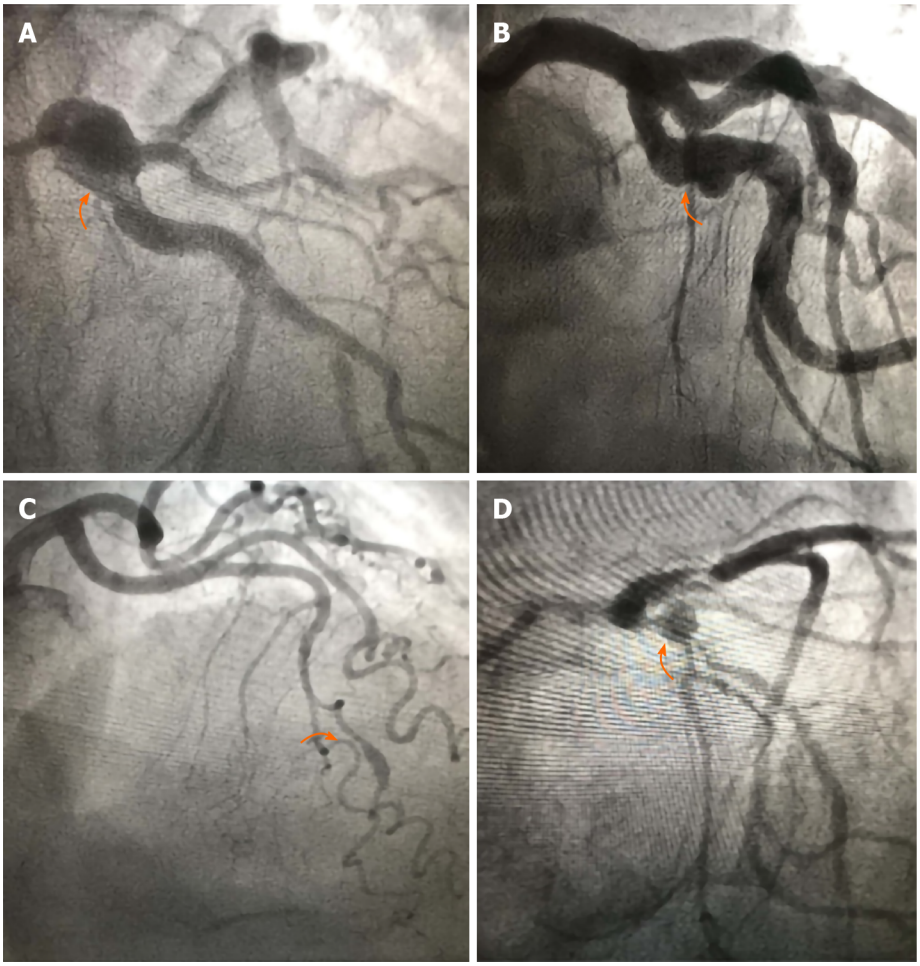


Figure 1 Coronary angiograms showing saccular aneurysm of the left main (A), saccular aneurysm of the left circumflex (B), fusiform aneurysm of the distal left anterior descending (C) and saccular aneurysm of the bifurcation left anterior descending/diagonal (D).

Otherwise, matrix-degrading enzymes play a pivotal role in the pathogenesis of CAA. A proteolytic imbalance caused by a high level of matrix metalloproteinases (MMP-2,-3,-9,-12) and a reduced level of matrix metalloproteinase inhibitors (tissue-specific inhibitors of metalloproteinases, TIMP-1,-2,-3,-4) resulting in connective tissue proteins and arterial wall matrix degradation, is reported in aneurysmal vessels[33-35]. Genetic susceptibility such as variants on chromosome 9p21.3, HLA-DR B1*13, DR16, DQ2, DQ5 and several hereditary disorders such as Marfan syndrome and Ehler-Danlos were linked to CAA[9,36]. Infectious processes that directly invade the vascular wall or provoke immune complex deposition contribute to CAA formation [37].

Lastly, CAA may complicate coronary angioplasty with stent implantation[38-40]. Aneurysmal formation was observed with bare metal stents, drug eluting stents and biodegradable stents[38-40]. Coronary dissection, oversizing, stent malapposition, high pressure balloons and local wall injury are the main mechanisms associated to stent-related CAA[41,42].

COMPLICATIONS

Most patients with CAA are asymptomatic, and the occurrence of clinical manifestations is related to a concomitant atherosclerotic coronary artery disease or to the development of complications. Local thrombosis, distal embolization, aneurysm rupture, coronary spasm and compression of adjacent structure by massive enlargement of CAA are the most observed complications[17,18,43,44] (Figure 2). The stagnation of blood flow and the reduction of shear stress in CAA contribute to thrombus formation and subsequent potential distal embolization[45]. Several published cases reported the presence of thrombus inside the aneurysm[46,47] and described myocardial wall motion abnormalities following distal embolization in

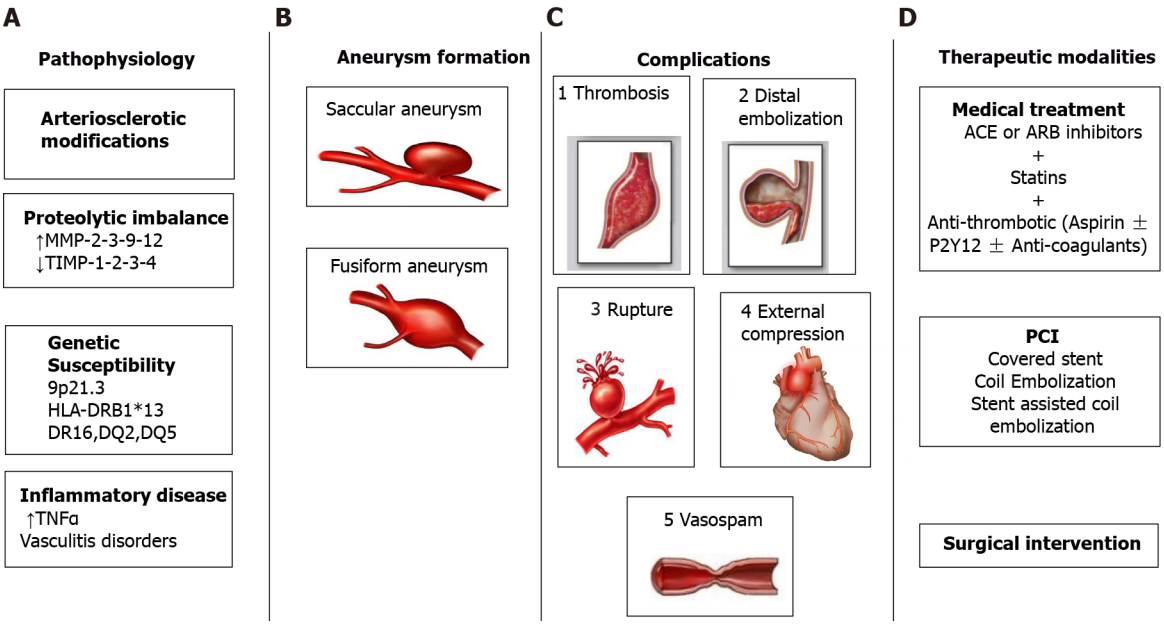


Figure 2 An illustration of the pathophysiology (A), types (B), complications (C) and therapeutic (D) modalities for coronary artery aneurysm. ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blockers; MMP: Matrix metalloproteinases; PCI: Percutaneous coronary intervention; TIMP: Tissue-specific inhibitors of metalloproteinases; TNF: Tumor necrosis factor.

patients with CAA[48]. Theoretically, CAA does not have enough intact smooth muscle to produce significant vasoconstriction knowing that smooth muscle hypercontractility is implicated in the pathophysiological mechanism of coronary artery spasm [49]. However, Bove *et al*[50] were the first to describe a recurrent angina linked to spasm of aneurysmal coronary arteries. The rupture of CAA is rare, unpredictable and a serious life-threatening condition that results in cardiac tamponade and sudden death. Since previously published data[51-53], the incidence of rupture of CAA was dramatically decreased[54]. An excessively enlarged CAA may compress the surrounding adjacent cardiopulmonary structures like the right atrium[55], the right ventricular wall[55], the pulmonary artery and the tricuspid valve[56].

MANAGEMENT OF CAA

Until now, there are no standardized international recommendations for the management of CAA due to the lack of data from randomized clinical trials. Most of the available data are based on case series and anecdotal evidence. The management of CAA is individualized and depends on clinical presentation (silent or symptomatic), characteristics of CAA (location, size, shape, evolution, etiology), patient profile (age, comorbidities, cardiovascular risk factors) and physician experience. Different approaches including medical treatment, percutaneous coronary intervention (stent angioplasty and coil embolization) and surgical excision were priorly performed. Indeed, the optimal therapeutic strategy leading to the best outcome was not yet defined due to the absence of comparative studies. Coronary angiography is the invasive gold standard tool to assess the anatomic features of CAA, while coronary CT is the alternative non-invasive technique of choice for the follow-up[57].

Medical management

First of all, an intense control of cardiovascular risk factors is advocated in patients with CAA regardless of the presence of concomitant obstructive coronary artery disease[58]. Basing on the association between the overexpression of angiotensin-converting enzyme and aneurysm formation, it was hypothesized that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may slow the progression of CAA[59]. Also, the use of statins in CAA patients is desirable. A beneficial role was attributed to statins by inhibiting the expression of matrix metalloproteinases, which play a crucial role in the physiological mechanism of aneurysm formation[60]. Otherwise, the proper indication of anti-thrombotic regimen for the management of CAA is a matter of debate noticing that data from previously

published studies are controversial.

Despite the risk of thrombus formation and distal embolization described above, few retrospective studies conclude that anticoagulation strategy is unbeneficial by showing a similar rate of thrombotic events in patients with and without CAA[61-63]. Contradictory results were revealed by Warisawa *et al*[21] and Baman *et al*[57] who showed greater rates of 5-year mortality and major cardiovascular adverse events (MACE) in patients with CAA. A recently published study found that prescribing oral anticoagulation led to positive outcomes in patients with coronary artery ectasia by reporting 0% of MACE in patients treated with oral anticoagulation compared to those who did not receive anti-thrombotic therapy after 49 mo of follow-up[22]. Therefore, coronary artery ectasia was identified as an independent predictor of cardiac events in patients presenting with acute coronary syndromes[22]. Myocardial infarction, MACE and death were two to four times higher in patients with coronary artery ectasia[22]. However, it is worthy to mention that prolonged anti-thrombotic therapy may provoke complications, such as bleeding. Lastly, intravenous immunoglobulin therapy in Kawasaki disease promotes CAA regression and decreases the incidence of MACE [64].

Percutaneous coronary interventions

Percutaneous coronary intervention (PCI) is a relatively new therapeutic option allowing to exclude CAA when the clinical and/or anatomical risk is high (Figure 3). Several techniques were reported in the literature, like covered stent implantation[65], coil embolization and stent-assisted coil insertion[66]. Conventionally, PCI is the preferred approach to exclude smaller CAA, while surgical approach is preferred for the larger aneurysms[67]. Several limitations like difficulty of stent delivery, occlusion of side branches and high percentage of restenosis were observed with covered stent angioplasty[68]. Bare metal stents were previously preferred over polytetrafluoroethylene covered stents due to the lower incidence of thrombosis and restenosis[69]. The last generation of covered stents, such as PK Papyrus stents, achieve a greater bending flexibility and a smaller crossing profile compared to the traditional sandwich designed stents that allow sealing of perforations and exclude aneurysms[70]. Therefore, stent-assisted coil insertion technique is favored over coil embolization in the management of wide-necked CAA because it reduces the risk of occlusion of the parent coronary vessel and rupture of CAA[66].

Previous studies investigating the outcomes of PCI performed in patients with CAA in the setting of acute myocardial infarction found a worst prognosis, thereby showing higher rates of procedural failure, mortality, no-reflow, stent thrombosis, distal embolization and target vessel revascularization[10-13,71]. Performing PCI in the setting of aneurysmal coronary arteries imposes technical challenges for physicians, such as appropriate sizing, landing zone assessment and thrombus burden. As a result, it is rare to intervene in asymptomatic patients with CAA.

Surgical interventions

Different surgical techniques have been described including aneurysmectomy with or without coronary artery bypass graft, aneurysm ligation, resection and marsupialization[72]. Indeed, the optimal surgical approach has not yet been defined. Overall, surgery is considered an alternative adequate therapeutic strategy for the management of symptomatic patients unsuitable for PCI, patients with concomitant obstructive coronary artery disease, CAA involving the large bifurcation or the left main, complicated CAA and giant CAA at high risk of rupture[72,73].

Imaging modalities for detection of CAA

A recently published study showed that CT angiography is superior to cardiac magnetic resonance imaging for detection, risk stratification and follow-up of CAA in patients with Kawasaki disease[74]. Also, CT angiography has already proven its value for the assessment of the diameter of coronary arteries in adults and patients with Kawasaki disease when compared to coronary angiography[75-78]. Indeed, the sensitivity of CT angiography for detection of CAA and related complications is remarkably high. Because radiation exposure is associated with an increase in lifetime cancer risk, especially in children, the lack of radiation exposure is the main described benefit to cardiac magnetic resonance imaging over coronary angiography and CT angiography for CAA detection[74]. Lastly, CT angiography provides accurate data concerning the coronary anatomy, calcification, luminal diameter, thrombi and aneurysmal features[79]. It represents the imaging of choice for the long-term monitoring of CAA[57].

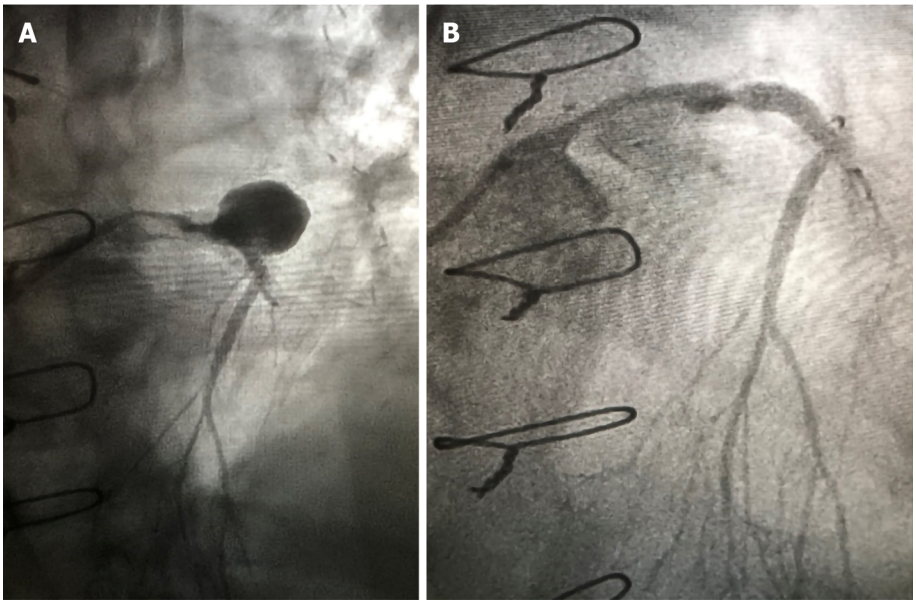


Figure 3 Coronary angiograms showing a giant coronary artery aneurysm of the proximal left anterior descending artery (A) excluded by implanting a bare metal stent with nonsignificant residual stenosis (B).

CONCLUSION

Usually, CAA is an incidental angiographic finding associated to atherosclerosis. The natural history of CAA is not well understood, but it is a progressive silent disease. Future prospective comparative trials to define the appropriate strategy and the optimal time to intervene are required in order to avoid the development of serious complications, especially in those with concomitant obstructive coronary artery disease.

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MINIREVIEWS

Coronary vasospasm: A narrative review

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Abstract

Coronary artery vasospasm (CAVS) plays an important role in acute chest pain syndrome caused by transient and partial or complete occlusion of the coronary arteries. Pathophysiology of the disease remains incompletely understood, with autonomic and endothelial dysfunction thought to play an important role. Due to the dynamic nature of the disease, its exact prevalence is not entirely clear but is found to be more prevalent in East Asian and female population. Cigarette smoking remains a prominent risk factor, although CAVS does not follow traditional coronary artery disease risk factors. Many triggers continue to be identified, with recent findings identifying chemotherapeutics, allergens, and inflammatory mediators as playing some role in the exacerbation of CAVS. Provocative testing with direct visualization is currently the gold-standard for diagnosis, but non-invasive tests, including the use of biomarkers, are being increasingly studied to aid in the diagnosis. Treatment of the CAVS is an area of active research. Apart from risk factor modification, calcium channel blockers are currently the first line treatment, with nitrates playing an important adjunct role. High-risk patients with life-threatening complications should be considered for implantable cardioverter defibrillator (ICD), although timing criteria for escalated therapy require further investigation. The role of pharmaceuticals targeting oxidative stress remains incompletely understood.

Key Words: Coronary artery vasospasm; Vasospastic angina; Prinzmetal angina; Variant angina; Coronary artery disease

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Core Tip: Coronary artery vasospasm (CAVS) represents a spectrum of transient coronary arterial occlusion which can lead to serious complications, including sudden cardiac death. CAVS, often underdiagnosed and undertreated, should be considered in symptomatic patients with nonobstructive coronary arteries. Recent studies have expanded upon the etiology, epidemiology, and treatment options for CAVS.

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INTRODUCTION

Coronary artery vasospasm (CAVS) was first described as a "variant" of typical angina pectoris by Dr. Myron Prinzmetal in 1959, hence launching the study of a Prinzmetal (or "variant") angina, which was subsequently termed vasospastic angina (VSA)[1]. Since then, the paradigm surrounding VSA has continued to expand. Symptoms develop upon transient partial or complete occlusion of coronary vessels resulting in a spectrum of clinical manifestations, ranging from stable angina to acute coronary syndrome (ACS), and in some cases sudden cardiac death (SCD)[1-6]. The disease process has been identified in patients both with and without coronary artery disease (CAD), affecting both epicardial and microvascular coronary arteries, and having both focal and diffuse involvement[2,4,7]. Certainly, traditional risk factors associated with CAD cannot be relied upon as predictors of CAVS, with the exception of cigarette smoking[1]. Although a prevailing precedent exists regarding the pathophysiology, diagnostics, and treatment of VSA, previous reviews have identified areas which require further study, especially in cases of refractory disease[8].

PATHOPHYSIOLOGY

A number of mechanisms have been proposed regarding the mechanism of CAVS, including impairment of parasympathetic activity, coronary vascular and microvascular endothelial dysfunction, enhanced smooth muscle vasoconstriction, chronic inflammation, and oxidative stressors[4,5,7]. Recent studies have highlighted rarer causes of CAVS resulting from excessive adrenergic stimulation in cases of catecholamine-induced cardiomyopathy in pheochromocytomas and paragangliomas [9].

EPIDEMIOLOGY

Approximately 5% to 30% of patients presenting with angina demonstrate normal or non-obstructive coronary arteries when worked up with coronary angiography, despite presenting with symptoms suggestive of acute coronary syndrome (ACS)[10-12]. Nearly half of these presentations may be attributed to CAVS[5,13], with an increased incidence amongst East Asians, especially Korean and Japanese populations [3,6,13,14]. This increased prevalence (in addition to environmental factors) has been attributed to genetic deficiency of variant aldehyde dehydrogenase 2 (ALDH2) genotype amongst these populations[15]. This correlates with increased toxic aldehyde accumulation, which may from the bases of future targeted treatment strategies in these populations[15]. Further studies demonstrate a need for exploring CAVS amongst Japanese adolescents less than 20 years old, whose clinical status matched severity of adults with refractory CAVS[16].

An increased incidence is additionally seen in women, with up to 70% of women showing ACS symptoms without CAD demonstrating findings suggestive of CAVS [17-19]. The incidence is particularly high for younger women under the age of 50 years, as well as non-white women[20,21]. For this reason, significant consideration should be given to a CAVS workup in patients from these demographics, especially

given the tendency for worse outcomes in women compared to men[21]. Women with myocardial ischemia and no obstructive coronary artery disease (MINOCA) should undergo coronary reactivity testing (CRT), which reliably identifies the presence of CAVS[17].

Consideration of CAVS requires high clinical suspicion, and should also be considered in patients with rest angina or patients with anginal symptoms despite unremarkable coronary angiography[6,18]. Patients often develop symptoms between midnight and early morning, at times awoken from sleep by symptoms[15].

ETIOLOGY

A number of triggers have been implicated in literature, with the most impactful trigger being cigarette smoking[2,18]. Other triggers include psychological stress, cold exposure, hyperventilation, alcohol consumption, stimulants (*e.g.*, cocaine)[5,22]. Given increasing legalization within the United States, marijuana consumption has been considered as a contributor to CAVS exacerbation in a number of case reports [23].

Chemotherapies are other important causes of CAVS. Studies suggest that fluoropyrimidines (including 5-fluorouracil and capecitabine) induce vascular endothelial damage which can cause ischemia secondary to coronary artery vasospasm[24]. In such cases, chemotherapy should be halted and standard therapy for CAVS initiated, which should include calcium channel blockers (CCBs) and nitrates[24]. Further research is required surrounding cardioprotective agents such as coenzyme complex, glucagon-like peptide-1 (GLP-1) analogues, degradation inhibitors [24], and uridine triacetate[25]. Other chemotherapies should be considered if feasible, otherwise a CAD workup should be considered to stratify the patient's risk for further fluoropyrimidine treatment[26].

Kounis syndrome (KS) is described as the occurrence of ACS in the setting of a mast-cell and platelet mediated hypersensitivity, anaphylactic, anaphylactoid, or allergic reaction[27,28]. One pathophysiology of KS includes CAVS, induced by inflammatory mediators[29]. Common triggers include antibiotics (especially beta-lactams[29]) and insect bites, which together account for half of reported cases[27]. Recent studies have expanded upon potential triggers, including supplements from traditional Chinese medicine (TCM)[27] and injection of cefuroxime[29].

Infectious myocarditis has been implicated in the development of CAVS in patients with otherwise non-obstructive coronary arteries. The underlying mechanism is believed to involve direct inflammatory and infectious interference with endothelial function of the coronary arteries[30]. Well documented etiologies include parasitic infections with *Treponema cruzi* (Chagas disease) and viral infections with parvovirus B19, amongst other causes[30].

DIAGNOSTICS

Studies indicate that CAVS is an underdiagnosed and underreported disease[3,6,14]. Correct diagnosis can guide appropriate treatment, which can not only improve patient's quality of life, but also reduce aforementioned serious risks associated with CAVS, including life-threatening arrhythmias and SCD[14]. Current gold standard diagnosis of CAVS utilizes pharmacological provocative testing with high-dose boluses of acetylcholine, ergonovine, or methylergonovine *via* intracoronary injection [2,3,5,13,14]. The response is then visualized as a coronary vasospasm with transient > 90% occlusion of coronary arteries[19], during coronary angiography, or *via* abnormalities of ventricular wall motion on echocardiogram[2,3]. A standard cardiac workup should initially include standard 12-lead electrocardiogram (ECG) during an attack, ambulatory cardiac monitoring, or exercise stress testing to exclude underlying CAD[18].

The Coronary Vasomotion Disorder International Study Group (COVADIS) developed diagnostic criteria for CAVS, which include: (1) Nitrate responsiveness to angina during spontaneous episodes with at least one of rest angina, marked diurnal variation in exercise tolerance, hyperventilation precipitating episodes, or calcium channel blockers (but not β-blockers) suppressing episodes; (2) Transient ischemic changes during spontaneous episodes including at least two contiguous leads with ST segment elevations ≥ 0.1 mV, ST segment depressions ≥ 0.1 mV, or new negative U waves; and (3) Coronary artery spasm visualized either spontaneously or during

provocative testing[31]. Definitive CAVS is diagnosed if the first and either second or third criteria are fulfilled, which can guide further testing[31].

Although provocative testing is favored in the diagnosis of CAVS and is generally considered safe, the procedure does carry a small chance of serious complications. Recent studies have explored the use of biomarkers *via* blood test as a possible component in the workup for CAVS. One study explored a number of biomarkers including: (1) Inflammatory markers including C-reactive proteins (CRP), cytokines, lipoprotein (a), and cystatin-C as precipitating factors; (2) Vasoconstrictors including rho-kinase, serotonin (5-hydroxytryptamine), and endothelin-1 (ET-1); and (3) Oxidative stressors including thioredoxin and nitrotyrosine[32].

Previous studies have stipulated that increased testing and sensitivity of provocative testing can enhance detection of CAVS worldwide (especially Western countries), but this must be weighed against the risks associated with such testing[14,32]. Notably, rapid administration of intracoronary nitrate following provocative testing has resulted in no reported procedure-related deaths[13]. Furthermore, recent studies have demonstrated more efficacy and safety with local administration of nitroglycerin to spasming areas through a perforated balloon rather than proximal administration of nitroglycerin, which may further reduce minor risks associated with provocative testing[33]. The impact of local nitroglycerin administration on a spasming area of coronary artery can be visualized in Figures 1 and 2.

TREATMENTS

Initial approach to patients with CAVS should include lifestyle modifications, with the most prominent impact coming from smoking cessation[2,18]. Once this initial approach has been exhausted and symptoms remain refractory, a number of pharmacological options are available to supplement lifestyle notifications, noted in Table 1. First line pharmacologic treatment should include CCBs, with non-dihydropyridine being preferred but with similar efficacy to dihydropyridine CCBs[2,5]. Patients with persistent symptoms may benefit from the addition of long-acting nitrates, which reduce the frequency of anginal symptoms[2]. Additionally, sublingual nitrates may be useful for relieving acute episodes of angina[5]. Statins and angiotensin converting enzyme (ACE) inhibitors have shown efficacy in preventing CAVS episodes, and should be considered in all patients presenting with CAVS[2,5,19]. One study analyzed the use of sarpogrelate (a serotonin receptor antagonist) in addition to high-dose statins for CAVS, but did not find significant improvement of outcomes[34]. The use of magnesium and antioxidants (such as vitamin C and E) have demonstrated efficacy in many patients[5].

Patients with refractory disease who do not respond to lifestyle changes and first line pharmacotherapy may consider alpha 1-adrenergic receptor antagonists, rho-kinase inhibitors, or nicorandil[2,5,19]. Patients with significant atherosclerosis may benefit from percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), which has shown benefit in patients with concomitant CAVS[5].

Patients who have experienced adverse outcomes of CAVS including life-threatening ventricular arrythmias or SCD may benefit from an implantable cardioverter defibrillator (ICD) in addition to medical therapy[2]. Notably, other reversible causes of SCD should be considered before escalating therapy. Although CAVS generally has a favorable prognosis, patients experiencing these adverse outcomes have worse outcomes[35]. Predictors of SCD in CAVS patients include advanced age, hypertension, hyperlipidemia, family history of sudden cardiac death, multivessel spasm, and left anterior descending (LAD) artery spasm, and should be considered for escalated therapy[35]. Recent studies have also explored the use sympathectomy, which reduced major adverse cardiac events in patients with refractory CAVS when compared to conventional treatment[36].

Beta blockers (BBs), both selective and nonselective forms (especially propranolol), should generally be avoided in patients with CAVS[2,5]. Blockage of beta-2 receptors, which prevents smooth muscle relaxation, can exacerbate anginal symptoms. The use of nebivolol, a BB with nitric oxide-releasing effects, has been compared to diltiazem for CAVS – both reduced the effects of CAVS, but diltiazem had greater reduction in symptoms at 12 wk[37]. A notable recent exception to this is drug-eluting stent-induced vasospastic angina (DES-VSA), which showed lower 2-year major cardiovascular events (MACE) with BBs compared to CCBs[38]. The use of aspirin (especially at high doses) in CAVS remains controversial, and there has been no clear demonstrated benefit of its use in patients with any degree of CAVS[2,5].

Table 1 Pharmacologic therapies for coronary artery vasospasm

Drug class	Common drugs	Usual drug dosage	Indication
CCB	Amlodipine; Diltiazem; Nifedipine-ER	10 mg qD; 240 mg qD; 30-120 mg qD	First line for CAVS[40-42]
Long-acting nitrate	Isosorbide mononitrate	60–240 mg qD (maintenance)	Symptomatic improvement in combination with first line therapy[2]
Short-acting nitrate	Sublingual nitroglycerin	0.3 mg	Acute attack[43]
Statin	Lovastatin; Fluvastatin	80 mg qD; 20-80 mg qD	All patients experiencing CAVS[15,44]
ACE inhibitor/ARB	Candesartan; Losartan	8-16 mg qD; 25–50 mg qD	All patients experiencing CAVS[45]
BB	Bisoprolol; Nebivolol	1.25–5 mg qD; 5–10 mg qD	DES-VSA[37,38]
Rho kinase inhibitors	Fasudil	240 mg qD	Refractory CAVS[46]
Antioxidants	Vitamin E	400 mg qD	Adjunct therapy[47]
Magnesium	Magnesium Chloride	20 mEq	Replenishing deficiency[5]
Potassium channel activator	Nicorandil	10–20 mg BID	If nitrates are ineffective[12]

CCB: Calcium channel blocker; ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; BB: Beta blocker; DES-VSA: Drug-eluting stent-induced vasospastic angina; CAVS: Coronary artery vasospasm; qD: Daily; BID: Twice a day.

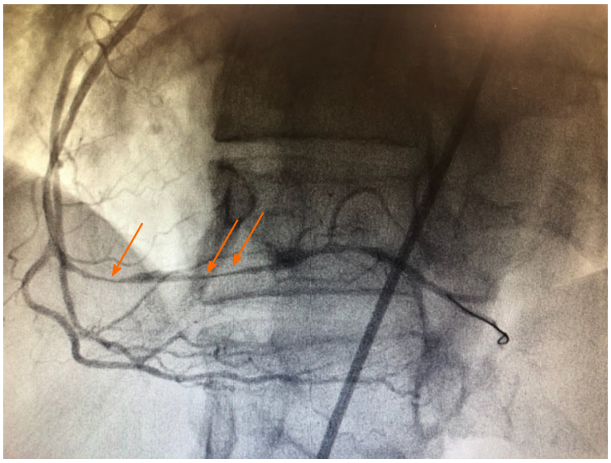


Figure 1 Coronary angiography demonstrating stenosis of the right coronary artery (arrows).

FUTURE DIRECTION

Although an understanding of CAVS continues to expand, there remains an ongoing need to better stratify the pathology. The effect of pharmacologic therapy, especially when considering generally avoided medications like BBs, should be tested in larger studies to ensure efficacy[38]. Studies have also emphasized the need to explore the use of fractional flow reserve (FFR) in the evaluation of moderate stenosis in the setting of MINOCA, nearly half of whom may have underlying CAVS[13,39]. Heart-type fatty acid-binding protein (h-FABP), myocardial performance (Tei) index, and genetic testing have been identified as potentially useful methods for tracking the development of CAVS in patients taking fluoropyrimidines[24,25]. Further studies should explore the timing of ICD implantation in high-risk patients with CAVS who would benefit from such therapy[3,35]. Future studies should consider populations in Western countries, where CAVS is generally underdiagnosed and undertreated[32].

CONCLUSION

CAVS is an important but underrecognized disease that can result in significant clinical symptoms and/or life-threatening complications. Its prevalence is decreasing



Figure 2 Coronary angiography demonstrating resolution after intracatheter injection of nitroglycerin.

due to decreasing prevalence of smoking, increasing use of the medications like calcium channel blockers, statins, and increasing use of non-invasive testing for CAD. It is important to consider CAVS in the differential of anginal chest pain in patients with non-obstructive CAD and treat it appropriately.

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MINIREVIEWS

Sodium glucose cotransporter 2 inhibitors: New horizon of the heart failure pharmacotherapy

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained momentum as the latest class of antidiabetic agents for improving glycemic control. Large-scale clinical trials have reported that SGLT2 inhibitors reduced cardiovascular outcomes, especially hospitalization for heart failure in patients with type 2 diabetes mellitus who have high risks of cardiovascular disease. Accumulating evidence has indicated that beneficial effects can be observed regardless of the presence or absence of type 2 diabetes mellitus. Accordingly, the Food and Drug Administration approved these agents specifically for treating patients with heart failure and a reduced ejection fraction. It has been concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended for preventing hospitalization associated with heart failure in patients with type 2 diabetes and established cardiovascular disease or those at high cardiovascular risk. In the present review, we explore the available evidence on SGLT2 inhibitors in terms of the cardioprotective effects, potential mechanisms, and ongoing clinical trials that may further clarify the cardiovascular effects of the agents.

Key Words: Sodium glucose cotransporter 2 inhibitors; Heart failure; Clinical trials; Potential mechanisms; Diuretics

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Core Tip: Sodium glucose cotransporter 2 inhibitors are newly approved by the Food and Drug Administration as treatment choice for heart failure based on evidence from several large-scale clinical trials demonstrating reduction in cardiovascular outcomes, especially hospitalization for heart failure or cardiovascular death. The background of the approval and potential mechanisms are discussed in this review. As well, summary of available evidence from clinical trials and ongoing trials examining beneficial effects of the agents are written.

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INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as the latest class of antidiabetic agents for improving glycemic control. Interestingly, the EMPA-REG OUTCOME trial, which evaluated empagliflozin in patients with type 2 diabetes and cardiovascular disease, demonstrated a greater-than-expected reduction in cardiovascular death, hospitalization for heart failure, and all-cause death[1,2]. Subsequent cardiovascular outcome trials assessing other SGLT2 inhibitors reported similar results; for instance, the Canagliflozin Cardiovascular Assessment Study (CANVAS), involving 10142 type 2 diabetic patients with high cardiovascular risk, demonstrated that canagliflozin decreased the risk of the primary outcome of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 14%[3-5]. In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, dapagliflozin lowered the rate of cardiovascular death or heart failure hospitalization by 17% in patients with type 2 diabetes who had or were at risk for cardiovascular disease. Those trials are summarized in Table 1. A recent meta-analysis including these clinical trials reported that SGLT2 inhibitors reduced the risk of cardiovascular death or heart failure hospitalization by 23% (HR, 0.77; 95%CI, 0.71–0.84; $P < 0.0001$), with a similar benefit in patients with and without a history of heart failure[6]. The magnitude of benefit associated with SGLT2 inhibitors varied with baseline renal function, with greater reductions in hospitalization for heart failure (P for interaction = 0.0073) observed in patients with more severe renal dysfunction at baseline. Additionally, sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, has reduced the risk of cardiovascular death or heart failure events in patients with type 2 diabetes and chronic kidney disease[7] or type 2 diabetes complicated with heart failure[8] (Table 2). Despite these positive findings, the benefit of SGLT2 inhibitors on heart failure events was not primarily investigated in these studies, where study participants were patients with diabetes; accordingly, background medical therapy for heart failure might not be optimized. When investigating new heart failure pharmacotherapies, it is crucial to consider whether the therapies provide any additional benefits to established therapies. Therefore, it is uncertain whether these benefits can be generalized.

CARDIOPROTECTIVE EFFECTS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION, REGARDLESS OF DIABETIC STATUS

A meta-analysis incorporating data from EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 revealed that the decrease in the composite of cardiovascular death or heart failure hospitalization did not statistically differ among patients with (HR, 0.71; 95%CI, 0.61–0.84) or without (HR, 0.79; 95%CI, 0.71–0.88) history of heart failure at baseline (P for interaction = 0.51). However, the cardioprotective effects of SGLT2 inhibitors in patients with heart failure, regardless of the presence or absence of diabetes, are uncertain. The question was answered by the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, wherein 4744

Table 1 Landmark clinical trials of sodium-glucose cotransporter 2 inhibitors

Ref.	Population (*n*)	Age, yr (mean)	Intervention	Follow-up period (median)	Patients with a history of HF	Patients with a history of CVD	Main results
EMPA-REG[1]	T2DM (7028)	63.1	Empagliflozin	3.1 yr	10.1%	100%	CV death or HF (HR, 0.66; 95%CI, 0.55–0.79) HF (HR, 0.65; 95%CI, 0.50–0.85) CV death (HR, 0.62; 95%CI, 0.49–0.77)
CANVAS[3]	T2DM (9734)	63.3	Canagliflozin	2.4 yr	14.4%	65.6%	CV death or HF (HR, 0.78; 95%CI, 0.67–0.91) HF (HR, 0.67; 95%CI, 0.52–0.87) CV death (HR, 0.87 95%CI, 0.72–1.06)
DECLARE-TIMI 58[4]	T2DM (17160)	63.9	Dapagliflozin	4.2 yr	10.0%	40.6%	CV death or HF (HR, 0.83; 95%CI, 0.73–0.95) HF (HR, 0.73; 95%CI, 0.61–0.88) CV death (HR, 0.98; 95%CI, 0.82–1.17)
VERTIS-CV[5]	T2DM (8246)	64.4	Ertugliflozin	3.5 yr (mean)	23.7%	71.4%[1]	CV death or HF (HR, 0.88; 95%CI, 0.75–1.03) HF (HR, 0.70; 95%CI, 0.54–0.90) CV death (HR, 0.92; 95%CI, 0.77–1.11)

[1]Numbers are % of patients with coronary artery disease. T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

Table 2 Summary of clinical trials of sotagliflozin

Ref.	Population (*n*)	Age, yr (median)	Follow-up period (median)	Patients with a history of HF	Patients with a history of CAD	Main results
SCORED[7]	T2DM and CKD (10584)	63	16 mo	31.0%	22.4%	CV death or HF (HR, 0.74; 95%CI, 0.63–0.88) CV death (HR, 0.90; 95%CI, 0.73–1.12)
SOLOIST-WHF [8]	T2DM and HF (1222)	70	9.2 mo	100%	58.3%	CV death or HF (HR, 0.67; 95%CI, 0.52–0.85) CV death (HR, 0.84; 95%CI, 0.58–1.22)

HF: Heart failure; CAD: Coronary artery disease (numbers indicate % of patients with coronary revascularization in the SCORED trial and % of those with ischemic heart disease in the SOLOIST-WHF trial); T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

patients with heart failure with reduced left ventricular ejection fraction (LVEF) were randomly assigned to receive either dapagliflozin or placebo, in addition to standard therapy for heart failure. Among the participants, 41.8% had diabetes mellitus. During a median follow-up of 18 months, the incidence of cardiovascular death or worsening heart failure was significantly lower in the dapagliflozin group than in the placebo (16.3% *vs* 21.2%; HR, 0.74; 95%CI, 0.65–0.85; $P < 0.001$). Subgroup analysis indicated that the benefit was observed regardless of diabetic status. The empagliflozin outcome trial in patients with chronic heart failure with reduced LVEF (EMPEROR-Reduced) followed the results, examining the potential benefit of empagliflozin in 3730 patients

with heart failure and reduced LVEF[9]. As observed in DAPA-HF, 50.2% of the study participants did not present with diabetes mellitus. The two trials are summarized in Table 3. The study participants in the EMPEROR-Reduced presented greater severity of heart failure than those in the DAPA-HF, with a mean LVEF of 27% *vs* 31% and a median N-terminal prohormone of brain natriuretic peptide (NT-proBNP) value of 1907 *vs* 1437. Furthermore, more than 70% of the patients enrolled in EMPEROR-Reduced had a LVEF less than 30%. As in the DAPA-HF, the emapagliflozin group had lower incidence of cardiovascular death or hospitalization for heart failure than the placebo (19.4% *vs* 24.7%; HR, 0.75; 95%CI, 0.65–0.86; $P < 0.001$) during the median follow-up of 16 months. Moreover, the benefit was observed regardless of the diabetes status. A meta-analysis that included DAPA-HF and EMPEROR-Reduced reported that SGLT2 inhibitors reduced both cardiovascular (HR, 0.86; 95%CI 0.76–0.98) and all-cause mortality (HR, 0.87; 95%CI, 0.77–0.98), without evident statistical heterogeneity between dapagliflozin and empagliflozin[10]. Similarly, SGLT2 inhibitors reduced the risk for the first hospitalization for heart failure (HR, 0.69; 95%CI, 0.62–0.78), the total number of heart failure hospitalizations or cardiovascular death (HR, 0.75; 95%CI, 0.68–0.84), and worsening renal function (HR, 0.62; 95%CI, 0.43–0.90). These findings were generally consistent in subgroup analyses (Table 4). Furthermore, both agents showed no excess risk of adverse events when compared with placebo, including renal adverse events, volume depletion, severe hypoglycemia, or bone fractures. Based on this evidence, the Heart Failure Association of the European Society of Cardiology has recently issued a position paper highlighting results of clinical trials on the role of SGLT2 inhibitors in patients with heart failure[11]. On May 5, 2020, the Food and Drug Administration approved dapagliflozin, specifically, to treat patients with heart failure and reduced ejection fraction. The position paper has concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended to prevent hospitalization for heart failure in type 2 diabetic patients with established cardiovascular disease or high cardiovascular risk[11]. Dapagliflozin and empagliflozin are recommended to reduce the risk for heart failure hospitalization and cardiovascular death in symptomatic patients with heart failure with reduced LVEF already receiving guideline-directed medical therapy, regardless of diabetic status. The Canadian Cardiovascular Society and the Canadian Heart Failure Society have recommended that SGLT2 inhibitors are to be used in patients with mild or moderate heart failure who have an LVEF of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular death[12].

MECHANISMS LINKING SGLT2 INHIBITORS AND REDUCTIONS IN CARDIOVASCULAR EVENTS ARE UNKNOWN

Potential mechanisms

The mechanisms underlying the cardioprotective effects of SGLT2 inhibitors have not been comprehensively elucidated. SGLT2 is predominantly located in the proximal tubule of the kidney and reabsorbs glucose and sodium. Thus, SGLT2 inhibitors reduce not only glucose reabsorption but also sodium reabsorption. These inhibitors behave as diuretics presenting mechanisms such as natriuresis and enhanced diuresis, which can be attributed to an osmotic effect dependent on glycosuria, resulting in a decrease in blood pressure. Research has reported that the drug provides cardiovascular benefits by reducing plasma volume, blood pressure, arterial stiffness, and vascular resistance[2,13]. Blood pressure reduction and renal protection could be the main mechanisms contributing to favorable outcomes. Recently, basic research has suggested that SGLT2 inhibitors induce sympathetic nervous system inhibition[14]. Other studies have reported that SGLT2 inhibitors improved the circadian rhythm of sympathetic activity and reduced high fat diet-induced elevation of tyrosine hydroxylase and noradrenaline in animal models[15,16]. In agreement with this evidence, cardiovascular events that were reduced by SGLT2 inhibitors included sudden cardiac death and hospitalization for heart failure[3]. This evidence presents the hypothesis that the inhibition of sympathetic nervous activity could explain the cardiovascular benefits of SGLT2 inhibitors. Several other hypotheses beyond effects on glycemia, blood pressure lowering, and weight loss have been postulated, including improvement in myocardial energetic efficiency[17] and inhibition of sodium-hydrogen exchangers in the heart, which could prevent cardiomyocyte injury [18].

Table 3 Summary of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Ref.	Population (*n*)	Patients with T2DM	Intervention	Follow-up period (median)	Main results
DAPA-HF[22]	HFrEF with or without T2DM (4744)	42%	Empagliflozin	18 months	CV death or HF (HR, 0.71; 95%CI, 0.65–0.85) HF (HR, 0.70; 95%CI, 0.59–0.83) CV death (HR, 0.82; 95%CI, 0.69–0.98)
EMPEROR-Reduced[9]	HFrEF (3730)	49.8%	Empagliflozin	16 months	CV death or HF (HR, 0.75; 95%CI, 0.65–0.86) HF (HR, 0.69; 95%CI, 0.59–0.81) CV death (HR, 0.92; 95%CI, 0.75–1.12)

T2DM: Type 2 diabetes mellitus; CV: Cardiovascular disease; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

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Table 4 Subgroup analyses for the primary outcomes in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Subgroup	HR (95%CI) of dapagliflozin compared to placebo	HR (95%CI) of empagliflozin compared to placebo
Age		
≤ 65 yr	0.78 (0.63–0.96)	0.71 (0.57–0.89)
> 65 yr	0.72 (0.60–0.85)	0.78 (0.66–0.93)
Sex		
Male	0.73 (0.63–0.85)	0.80 (0.68–0.93)
Female	0.79 (0.59–1.06)	0.59 (0.44–0.80)
T2DM		
Yes	0.75 (0.63–0.90)	0.72 (0.60–0.87)
No	0.73 (0.60–0.88)	0.78 (0.64–0.97)
eGFR < 60 mL/min/1.73 m^2		
Yes	0.72 (0.59–0.86)	0.83 (0.69–1.00)
No	0.76 (0.63–0.92)	0.67 (0.55–0.83)

T2DM: Type 2 diabetes mellitus; HR: Hazard ratio; CI: Confidence interval.

Differences between SGLT2 inhibitors and loop diuretics

Loop diuretics that act in the ascending limb of the Henle loop alleviate symptoms related to heart failure by promoting urinary sodium excretion. Despite their clinical usefulness, diuretics have failed to demonstrate prognostic effects, partly due to counter-regulatory responses through activation of the renin-angiotensin system, neurohormonal activation, and development of diuretic resistance[19]. SGLT2 inhibitors lower plasma glucose by blocking glucose reabsorption in the proximal tubule, resulting in glucose excretion into the urine. The diuretic effect of SGLT2 inhibitors was initially assumed to originate from mild osmotic diuresis owing to glycosuria. Griffin *et al*[20] recently conducted a double-blind, placebo-controlled, crossover study involving treatment with either empagliflozin of 10 mg or matched placebo for 2 wk, followed by a 2-wk washout period and crossover at 2 wk with the alternative treatment in diabetic patients with heart failure[20]. They reported that the natriuretic effect was synergistic with loop diuretics, resulting in a reduced blood and plasma volume, which did not activate the sympathetic nervous system or renin-angiotensin system. Renal dysfunction did not affect the natriuretic effect.

Table 5 Summary of ongoing heart failure outcome trials of sodium-glucose cotransporter 2 inhibitors

	PRESERVED-HF	DELIVER	DAPA ACT HF-TIMI 68	EMPEROR-Preserved	EMPULSE
NCT number	03030235	03619213	04363697	03057951	04157751
Population	HFpEF with or without T2DM	HFpEF with or without T2DM	Acute heart failure with reduced ejection fraction	HFpEF with or without T2DM	Acute Heart Failure
Sample size	320	4700	2400	5750	500
Intervention	Dapagliflozin/placebo	Dapagliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo	Empagliflozin/placebo
Primary endpoint	Change from baseline in NT-proBNP	Time-to-first occurrence of CV death, HF hospitalization, or urgent HF visit	CV death or worsening HF	Time-to-first event of HF hospitalization	Death, number of HF events
Status	Estimated completion; February 2021	Estimated completion; June 2021	Estimated completion; October 2022	Estimated completion; April 2021	Estimated completion; June 2021

HFpEF: Heart failure with preserved ejection fraction; T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; NT-proBNP: N-terminal pro-brain natriuretic peptide.

OPTIMAL TIME FOR ADMINISTERING THE AGENT

The EMPA-RESPONSE-AHF study is a multicenter pilot study that included 80 patients with acute heart failure receiving standard diuretic therapy, randomized to receive either empagliflozin of 10 mg or matched placebo daily for 30 d[21]. Empagliflozin did not demonstrate reduction in the primary outcomes of the visual analog scale of dyspnea, diuretic response, change in NT-proBNP, or length of hospital stay. A secondary composite outcome of in-hospital exacerbation of heart failure, re-hospitalization for heart failure, or death within 60 d reportedly occurred less frequently in the empagliflozin group (10% *vs* 13%, $P = 0.014$). The occurrence of adverse events related to renal function, blood pressure, and heart rate was comparable between the groups. Future trials investigating the benefits of SGLT2 inhibitors in patients with acute heart failure are warranted.

Another clinical question remains whether the effects of SGLT2 inhibitors are affected by the left ventricular ejection fraction. Heart failure treatments in patients with HFrEF have long been established, while evidence is scarce in patients with heart failure with preserved ejection fraction (HFpEF). Similarly, available evidence has revealed that the beneficial effects of SGLT2 inhibitors have been observed in HFrEF but not necessarily in HFpEF. Ongoing studies may provide some data on this issue. The ongoing heart failure outcome trials for SGLT2 inhibitors are summarized in Table 5.

CONCLUSION

Accumulated evidence from large-scale randomized placebo-controlled trials has demonstrated the consistent effect of SGLT2 inhibitors on the clinical course of heart failure, mainly driven by a substantial decrease in hospitalization for heart failure. These benefits were attained regardless of the presence or absence of diabetes, with agents administered once daily and requiring no up-titration; additionally, no serious adverse effects were observed. This evidence supports the role of SGLT2 inhibitors as a new standard of care for HFrEF. Further studies are needed to clarify the optimal time for administering these agents, proper candidates who most benefit from these agents, and mechanisms explaining the cardioprotective effects of SGLT2 inhibitors.

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MINIREVIEWS

Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol

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Abstract

Statins have been shown to be effective in reducing cardiovascular events. Their magnitude of benefits has been proportionate to the reduction in low-density lipoprotein cholesterol (LDL-c). Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have further improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by LDL-c level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous, including thrombosis and inflammation risks. Moreover, the lipoprotein related risk is increasingly recognised to be related to other non-LDL-c markers such as Lp(a). Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plagues at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

Key Words: Intensive lipid-lowering; Proprotein convertase subtilisin kexin 9 inhibitors; Ezetimibe; Plaque imaging; Low-density lipoprotein cholesterol

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Core Tip: Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by low-density lipoprotein cholesterol level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous. Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plagues at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

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INTRODUCTION

Despite optimal, guideline-recommended medical therapy for secondary prevention, patients remain at increased risk of cardiovascular events. This risk, referred to as residual risk, is attributable to different processes such as lipid accumulation, inflammation, and thrombosis[1]. Estimating lipid risk has always been guided by the use of low-density lipoprotein cholesterol (LDL-c)[2]. The magnitude of LDL-c reduction was associated with proportionate decrease in cardiovascular events in response to lipid lowering treatment[3]. The Cholesterol Treatment Trialists Collaboration (CTTC) reported from 26 trials including 169138 patients that for every 1.0 mmol/L reduction in LDL-c, there was 22% reduction in cardiovascular events[3]. Importantly, these benefits were derived using HMG CoA reductase inhibitors *i.e.*, statins.

Recent development in lipid-lowering therapies, including ezetimibe and proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have confirmed the LDL-c hypothesis[4,5]. In other words, the reduction in cardiovascular outcomes was related to LDL-c reduction and reproduced using non-statin treatments[6-8]. Therefore, the concept of lower is better should ideally be applied to all patients with vascular disease and LDL-c should be targeted using statin alongside non-statin drugs. Nonetheless, current guidelines recommend intensifying lipid-lowering therapy using ezetimibe or PCSK9 guided by LDL-c level[2]. Whilst the recommended targets for LDL-c has been lowered to reflect the reported cardiovascular benefits from recent intensive lipid-lowering trials[6-8], such an approach may deprive a subset of patients from potential benefits in response to intensive LDL-c reduction. This Review discusses the limitations of solely using LDL-c to guide intensive lipid-lowering therapy and highlights a strategy to identify patients who would benefit from adding a second lipid-lowering treatment, mainly PCSK9 inhibitor, on top of statin.

CAVEATS OF ROUTINELY USING INTENSIVE LIPID LOWERING TREATMENT

Data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trials highlighted better cardiovascular outcomes in response to LDL-c reduction in patients on maximally-tolerated statin dose[6-8]. Notably, the magnitude of reduction in LDL-c did not match the decrease in clinical events[5,9]. This becomes more evident when comparing data of PCSK9 inhibitors to CTTC clinical outcomes[5,9]. When juxtaposed to the reduction in LDL-c level, there may be diminished benefits in response to very low LDL-c with lack of significant incremental benefits below a certain level of LDL-c[5,9]. This possible "plateau effect" was also highlighted on a

mechanistic level in the GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound (GLAGOV) trial[10]. Further reduction in LDL-c did not lead to commensurately greater plaque regression, highlighting a possible phenomenon that could be referred to as "LDL-c exhaustion". Whether longer exposure to low LDL-c may be translated into larger plaque regression using PCSK9 inhibitors is yet to be determined. A recent large meta-analysis of 34 trials highlighted that the reduction in mortality in response to intensive lipid-lowering therapy compared to less-intensive regimen was only evident at LDL-c level of 100 mg/dL[11]. The presence of a threshold is in line with the proposed concept of "LDL-c exhaustion", however, future studies are needed to identify the optimal threshold according to patients' clinical syndromes.

Importantly, residual cardiovascular risk is recognised even after achieving low LDL-c[1,12] a reflection of the multiple mechanisms underlying atherothrombotic vascular disease. Almost one in ten patients had a second vascular event within 3 years follow up despite attaining LDL-c to < 70 mg/dL[7]. Therefore, using LDL-c as the only surrogate of future adverse events has significant limitations, and there is need to characterise atherosclerotic disease processes beyond estimating future cardiovascular risk. Other disease characteristics, such as thrombosis or inflammation, maybe more prominent and tailored therapies might be more effective in reducing the residual risk.

Moreover, costs may challenge the routine use of PCSK9 inhibitors in patients with cardiovascular disease. Subjecting patients to PCSK9 inhibitors guided by the FOURIER and ODYSEEY Outcomes trials criteria would incur an increase in health care costs by $450000 and $315000 per QALY, factoring in late effect on mortality[9,13-15]. The cost would remain significant even when including patients with baseline LDL-c ≥ 100 mg/dL[9,13,14].

Overall, unselective implementation of PCSK9 inhibitors is undesirable and unaffordable given the modest effect on preventing cardiovascular events at a significant increase of health costs. Therefore, adopting a new strategy based on the characteristics of the atherosclerotic disease process may be more promising. Emerging data provide new insights into the role of certain atherosclerotic features to identify patients who sustain larger clinical benefits when using intensive lipid-lowering therapy. Such features include polyvascular disease, diabetes and post coronary artery bypass graft (CABG)

Polyvascular disease

Polyvascular disease refers to atherosclerotic involvement of two or more of arterial vascular beds[16]. Exposure to high concentrations of low-density lipoprotein, including very small, small, intermediate and large particles was associated with developing polyvascular disease in patients with peripheral arterial disease[17]. Several trials have shown the close correlation between the number of involved vascular beds with increased mortality[18,19]. Polyvascular disease is considered as one of the high risk features in initial Task Force of European Society of Cardiology (ESC)/European Atherosclerosis Society. To mitigate the risk, commencing PCSK9 in addition to statin, was recommended, albeit, to achieve LDL-c level of < 100 mg/dL, and even lower according to the new European guidelines[2,20]. Nonetheless, LDL-c remains key in titrating intensive lipid-lowering therapy in this high risk group.

The IMPROVE IT trial revealed a higher cardiovascular event rates with almost 50% increased risk in cardiovascular death in patients with polyvascular compared to monovascular disease[19]. The combination of CAD and peripheral vascular disease was associated with more than 25% incidence rate of myocardial infarction[19]. Importantly, the benefits of adding ezetimibe to statin therapy were seen regardless of the number of diseased vascular beds, although patients with polyvascular disease sustained a numerically larger absolute risk reduction in response to intensive statin therapy[19]. In pre-specified subgroup analysis of the ODYSSEY Outcomes trial, alirocumab was associated with absolute risk reduction in cardiovascular events proportional to the number of diseased vascular beds *i.e.*, 1.4% for monovascular disease, 1.9% for two beds vascular disease and 13% in three beds polyvascular disease [21]. However, in the FOURIER trial, the risk reduction associated with evolocumab was relatively modest (2.7%) in the polyvascular disease group despite having heightened residual cardiovascular risk (19.9%)[22]. The inconsistency may be related to statistical power, although other factors, such as the targeted population, definition and aetiologies of vascular disease need to be factored in when interpreting these results.

To overcome these issues, Alkhalil *et al*[23] conducted a meta-analysis of 7 studies including 94362 patients, reporting the role of intensive lipid-lowering therapy in polyvascular *vs* monovascular disease groups. They highlighted that the absolute risk reduction was more marked in patients with polyvascular disease [(6.5% (95%CI, 5.0–7.9)] compared to monovascular disease [1.8% (95%CI, 1.3–2.3)]. Notably, when the analysis was performed according to the level of baseline LDL-c, there was a differential treatment effect in response to intensive lipid-lowering therapy in patients with monovascular disease. Patients with monovascular disease and LDL-c > 100 mg/dL had absolute risk reduction of 3.2% (95%CI, 2.3–4.1) compared to 1.2% (95%CI, 0.6–1.8) in patients with monovascular disease and LDL-c ≤ 100 mg/dL. In contrast, patients with polyvascular disease had comparable treatment effects irrespective of LDL-c [5.7% (95%CI, 3.6–7.8) in patients with LDL-C >100 mg/dL and 7.2% (95%CI 5.2–9.2) in those with LDL-C ≤ 100 mg/dL)[23]. Moreover, recent data from the ODYSSEY Outcomes trial suggest that the magnitude of LDL-c reduction across the strata of evident vascular disease was comparable, yet, the reduction in clinical outcomes was more pronounced in those with polyvascular disease[21]. This was in contrast with CTTC data whereby lowering LDL-c was associated with a consistent reduction in vascular events among patients with different clinical characteristics[24]. Collectively, this may suggest that monitoring response to intensive lipid-lowering therapy can no longer be guided using LDL-c in the post statin era. A notion that was recently highlighted from the Copenhagen General Population Study.

PATIENTS WITH PRIOR CABG

Patients with previous CABG have extensive coronary artery disease and are at increased risk of adverse cardiovascular events, including mortality[25,26]. Early data showed the beneficial effect of statins in patients with previous CABG[27]. More recently, alirocumab was reported to have heterogeneity in treatment effects according to the status of previous CABG. The absolute risk reduction of major adverse events was remarkably larger [6.4%, (95%CI: 0.9 to 12.0)] in patients with CABG compared to those with no previous CABG [1.3%, (95%CI: 0.5 to 2.2)[28].

Similar outcomes were reported in the pre-specified analysis from the IMPROVE IT trial[29]. Adding ezetimibe to simvastatin was translated into 8.8% (95%CI: 3.1 to 14.6) absolute risk reduction in patients with previous CABG compared to merely 1.3% (95%CI: 0 to 2.6%) in those patients without previous CABG history[29]. Moreover, a recent meta-analysis revealed the incremental benefits of intensive lipid lowering therapy in patients post CABG[30]. Remarkably, there was a significant 14% reduction in all-cause mortality [rate ratio (RR) 0.86; (95%CI, 0.74 to 0.99)] and 25% reduction in cardiovascular mortality [RR 0.75; (95%CI, 0.65 to 0.86)] when subjecting patients post CABG to intensive lipid lowering therapy[30]. Unpublished data suggest that the mortality benefit in patients post CABG was independent of the level of baseline LDL-c. In other words, patients post CABG with LDL-c > 100 mg/dL sustained 2.5% (95%CI: 0 to 4.8%) absolute risk reduction compared to 1.2% (95%CI: -1.0 to 3.5) in patients without previous CABG.

The heightened risk in patient post CABG warrants consideration of early introduction of intensive lipid-lowering therapy, particularly since the benefits were not merely related to a composite clinical endpoint but was extended to include all-cause and cardiovascular mortality. Importantly, the level of LDL-c does not determine the efficacy of intensive lipid-lowering therapy and whether upfront and targeted approach for this group would be an alternative option in a cost-effective, sustainable platform in most health care systems needs to be explored.

PATIENTS WITH DIABETES AND METABOLIC SYNDROME

Patients with diabetes mellitus are at increased risk of future cardiovascular events[31-34]. The aggressive nature and extent of atherosclerosis burden, despite glucose normalisation, is recognised as a potential mechanism of this increased risk[31-34]. Statin is recommended in this group for primary and secondary prevention[2]. Notably, statin treatment is associated with 0.5-1.0% increase in the incidence of new-onset diabetes[24]. Similarly, certain variants in PCSK9 genes were also reported to increase the risk of diabetes. Data suggest that there is 10% increase in the risk of diabetes for each 10 mg/dL reduction in LDL-c[9,35]. Nonetheless, pharmacological inhibition of PCSK9 was not associated with an increase in the incidence of diabetes

mellitus, nor affect glycaemic control[36-38]. Moreover, in a large meta-analysis of 33 randomized trials including 163688 non-diabetic patients, PCSK9 inhibitors were not associated with new onset diabetes[39].

In the IMPROVE-IT and ODYSSEY Outcomes trials, intensive lipid-lowering therapies using ezetimibe and alirocumab, respectively, lowered LDL-c compared to placebo, irrespective of the diabetic status of patients[37,40]. Nevertheless, the absolute risk reduction using ezetimibe was 5.5% in diabetic patients, which was significantly larger compared to 0.7% in non-diabetic patients (P = 0.002 for interaction)[40]. Likewise, in response to intensive LDL-c reduction using PCSK9 inhibitors, the absolute reduction in adverse cardiovascular events in diabetic patients (2·3%, 95%CI 0·4 to 4·2) was better than in those with prediabetes (1.2%, 95%CI: 0.0 to 2.4) or normoglycaemia (1.2%, 95%CI: −0.3 to 2.7) (P = 0·0019 for interaction)[37]. Similarly, evolocumab in the FOURIER trial showed more absolute risk reduction in the primary end point in diabetic *vs* non-diabetic groups [(2.7%; 95%CI: 0.7 to 4.8) and (1.6%; 95%CI, 0.1 to 3.2)][38]. Interestingly, the reduction in atherosclerosis burden on intravascular ultrasound (IVUS) was comparable between diabetic and non-diabetic in response to PCSK9 inhibition[10].

Patients with metabolic syndrome are at increased risks of developing diabetes and cardiovascular disease[41]. It is characterised as a cluster of conditions including central obesity, insulin resistance, hypertension and dyslipidaemia. Metabolic syndrome is common and was reported in almost 60% of recruited patients in the FOURIER trial, and more importantly, was associated with 30% increase in the risk of future adverse cardiovascular events[42]. Evolocumab was associated with similar LDL-c reduction, irrespective of the status of metabolic syndrome[42]. Moreover, it reduced cardiovascular events by 17% in this subgroup HR 0.83 95%CI: 0.76 to 0.91 [42].

ELDERLY PATIENTS

Old age is a risk for adverse cardiovascular events and most individuals aged 65 or above are already at high or very high risk[43]. Elderly population are under-represented in clinical trials and the recent CTTC reported that previous statin trials included only 8% of patients > 75[44]. Moreover, side effects, co-morbidities, and interactions with other medications add more challenges to intensive lipid-lowering therapy in the elderly. Nonetheless, LDL-c reduction using statin was associated with 21% proportionate reduction in major vascular events in the elderly[44]. There was a trend towards diminishing efficacy with increased age, although this did not reach statistical significance[44].

In a pre-specified secondary analysis of the IMPROVE-IT trial, Bach *et al*[45] reported 8.7% absolute risk reduction when adding ezetimibe to simvastatin in elderly patients (> 75 years). In comparison, for patients below 65 years and between 65-74 years, their absolute risk reduction was 0.9% and 0.8%, respectively. Similar findings were reported from the ODYSSEY Outcomes trial, whereby alirocumab was associated with larger absolute risk reduction with increasing age: 2.3% at age 45; 3.8% at age 75; and 8.3% at age 85 years[46]. Interestingly, data from the FOURIER trial suggest small variations in the incidence of major vascular events according to age groups with a consistent finding that evolocumab reduced adverse events regardless of patient age [47]. Similarly, in the ODYSSEY OUTCOMES trial age did not appear to modify the beneficial effects of LDL-c lowering using PCSK9 inhibitors[7]. In contrast, the relative risk reduction associated with ezetmibe was only evident in the group of patients > 75 years (HR, 0.80; 95%CI, 0.70-0.90) while the other groups had relative risk reduction of less than 5% (P = 0.02 for interaction). Notably, the difference in LDL-c reduction was comparable across the age groups.

This apparent inconsistency in the impact of intensive lipid lowering across age in different studies should not be surprising. In fact, this phenomenon could possibly be extended to other "high risk" clinical features (Table 1). The mechanism by which lipid-lowering therapy exerts clinical benefit is by evacuating lipid from atherosclerotic plaque, rendering them more stable[5,48]. Therefore, patients with large burden of atherosclerotic plaque or more specifically lipid rich plaque are likely to benefit more from intensive lipid lowering therapy. In other words, the largest absolute risk reduction is anticipated in the highest risk group and the benefit should be proportionate to the baseline absolute risk. However, this is only true if the residual risk is homogeneous and if the applied therapy targets that specific risk[1,5,9]. However, in elderly populations the residual risk is heterogeneous, and intensive lipid

Table 1 Cardiovascular outcome of proprotein convertase subtilisin kexin 9 inhibitors *vs* Placebo in different studies and subgroups

ODYSSEY trial subgroup (*n* = 18924)	Alirocumab *vs* placebo
Patients with Polyvascular disease	
Monovascular (*n* = 17370)	Cardiovascular events: ARR 1.4% (CI 95%; 0.6%-2.3%)Mortality: 0.4% (95%CI: -0.1% to 1.0%)
2 vascular beds (*n* = 1405)	Cardiovascular events: ARR 1.9% (CI 95%; -2.4%-6.2%)Mortality: ARR 1.3% (95%CI: -1.8% to 4.3%)
3 vascular beds (*n* = 149)	Cardiovascular events: ARR 13% (CI 95%; -2%-28%)Mortality: ARR 16.2% (95%CI: 5.5% to 26.8%)
FOURIER Trial (*n* = 27564)	**Evolocumab *vs* placebo**
With PAD (*n* = 2642)	Composite of major cardiac events ARR 3.5% HR 0.79; 95%CI, 0.66-0.94; *P* = 0.0098
Without PAD (*n* = 24922)	Composite of major cardiac events ARR: 1.6% HR 0.86; 95%CI, 0.80-0.93; *P* = 0.0003
Patients with prior CABG	
ODYSSEY trial subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
With Prior CABG (*n* = 1003)	Composite of major cardiac events ARR: 6.4%; 95%CI: 0.9 to 12.0
With index CABG (*n* = 1025)	Composite of major cardiac events ARR: 0.9%; 95%CI: 2.3 to 4.0
Without prior CABG (*n* = 16896)	Composite of major cardiac events ARR: 1.3%; 95%CI: 0.5 to 2.2
Patients with diabetes mellitus or metabolic syndrome	
FOURIER Trial diabetic subgroup (*n* = 27564)	**Evolocumab *vs* placebo**
With diabetes (*n* = 11031)	Composite of major cardiac events HR 0 ·83 (95%CI 0.75-0.93; *P* = 0.0008), Absolute risk reduction 2.7% (95%CI 0.7–4.8)
Without diabetes (*n* = 16533)	Composite of major cardiac events HR 0.87 (0.79-0.96; *P* = 0.0052)Absolute risk reduction 1.6% (95%CI 0.1–3.2)
FOURIER trial metabolic syndrome subgroup (*n* = 27342)	**Evolocumab *vs* placebo**
With met syndrome (*n* = 16361)	Composite of major cardiac events HR 0.83 (95%CI; 0.76-0.91)
Without met syndrome (*n* = 10981)	Composite of major cardiac events HR:0.89, CI 95% (0.79-1.01)
ODYSSEY trial subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
With diabetic (*n* = 5444)	Composite of major cardiac events ARR 2.3%, 95%CI 0.4 to 4.2
Prediabetic (*n* = 8246)	Composite of major cardiac events ARR 1.2%, 95%CI: 0.0 to 2.4
Normoglycemic (*n* = 5234)	Composite of major cardiac events ARR 1.2%, 95%CI: −0.3 to 2.7
Elderly patients	
FOURIER trial (*n* = 27564) age subgroup[8]	**Evolocumab *vs* placebo**
Q1	Composite of major cardiac events HR 0.83, 95%CI 0.72-0.96
Q2	Composite of major cardiac events HR 0.88, 95%CI 0.76-1.01
Q3	Composite of major cardiac events HR 0.82, 95%CI 0.71-0.95
Q4	Composite of major cardiac events HR 0.86, 95%CI 0.74-1.00
ODYSSEY trial age subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
≥ 65 yr	Composite of major cardiac events HR 0.78, 95%CI 0.68-0.91
< 65 yr	Composite of major cardiac events HR 0.89, 95%CI 0.80-1.00

lowering therapies were applied unselectively without measures of atherosclerosis disease burden. Recent developments have allowed *in-vivo* plaque imaging and lipid quantification to aid decision making in using intensive lipid lowering drug[49-51].

ROLE OF PLAQUE IMAGING TO GUIDE INTENSIVE LIPID-LOWERING TREATMENTS

The lipoprotein-related risk is heterogeneous and likely to be related to other non-LDL-c parameters. As highlighted above the use of LDL-c in the post statin era could

be challenged as the magnitude of LDL-c reduction did not reflect clinical outcomes in patients using intensive lipid lowering therapy. High-density lipoprotein (HDL-c) was highlighted as a prognostic marker with an inverse relationship with adverse outcomes in patients with cardiovascular disease[52]. Nonetheless, it failed as a therapeutic target with no effect on cardiovascular outcomes despite significant increase in HDL-c levels using niacin and cholesterol-ester transfer protein inhibitors [53-55]. Recent data suggest that the level of triglyceride and remnant cholesterol are associated with cardiovascular outcomes, independent of other risk factors, including LDL-c[56]. Moreover, VLDL-c was associated with double the hazard of myocardial infarction in the Copenhagen General Population Study which included more than 100000 individuals[57]. Targeted therapies are in development to assess whether certain lipid biomarkers, such as Lp(a), could be used as therapeutic target, in addition to LDL-c[58]. This approach is promising as certain markers such as lipoprotein (a) would identify high risk patients and, therefore, targeting this particular biomarker maybe associated with a reduction in future cardiovascular events.

Overall, the complex interaction between lipid biomarkers would render a single marker imprecise in predicting clinical outcomes. Collectively, these markers target atherosclerotic plaque progression or regression, and therefore, characterising plaque would provide a better and more comprehensive picture on future plaque, and patient risk. Invasive and non-invasive imaging tools, such as near infra-red spectroscopy and T2 mapping, would allow precise measurement and characterisation of lipid core within atherosclerotic plaque. Patients with propensity to develop lipid-rich plaque may be suitable candidate for intensive lipid-lowering drug. Remarkably, clinical entities that demonstrate large improvement in clinical outcomes shared similar profile in the atherosclerotic disease process. Patients with polyvascular disease, post CABG and diabetes are reported to have advanced and aggressive atherosclerotic disease and, therefore, intensive lipid lowering therapy had produced mortality benefits in certain cases. The use of plaque imaging may risk stratify patients and provide a platform to monitor patients response to lipid-lowering therapy. Patients with large lipid-rich plaques in multiple vascular territories or those who have poor or suboptimal response to statin, may be suitable candidates for more expensive therapies. These treatments would be rationalised according to the atherosclerotic disease characteristics and not merely based on a single marker that is unlikely to reflect patient future risk. Future randomised clinical trials are needed to assess whether the proposed approach would prove to be cost-effective. The use of atherosclerotic disease characteristics to guide decision making for intensive, yet, expensive lipid-lowering therapy is a step toward more personalised and precision medicine.

CONCLUSION

LDL-c plays an important role in the development of atherosclerotic disease as evidenced by the proportionate reduction in LDL-c improving cardiovascular outcomes with statin use. Nevertheless, the heterogeneous residual risk post statin challenges the use of LDL-c as a single maker to guide additional lipid lowering therapy. Emerging data suggest that patients with large atherosclerotic burden appear to sustain increased benefits from intensive lipid-lowering therapy. Future studies are in development to assess whether plaque imaging and phenotypic features associated with larger atherosclerotic burden would help identify patients who may benefit from additional intensive lipid lowering treatments.

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ORIGINAL ARTICLE

Retrospective Study

Patients' time in therapeutic range on warfarin among atrial fibrillation patients in Warfarin Medication Therapy Adherence Clinic

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Abstract

BACKGROUND

The quality of warfarin therapy can be determined by the time in the therapeutic range (TTR) of international normalized ratio (INR). The estimated minimum TTR needed to achieve a benefit from warfarin therapy is ≥ 60%.

AIM

To determine TTR and the predictors of poor TTR among atrial fibrillation patients who receive warfarin therapy.

METHODS

A retrospective observational study was conducted at a cardiology referral center in Selangor, Malaysia. A total of 420 patients with atrial fibrillation and under follow-up at the pharmacist led Warfarin Medication Therapeutic Adherence Clinic between January 2014 and December 2018 were included. Patients' clinical data, information related to warfarin therapy, and INR readings were traced through electronic Hospital Information system. A data collection form was used for data collection. The percentage of days when INR was within range was calculated using the Rosendaal method. The poor INR control category was defined as a TTR < 60%. Predictors for poor TTR were further determined by using logistic regression.

RESULTS

anonymous clinical data that were obtained after each patient agreed to treatment. Permission to use the patient data from this facility has been obtained from the Head of Department of Cardiology, Hospital Serdang.

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A total of 420 patients [54.0% male; mean age 65.7 (10.9) years] were included. The calculated mean and median TTR were 60.6% ± 20.6% and 64% (interquartile range 48%-75%), respectively. Of the included patients, 57.6% (n = 242) were in the good control category and 42.4% (n = 178) were in the poor control category. The annual calculated mean TTR between the year 2014 and 2018 ranged from 59.7% and 67.3%. A high HAS-BLED score of ≥ 3 was associated with poor TTR (adjusted odds ratio, 2.525; 95% confidence interval: 1.6-3.9, P < 0.001).

CONCLUSION

In our population, a high HAS-BLED score was associated with poor TTR. This could provide an important insight when initiating an oral anticoagulant for these patients. Patients with a high HAS-BLED score may obtain less benefit from warfarin therapy and should be considered for other available oral anticoagulants for maximum benefit.

Key Words: Atrial fibrillation; Time in therapeutic range; International normalized ratio; HAS-BLED score; Oral anticoagulants; Warfarin Medication Therapeutic Adherence Clinic

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Core Tip: This is a retrospective observational study to determine time in therapeutic range (TTR) and the predictors of poor TTR among patients with atrial fibrillation under follow-up at the Warfarin Medication Therapeutic Adherence Clinic of a tertiary cardiology referral center in Selangor, Malaysia. In this study cohort, we found that high HAS-BLED score (≥ 3) was a significant predictor of poor TTR.

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INTRODUCTION

Atrial fibrillation (AF) is usually asymptomatic and is associated with an increased risk of major adverse cardiovascular events (MACE) and mortality in patients with coronary artery disease (CAD)[1]. The prevalence of AF in the Malaysian population is low at 0.54%, compared to the global average of 1%[2].

Warfarin is the most widely used anticoagulant in the world[3-5]. Although novel oral anticoagulants are available, warfarin remains a viable oral anticoagulant for many patients because of its availability and cost[4,6,7]. The time in therapeutic range (TTR) estimates the percentage of time a patient's international normalized ratio (INR) is within the desired treatment range or goal and is widely used as an indicator of anticoagulation control[4,9-12]. TTR is commonly used to evaluate the quality of warfarin therapy and is an essential tool for assessing the risks *vs* benefits of warfarin therapy[4,8,13,14]. A 10% increase in time spent out of TTR is associated with a 29% increase in the risk of mortality and a 10%-12% increase in the risk of an ischemic stroke and other thromboembolic events[13,15-17].

The aim of this study is to determine the percentage of time a patient's INR is within the desired treatment range and the predictors of poor TTR among patients with AF who receive warfarin therapy.

MATERIALS AND METHODS

Study design

This is a retrospective observational study that was conducted in Hospital Serdang

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located in Kajang, Selangor. Hospital Serdang is a cardiology reference center that covers patients from Serdang, Bangi, Putrajaya, Kajang, Dengkil, and Puchong area in the state of Selangor, Malaysia. Ethical approval for this study was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-19-839-46462). The study was carried out in accordance with the Declaration of Helsinki.

Study setting and study population

All AF patients under Warfarin Medication Therapeutic Adherence Clinic follow-up between 2014 to 2018 were included. The electronic Hospital Information System (eHIS) was used to extract patients' demographics, comorbidities, information related to warfarin therapy, and INR readings. Baseline comorbidities were retrospectively retrieved according to available medical records in eHIS. The consecutive sampling method was used. A case report form was used for data collection. Each patient was allocated a patient identifier number that matched their patient registration number, in order to protect confidentiality. Patients were excluded if they discontinued warfarin therapy, died, or had less than three INR readings.

TTR

For patients with AF, the target INR range was between 2.0 to 3.0. TTR is defined as an estimate of the average time that a medication is dosed with optimal efficacy and safety[4]. From previous literature, the estimate of the minimum TTR needed to achieve a benefit from warfarin therapy is between 58% and 65%[18]. The percentage of days that INR was within range was calculated using the Rosendaal method[8]. Thus, based on these references, we defined the "poor" TTR category as TTR < 60% and the "good" TTR category as TTR > 60%.

Statistical analysis

This study aimed to determine to what extent the following factors are associated with poor TTR: Age, gender, ethnicity, diabetes mellitus, hypertension, previous ischemic heart disease, chronic kidney disease, peripheral vascular disease, stroke/transient ischemic attack, deep vein thrombosis/pulmonary embolism, heart failure, chronic obstructive pulmonary disease/asthma, chronic kidney disease, dyslipidaemia, chronic rheumatic heart disease, CHA2DS2-VASc score, and HAS-BLED score. A study by Peduzzi *et al*[19] on sample size for logistic regression suggests using a minimum event per variable value of ten. Since our study was interested in studying 17 risk factors, a minimum sample of 170 patients in the poor TTR category group was required. The study planned to recruit at least 400 samples in order to exceed the minimum sample size, as the prevalence of poor TTR was estimated at 38%[19].

Categorical variables were summarized using frequencies and proportions while continuous variables were summarized using mean ± standard deviation or median (inter-quartile range) values. Logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to model the predictors of poor TTR. This analysis was repeated and adjusted to variables that were significant from the previous studies: Heart failure, chronic kidney disease, CHA2DS2-VASc score, and HAS-BLED score[20]. A $P < 0.05$ was considered significant. Point estimates and 95%CI are presented for all results. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20 (Armonk, NY, United States).

RESULTS

A total of 420 patients with AF were included in this study (Figure 1). Baseline characteristics are shown in Table 1. The mean age of the study population was 65.7 (10.9) years. There were slightly more male patients (54%, $n = 227$) than female patients (46%, $n = 193$). The largest ethnic population was Malay, followed by Chinese and Indian. Hypertension accounted for the highest percentage of comorbidities among patients with AF, followed by diabetes mellitus, dyslipidaemia, and ischemic heart diseases. Median CHA2DS2-VASc score was 3 (moderate risk of stroke), and median HAS-BLED score was 2 (low bleeding risk).

Time in therapeutic range

Over 5 years, the mean (standard deviation) TTR was 60.6% (20.6%) with a median of 64% (interquartile range 27%). Of the included patients, 57.6% ($n = 242$) were in the good control category, and 42.4% ($n = 178$) were in the poor control category (Table 2). The annual calculated mean TTR between the year 2014 and 2018 ranged between

Table 1 Baseline characteristics

Baseline characteristic	All patients, *n* = 420	TTR < 60%, *n* = 178	TTR ≥ 60%, *n* = 242
Age, yr			
mean ± SD	65.7 ± 10.9	65.7 ± 10.8	65.7± 10.9
Median (IQR)	67 (15)	66 (14)	67 (15)
Male	227(54.0)	99 (55.6)	128 (52.9)
Female	193 (46.0)	79 (44.4)	114 (47.1)
Ethnicity			
Malay	210 (50.0)	96 (53.9)	114 (47.1)
Chinese	179 (42.6)	64 (36.0)	115 (47.5)
Indian	26 (6.2)	16 (9.0)	10 (4.1)
Others	5 (1.2)	2 (1.1)	3 (1.2)
Comorbidities			
Diabetes mellitus	170 (40.5)	85 (47.8)	85 (35.1)
Hypertension	291 (69.3)	128 (71.9)	163 (67.4)
Ischemic heart disease	90 (21.4)	48 (27.0)	42 (17.4)
Peripheral vascular disease	8 (1.9)	2 (1.1)	6 (2.5)
Stroke/transient ischemic attack	49 (11.7)	20 (11.2)	29 (12.0)
Deep vein thrombosis/pulmonary embolism	2 (0.5)	1 (0.6)	1 (0.4)
Heart failure	27 (6.4)	12 (6.7)	15 (6.2)
Chronic obstructive pulmonary disease/asthma	22 (5.2)	8 (4.5)	14 (5.8)
Chronic kidney disease	49 (11.7)	28 (15.7)	21 (8.7)
Dyslipidaemia	125 (29.8)	47 (26.4)	78 (32.2)
Chronic rheumatic heart disease	17 (4.0)	10 (5.6)	7 (2.9)
Liver disease	0 (0.0)	0 (0.0)	0 (0.0)
CHA_2DS_2-VASc score			
Mean ± SD	2.6 ± 1.4	-	-
Median (IQR)	3 (1.0)	3 (2)	2(1)
Score 0-1	91 (21.7)	34 (19.1)	57 (23.6)
Score 2-4	297 (70.7)	125 (70.2)	172 (71.1)
Score ≥ 5	32 (7.6)	19 (10.7)	13 (5.4)
HAS-BLED score			
Median (IQR)	2 (2.0)	3 (1.0)	2 (2.0)
Low bleeding risk (score ≤ 2)	257 (61.2)	83 (46.6)	174 (71.9)
High bleeding risk (score ≥ 3)	163 (38.8)	95 (53.4)	68 (28.1)

All values are reported as *n* (%) unless otherwise noted. IQR: Interquartile range; TTR: Time in therapeutic range; SD Standard deviation.

59.7% and 67.3%. The highest percentage was in 2018, with 67.3% of days within therapeutic range in AF patients. Figure 2 shows the mean TTR for AF patients from 2014 to 2018. Patient with a high HAS-BLED (score ≥ 3) had a median TTR of 55% compared to patients with a low HAS-BLED score, who had a median TTR of 68% (Figure 3).

Predictors of poor TTR

From the multivariate analysis, a high HAS-BLED score (score ≥ 3) was significantly associated with a poor TTR (< 60%) (adjusted OR, 2.5;1.6-3.9, $P < 0.001$) compared to a

Table 2 Time in the therapeutic range of the study population

Variables	All patients, *n* = 420	TTR < 60%, *n* = 178	TTR ≥ 60%, *n* = 242
TTR			
mean ± SD	60.6 ± 20.6	41.1 ± 14.7	75.0 ± 9.6
Median (IQR)	64 (27)	44 (22)	74 (14)
Good (≥ 60%)	242 (57.6)	-	-
Poor (< 60%)	178 (42.4)	-	-

SD: Standard deviation; TTR: Time in therapeutic range.

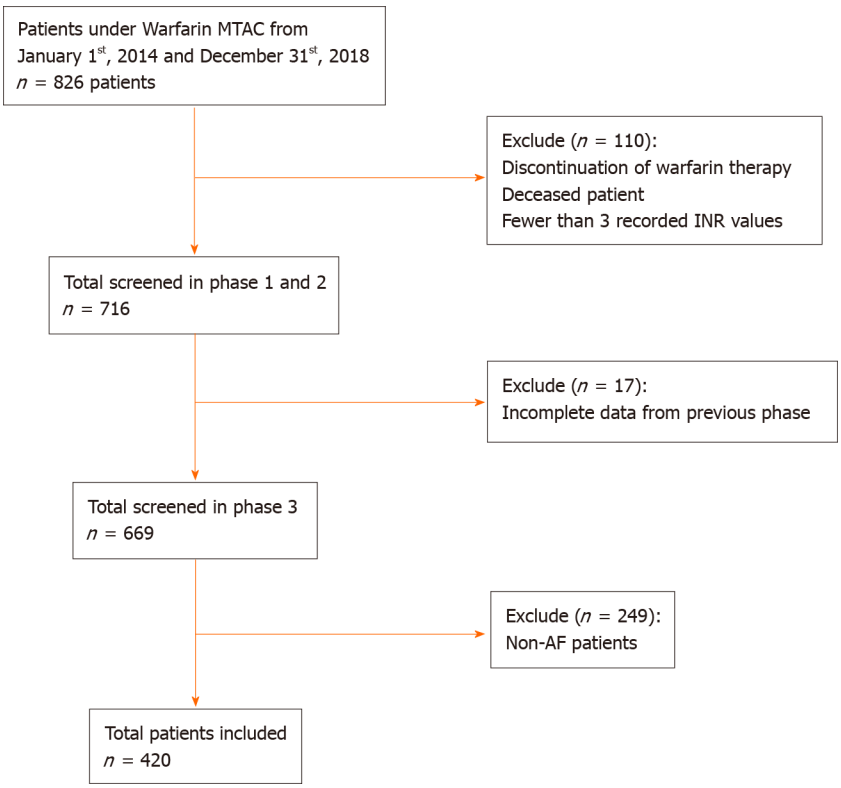


Figure 1 Flow diagram describing the selection of data for the analysis reported. AF: Atrial fibrillation; INR: International normalized ratio; MTAC: Medication Therapeutic Adherence Clinic.

low HAS-BLED score (score ≤ 2). Similarly, in the model adjusted for predictors previously described in previous reports[20] (model 2), only HAS-BLED score was found to be a significant predictor of poor TTR (adjusted OR, 2.9;1.8-4.7, $P < 0.001$) (Table 3).

DISCUSSION

This study assessed the percentage of time a patient's INR is within the desired treatment range or TTR and explored the predictors of poor TTR. Overall, the study population had a majority of men and people of Malay ethnicity. This could be explained by the Malaysian population distribution, whereby more than half of the population are of Malay ethnicity, and there are more men than women with the ratio of 107:100[21]. Our results showed similarity with other international studies, with a majority of warfarin users being male[22,23].

Hypertension had the highest prevalence, followed by diabetes mellitus, hyperlipidemia, and ischemic heart disease. The higher prevalence of cardiac-related comorbidities could be explained by Hospital Serdang's status as a cardiology center,

Table 3 Univariate and multivariate logistic regression analysis for predictors of poor time in therapeutic range < 60% among atrial fibrillation patients

Baseline characteristic	Univariate			Multivariate					
				Model 1[1]			Model 2[2]		
	OR	95%CI	*P*	aOR	95%CI	*P*	aOR	95%CI	*P*
Age	1.0	0.9-1.0	0.976						
Ethnicity									
Malay	1.0	Reference	-						
Chinese	1.3	0.2-7.7	0.800						
Indian	0.8	0.1-5.1	0.845						
Others	2.4	0.3-16.9	0.380						
Gender									
Male	1.0	Reference	-						
Female	0.9	0.6-1.3	0.580						
Comorbidities									
Diabetes mellitus	1.7	1.1-2.5	0.009	1.3	0.8-1.9	0.240			
Hypertension	1.2	0.8-1.9	0.318						
Ischemic heart disease	1.8	1.1-2.8	0.018	1.3	0.8-2.1	0.317			
Peripheral vascular disease	0.4	0.1-2.2	0.328						
Stroke/transient ischemic attack	0.9	0.5-1.7	0.814						
Deep vein Thrombosis/pulmonary embolism	1.4	0.1-21.9	0.828						
Heart failure	1.1	0.5-2.4	0.823				1.0	0.5-2.4	0.913
Chronic obstructive pulmonary disease/asthma	0.8	0.3-1.9	0.558						
Chronic kidney disease	1.9	1.1-3.6	0.028	1.2	0.6-2.3	0.585	1.2	0.7-2.4	0.514
Dyslipidaemia	0.7	0.5-1.2	0.197						
Chronic rheumatic heart disease	1.9	0.8-5.4	0.169						
CHA2DS2-VASc score	1.4	0.9-2.1	0.060				0.9	0.6-1.4	0.629
HAS-BLED Score									
Low bleeding risk (score ≤ 2)	1.0	Reference	-						
High bleeding risk (score ≥ 3)	2.9	1.9-4.4	< 0.001	2.5	1.6-3.9	< 0.001	2.9	1.8-4.7	< 0.001

[1]Model 1, adjusted to significant variables of the study populations.
[2]Model 2, adjusted to heart failure, chronic kidney disease, CHA2DS2-VASc score and HAS-BLED score. aOR: Adjusted odds ratio; CI: Confidence interval; TTR: Time in therapeutic range.

therefore catering towards patients with cardiovascular disease in the region. Additionally, these are the main risk factors for AF, which is the study population in question[24].

Interestingly, when compared to other Asian studies, the mean TTR of patients obtained in the study was 60.6%. In comparison, a study from Korea recorded a mean TTR of 49.1%[23], and a study from Singapore recorded a mean TTR of 58%[25]. Possible reasons for the higher mean TTR percentage may be due to the involvement of pharmacists in the pharmacist-led warfarin therapy. This translates to improved patient counselling, dosage adjustment, and identification of possible food-drug and drug-drug interactions.

This study found that patients with a high HAS-BLED score (≥ 3) had a lower median TTR of 55%, compared to patients with a low HAS-BLED score (score < 2) who had a higher median TTR of 68%. Previous reports have suggested that heart failure,

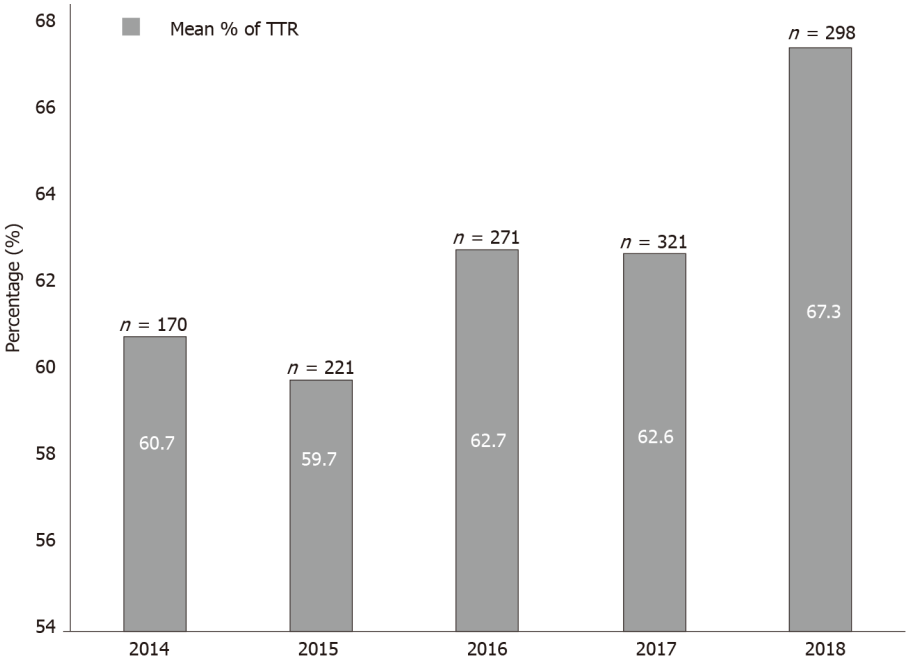


Figure 2 Mean percentage of the time in therapeutic range among atrial fibrillation patients. TTR: Time in therapeutic range.

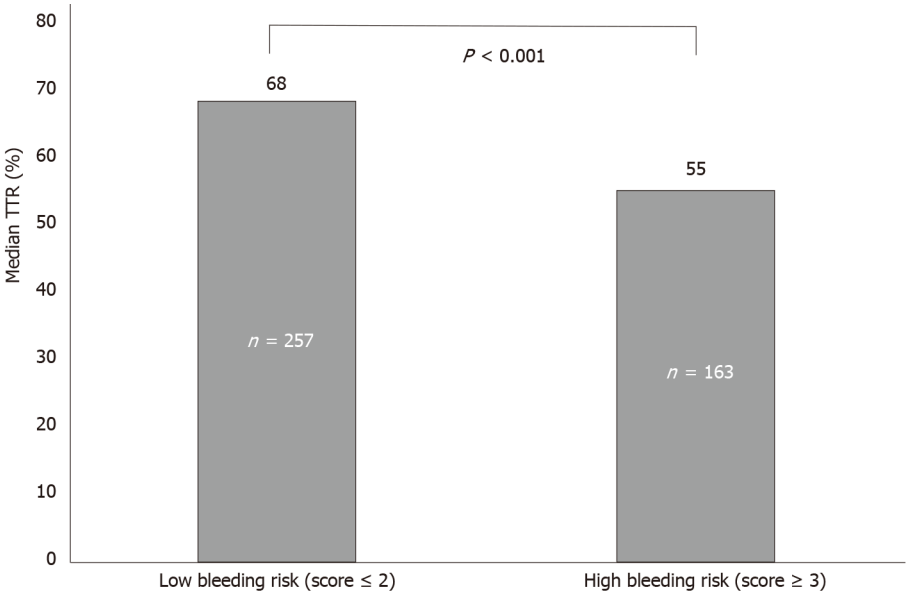


Figure 3 HAS-BLED score *vs* median time in therapeutic range (%). TTR: Time in therapeutic range.

chronic kidney disease, and CHA2DS2-VASc score in addition to high bleeding risk may also contribute to poor TTR[20]. After adjusting for these variables, we found only high HAS-BLED (score ≥ 3) was associated with poor TTR. This is supported by the study from Urbonas *et al*[15], which found median TTR was significantly lower in patients with high bleeding risk (36.4%) as compared to low-risk patients (55.6%). They suggested that the poor TTR in these patients may be due to biological variation in clotting factors[15].

Strength and limitations

Our patients' data were derived from the eHIS database, an electronic storage system of patient records, enabling straightforward access to patient records. The INR results collected in the study were obtained either through point-of-care testing (POC) or clinical laboratory INR. There may be bias in INR measurements calculated using POC compared with laboratory INR, as POC measurements tend to be higher[10], which may affect subsequent INR readings. We were unable to measure objectively patient

compliance to warfarin as a risk factor for poor TTR. Since it was a retrospective study, possible missed documentation may have occurred.

CONCLUSION

This study found the mean TTR was 60.6% in patients with AF and that a high HAS-BLED score (≥ 3) was associated with poor TTR. This could provide an important insight during the initiation of oral anticoagulant for patients with a high HAS-BLED score, who may obtain less benefit from warfarin therapy. They should therefore be considered for other available oral anticoagulants for maximum benefit.

ARTICLE HIGHLIGHTS

Research background

The time in therapeutic range (TTR) is a quality measure for anticoagulation therapy with warfarin.

Research motivation

TTR of international normalized ratio (INR) needs to be achieved with a percentage of ≥ 60% for patient to receive a maximal benefit from warfarin such as preventing stroke, major bleeding, and even death.

Research objectives

TTR and the predictors of poor TTR need to be evaluated among atrial fibrillation (AF) patients that received warfarin therapy.

Research methods

Eligible patients with AF from January 2014 to December 2018 for INR monitoring were included in this study. Demographic data, indication of warfarin therapy, INR target, and percentage of INR within range were collected using a data collection form. TTR was assessed using Rosendaal method.

Research results

In patients with AF, the mean TTR was 60.6% with the highest TTR score achieved in 2018, with a percentage of 67.3%.

Research conclusions

This study showed that high HAS-BLED score was associated to poor TTR.

Research perspectives

Patients with AF and high HAS-BLED score may have less benefit from warfarin therapy. Thus, other alternative oral anticoagulants should be considered for maximum benefit.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous coronary intervention of totally occluded coronary venous bypass grafts: An exercise in futility?

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Author contributions: Savage MP, Nardone EW, Madsen BM, Fischman DL and McCarey MM contributed to the design of the research study; Savage MP, Fischman DL, Walinsky P, Ruggiero NJ, and Vishnevsky A acquired the data and conducted the procedures. Nardone EW, Madsen BM, Savage MP and Melissa McCarey performed the research. Savage MP, Nardone EW, Melissa McCarey, Fischman DL, Madsen BM, Ruggiero NJ, Walinsky P, and Vishnevsky A analyzed the data and wrote or revised the manuscript; all authors read and approve the final manuscript.

Institutional review board statement: The retrospective saphenous vein graft study was approved by the IRB at Thomas Jefferson University.

Informed consent statement: This

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Abstract

BACKGROUND

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to pose a clinical challenge. Current PCI guidelines give a class III recommendation against performing PCI on chronically occluded SVG. However, contemporary outcomes after SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy.

AIM

To reassess the procedural and long-term outcomes of PCI for totally occluded SVG with contemporary techniques.

METHODS

This was a retrospective observational study conducted at a single university hospital. The study population consisted of 35 consecutive patients undergoing PCI of totally occluded SVG. Post-procedure dual antiplatelet therapy was continued for a minimum of one year and aspirin was continued indefinitely. Clinical outcomes were assessed at a mean follow-up of 1221 ± 1038 d. The primary outcome was freedom from a major adverse cardiac event (MACE) defined as the occurrence of any of the following: death, myocardial infarction, stroke, repeat bypass surgery, repeat PCI, or graft reocclusion.

RESULTS
The study group included 29 men and 6 women with a mean age of 69 ± 12 years. Diabetes was present in 14 (40%) patients. All patients had Canadian Heart Classification class III or IV angina. Clinical presentation was an acute coronary syndrome in 34 (97%) patients. Mean SVG age was 12 ± 5 years. Estimated duration of occlusion was acute (< 24 h) in 34% of patients, subacute (> 24 h to 30 d) in 26%, and late (> 30 d) in 40%. PCI was initially successful in 29/35 SVG occlusions (83%). Total stent length was 52 ± 35 mm. Intraprocedural complications of distal embolization or no-reflow occurred in 6 (17%) patients. During longer term follow-up, MACE-free survival was only 30% at 3 years and 17% at 5 years.

CONCLUSION
PCI of totally occluded SVG can be performed with a high procedural success rate. However, its clinical utility remains limited by poor follow-up outcomes.

Key Words: Coronary artery bypass grafting; Coronary stents; Chronic total occlusion; Percutaneous coronary intervention; Restenosis; Saphenous vein grafts

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Core Tip: Cardiovascular guidelines give a Class III recommendation against performing percutaneous coronary intervention (PCI) on chronically occluded saphenous vein grafts (SVG). Given contemporary advances in SVG intervention, the goal of this study was to reassess the outcomes of PCI for totally occluded SVG in 35 consecutive patients. PCI was initially successful in 29/35 (83%) SVG occlusions. However, at 3 years only 30% of patients survived without a major cardiac event. Although PCI of totally occluded SVG can be performed with a high procedural success rate, its clinical utility remains limited by poor follow-up outcomes.

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INTRODUCTION

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to be a clinical challenge[1-4]. According to present cardiovascular guidelines, PCI of SVG with chronic total occlusions is discouraged and given a class III recommendation[5]. However, outcomes after SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy (DAPT). The goal of this study was to reassess the procedural and long-term outcomes of PCI for totally occluded SVG in contemporary practice.

MATERIALS AND METHODS

A review of medical records and coronary angiographic films was performed to identify patients with PCI performed on totally occluded SVG. This retrospective study was approved by the Institutional Review Board of the Thomas Jefferson University Hospital. All patients had a 100% occlusion of a venous bypass graft with Thrombolysis In Myocardial Infarction (TIMI) 0 or 1 flow. Patients with subtotal occlusions and TIMI 2 or 3 flow were excluded. PCI of occluded arterial bypass grafts were also excluded.

was a retrospective study which did not require written consent.

Conflict-of-interest statement: All authors have no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at michael.savage@jefferson.edu. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Detailed procedural information was collected on the type of anticoagulation, use of thrombectomy and distal protection device, the number of stents implanted, total stent length, and type of stent. Procedural success was defined as restored SVG patency with > TIMI 2 flow and < 20% residual stenosis. Post-discharge, all patients with successful PCI were treated with dual antiplatelet therapy (DAPT) for at least 1 year and aspirin indefinitely.

The primary outcome was freedom from a major adverse cardiac event (MACE) during a mean follow- up period of 1121 ± 1038 d. MACE was defined as the occurrence of any of the following: Death, myocardial infarction (MI), stroke, repeat bypass surgery, repeat PCI of the target vessel, or graft reocclusion. Event rates were determined by Kaplan-Meier analysis. Event free survival was also assessed as a function of the duration of SVG occlusion classified as acute (< 24 h), subacute (> 24 h to 30 days), or late (> 30 d). Duration of occlusion was estimated on the basis of the patient's history of symptom onset. Subgroup analyses were performed based on the duration of occlusion, clinical presentation, and stent type. Fisher's exact test was used to evaluate the relationship of duration of occlusion and clinical presentation with initial clinical success. Between group comparison of the survival curves was performed using the Mantel-Cox log rank test. *P* values < 0.05 were considered significant. Descriptive statistics were used to analyze baseline patient and bypass graft characteristics. Continuous variables are reported as mean ± SD.

RESULTS

Baseline characteristics of the patients are presented in Table 1. The study population consisted of 29 men and 6 women. Mean age was 69 ± 12 years. Diabetes was present in 40% of patients. Twenty patients (57%) had a history of prior MI. Mean left ventricular ejection fraction was 43% ± 12%. All patients had Canadian Heart Classification III or IV angina. Clinical presentation included ST-elevation MI (STEMI) in 6 patients (17%), non-STEMI in 14 patients (40%), unstable angina in 14 patients (40%), and stable angina in 1 patient (3%).

Bypass graft characteristics are shown in Table 2. Mean SVG age was 12.1 ± 5.1 years. The grafted native coronary artery was the left anterior descending in 9 patients (26%), left circumflex in 13 patients (37%), right coronary artery in 10 patients (29%), and multiple vessels in 3 patients (9%). Previous PCI had been performed in 10 (29%) of the SVG. The duration of graft occlusion was acute in 12 (34%), subacute in 9 (26%), and late in 14 (40%).

Procedural features and outcomes are presented in Table 3. Glycoprotein IIbIIIa inhibitors were used in 15 (43%) of cases. Thrombectomy was performed in 20 (57%). Distal protection devices were used in 9 (26%). The mean number of stents implanted was 2.1 ± 1.3 and total stent length was 52 ± 35 mm. Drug-eluting stents were used in the majority of patients.

Procedural success in restoring SVG patency was achieved in 29 of the 35 patients (83%). Of the 6 unsuccessful procedures, 2 were due to the failure to cross through the occluded graft with any guidewire; in the remaining 4 cases, successful guidewire passage to the distal native vessel was accomplished but graft patency could not be restored despite balloon angioplasty and thrombectomy. Procedural success was not correlated with either clinical presentation ($P = 0.99$) or duration of graft occlusion ($P = 0.33$). Procedural complications included distal embolization or no-reflow in 6 (17%) patients. There were no instances of coronary perforation. In-hospital MACE occurred in 3 (9%) patients including 2 deaths and one nonfatal MI.

Follow-up event free survival is shown in Figure 1. MACE free survival was 58% at 1 year, 30% at 3 years, and 17% at 5 years. Distribution of specific MACE events during follow up is shown in Table 4. Longer term outcome was not related to the initial duration of SVG occlusion (Figure 2) ($P = 0.60$) or clinical presentation ($P = 0.87$). There was no difference in MACE free survival for patients with drug-eluting stents compared to bare metal stents ($P = 0.97$).

DISCUSSION

The management of patients who develop bypass graft disease after previous coronary artery bypass grafting (CABG) surgery continue to pose a clinical challenge. For post-CABG patients with unstable or medically refractory symptoms, all revascularization options entail heightened complexity and procedural risk. Redo CABG carries an

Table 1 Patient characteristics

Characteristic	*n* = 35
Men	29 (83%)
Age (mean ± SD)	69 ± 12 yr
Hypertension	33 (94%)
Hyperlipidemia	25 (71%)
Diabetes	14 (40%)
Smoking	14 (40%)
Renal insufficiency	14 (40%)
History of CHF	6 (17%)
Prior MI	20 (57%)
Ejection fraction (mean ± SD)	43% ± 12%
Clinical presentation	
STEMI	6 (17%)
NSTEMI	14 (40%)
Unstable angina	14 (40%)
Stable angina	1 (3%)
Canadian heart class	
I, II	0
III	7 (20%)
IV	28 (80%)

CHF: Congestive heart failure; MI: Myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; SD: Standard deviation; STEMI: ST elevation myocardial infarction.

increased risk of morbidity and mortality compared to the initial operation[6,7]. The outcomes of PCI in SVG have been significantly improved by coronary stenting[8]. Nevertheless, compared to native coronary arteries, PCI of SVG continues to be associated with higher risk of both procedural and long-term adverse events[9]. Accordingly, if revascularization is indicated in the presence of SVG disease, it is generally preferable to intervene on the native coronary artery if technically feasible. On the other hand, native coronary arteries long after bypass surgery often have complex, heavily calcified chronic total occlusions (CTO) which result in a significantly augmented risk of PCI failure and major complications[10-12].

Historically, before the introduction of distal protection devices and drug-eluting stents, PCI of totally occluded SVG has been associated with low initial procedural success, a high rate of complications, and frequent follow-up adverse events[13,14]. More contemporary PCI studies of SVG in the setting of acute thrombosis and STEMI while demonstrating improved procedural success still report poor longer term clinical outcomes[15,16]. A few studies have evaluated the outcome of PCI in chronically occluded SVG in the DES era[17-20]. An early small study of 11 patients with chronically occluded SVG suggested a high procedural success rate and favorable longer term outcomes after PCI[17]. Subsequent studies of chronically occluded SVG involving 22 to 34 patients reported PCI procedural success in 68% to 79% of cases with relatively high rates of MACE during medium term follow-up[18-20].

Citing low success rates, high complication rates, and poor long-term patency, ACC/AHA/SCAI PCI guidelines have a Class III: Harm recommendation against PCI for chronic SVG occlusions[5]. However, it is important to note that these guidelines were published over a decade ago. Accordingly, the unanswered question is whether the cumulative advances in SVG intervention have translated into improved outcome for totally occluded grafts. Distal protection devices have been shown to reduce periprocedural MACE, can be deployed with high success rate, and are given a Class I recommendation in PCI guidelines[5,21-23]. Intracoronary vasodilators have been shown to be effective in treating no-reflow which is a common complication during

Table 2 Bypass graft characteristics

Characteristic	*n* (%)
SVG age (mean ± SD)	12.1 ± 5.1 yr
Prior PCI of SVG	10 (29)
Grafted native vessel	
LAD	9 (26)
LCx	13 (37)
RCA	10 (29)
Multiple	3 (9)
Duration of graft occlusion	
Acute (< 24 h)	12 (34)
Subacute (> 24 h to 30 d)	9 (26)
Late (> 30 d)	14 (40)

LAD: Left anterior descending; LCx: Left circumflex; m: mean; PCI: Percutaneous coronary intervention; SD: standard deviation; SVG: Saphenous vein graft.

SVG PCI and may have benefits if given prophylactically[24-27]. Drug-eluting stents appear to reduce restenosis in SVG early after PCI although they exhibit a catch-up phenomenon during late follow-up[28-31]. Prolonged DAPT improves outcomes following PCI in high risk patient subsets and has been suggested as a possible strategy to improve the long-term outcome after PCI of SVG[4,32,33]. In addition to these advances in SVG intervention, significant improvements in CTO outcomes have been made through continued technical and procedural innovations[34,35].

Given the aforementioned advances, the goal of the current study was to reassess the procedural and long-term outcomes of occluded SVG PCI in the context of contemporary techniques. The initial procedural success in restoring SVG patency was achieved in 83% of patients. This procedural success rate is quite favorable compared to prior reports of totally occluded SVG. On the other hand, long-term clinical outcomes remained poor even though DAPT was continued for a minimum of one year and DES were used in most patients. MACE free survival was 58% at 1 year, 30% at 3 years, and only 17% at 5 years. There was no relation between the duration of SVG occlusion prior to PCI and long-term outcome. There was also no difference in outcome with drug-eluting compared to bare metal stents. The disappointing long-term results of DES in occluded SVG is consistent with the findings of other recent studies of DES for non-occluded SVG[29-31].

Limitations of the current study should be recognized. This study was retrospective and we do not have information into why PCI of the occluded vein graft was undertaken as opposed to other treatment options. Data is not available on the number of patients who were treated by other means such as PCI of the native vessel, redo CABG, or medical therapy alone. Patients in this study who underwent PCI likely represent a small select group with totally occluded SVG. These patients were treated in the drug-eluting stent era which now spans over the past decade and a half; the study population of this report represents less than 1% of patients undergoing PCI at our institution during this time. Accordingly, the outcomes of these patients could have been affected by the selection bias of the operators.

CONCLUSION

PCI of totally occluded SVG can be performed with a relatively high rate of procedural success. However, the vast majority of patients will experience a major clinical event within a few years following the procedure. Therefore, the clinical utility of PCI for totally occluded SVG continues to be limited due to poor long-term outcome.

Table 3 Procedural features and outcomes

Feature	*n* (%)
Anticoagulation	
Heparin only	12 (34)
Bivalirudin	8 (23)
Heparin + GP IIb IIIa inhibitor	15 (43)
Thrombectomy	20 (57)
Distal protection device	9 (26)
Number of stents (mean ± SD)	2.1 ± 1.3
Total stent length (mean ± SD)	52 ± 35 mm
Stent type	
Drug-eluting	19 (55)
Bare metal	11 (31)
None	5 (14)
Procedural outcome	
Success	29 (83)
Failed	6 (17)
Procedural complications	
Distal embolization	1 (3)
No reflow	5 (15)
In-hospital MACE	
Death	2 (5.7)
Myocardial infarction	1 (2.9)
Stroke	0
Repeat PCI or CABG	0
Any MACE	3 (8.6)

CABG: Coronary artery bypass grafting; GP: Glycoprotein; m: mean; MACE: Major adverse cardiac event; SD: Standard deviation.

Table 4 Follow-up major adverse cardiac event

MACE type	*n* (%)
Death	5 (14)
Stroke	1 (3)
MI	15 (43)
Repeat bypass surgery	0
Repeat PCI	6 (17)
Graft reocclusionAny MACE	7 (20) 28 (80)

MACE: Major adverse cardiac event; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

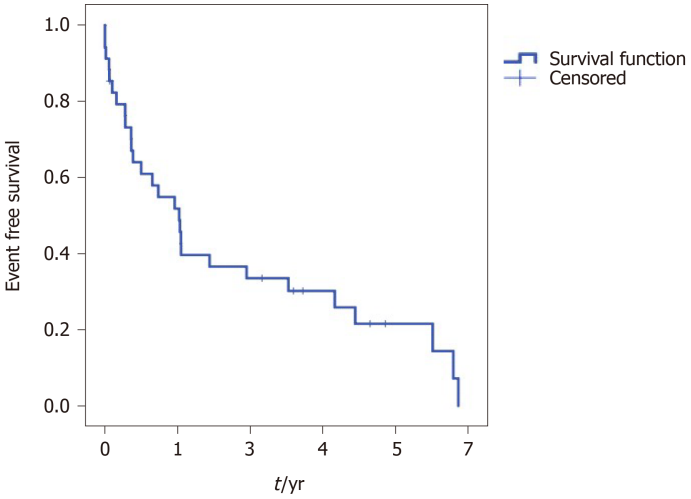


Figure 1 Major adverse cardiac event free survival after percutaneous coronary intervention of totally occluded saphenous vein grafts.

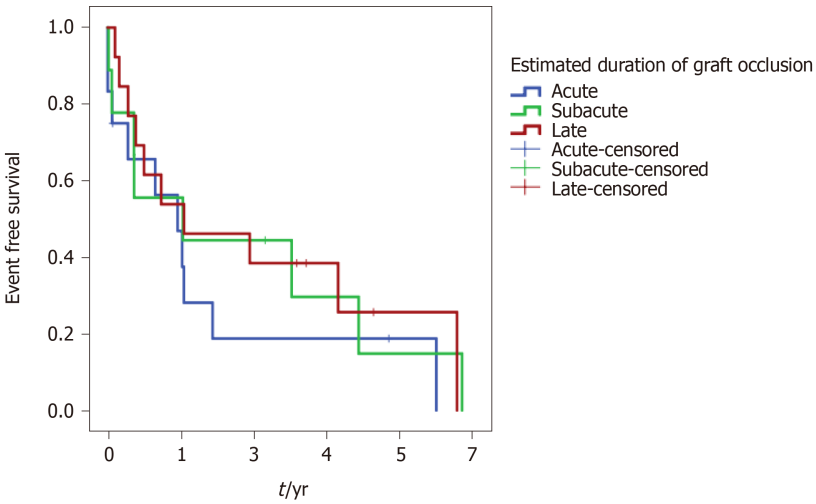


Figure 2 Duration of occlusion and major adverse cardiac event free survival.

ARTICLE HIGHLIGHTS

Research background

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to pose a clinical challenge. Given low success rates, high complication rates, and poor long term patency, current cardiovascular guidelines have a class III recommendation against PCI for chronically occluded SVG.

Research motivation

Contemporary outcomes of SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy. There is a paucity of studies on the outcome of PCI for totally occluded SVG using current techniques.

Research objectives

The goal of this study was to reassess the procedural and long term outcome of PCI for totally occluded SVG with contemporary techniques in the drug-eluting stent era.

Research methods

This was a retrospective observational study of 35 consecutive patients undergoing PCI of totally occluded SVG. The primary outcome was freedom from a major adverse cardiac event (MACE) defined as any of the following: Death, myocardial infarction,

stroke, repeat revascularization of the target vessel, or graft reocclusion. Mean follow-up was 1221 ± 1038 d.

Research results

The study group included 29 men and 6 women aged 69 ± 12 years. Mean SVG age was 12 ± 5 years. PCI was initially successful in 29/35 (83%) SVG occlusions. During long term follow-up, MACE-free survival was 30% at 3 years and 17% at 5 years.

Research conclusions

PCI of totally occluded SVG can be performed with a relatively high rate of procedural success. However, the vast majority of patients have a major clinical event within a few years following the procedure. Thus, the clinical utility of PCI for totally occluded SVG continues to be limited by poor long term outcomes.

Research perspectives

Although PCI of totally occluded SVG can be often initially accomplished, the long term clinical outcome remains poor. Future research is required to achieve a more sustained clinical benefit through further innovations in stent design and adjunct pharmacology.

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ORIGINAL ARTICLE

Prospective Study

Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease

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Abstract

BACKGROUND

Red blood cell distribution width (RDW) is elevated in patients with cardiovascular disease (CVD).

AIM

To determine RDW values and impact of CV and non-CV coexisting morbidities in elderly patients hospitalized with chronic CVD.

METHODS

This prospective study included 204 consecutive elderly patients (age 77.5 [7.41] years, female 94 [46%], left ventricular ejection fraction 53.00% [37.50, 55.00]) hospitalized with chronic CVD at the Cardiology Department of Larissa University General Hospital (Larissa, Greece) from January 2019 to April 2019. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population. Hospitalized patients with acute CVD (acute coronary syndromes, new-onset heart failure [HF], and acute pericarditis/myocarditis), primary isolated valvular heart disease, sepsis, and those with a history of blood transfusions or cancer were excluded. The evaluation of the patients within 24 h from admission included clinical examination, laboratory blood tests, and echocardiography.

RESULTS

manuscript; Giamouzis G participated, Vassilopoulos G, and Skoularigis J participated in the design and oversight of the study; Triposkiadis F participated in the design and oversight of the study and drafted the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the University General Hospital of Larissa, Larissa, Greece Institutional Review Board.

Informed consent statement: The need for written informed consent was waived by the ethics committee due to the observational nature of the study.

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The most common cardiac morbidities were hypertension and coronary artery disease, with acutely decompensated chronic heart failure (ADCHF) and atrial fibrillation (AF) also frequently being present. The most common non-cardiac morbidities were anemia and chronic kidney disease followed by diabetes mellitus, chronic obstructive pulmonary disease, and sleep apnea. RDW was significantly elevated 15.48 (2.15); 121 (59.3%) of patients had RDW > 14.5% which represents the upper limit of normal in our institution. Factors associated with RDW in stepwise regression analysis were ADCHF (coefficient: 1.406; 95% confidence interval [CI]: 0.830-1.981; $P < 0.001$), AF (1.192; 0.673 to 1.711; $P < 0.001$), and anemia (0.806; 0.256 to 1.355; $P = 0.004$). ADCHF was the most significant factor associated with RDW. RDW was on average 1.41 higher for patients with than without ADCHF, 1.19 higher for patients with than without AF, and 0.81 higher for patients with than without anemia. When patients were grouped based on the presence or absence of anemia, ADCHF and AF, heart rate was not increased in those with anemia but was significantly increased in those with ADCHF or AF.

CONCLUSION

RDW was elevated in elderly hospitalized patients with chronic CVD. Factors associated with RDW were anemia and CV factors associated with elevated heart rate (ADCHF, AF), suggesting sympathetic overactivity.

Key Words: Red blood cell distribution width; Elderly; Cardiovascular disease; Coexisting morbidities

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Core Tip: This was a prospective observational study with 204 consecutive elderly hospitalized patients seeking to evaluate the impact of cardiovascular (CV) and non-CV coexisting morbidities on red blood cell distribution width (RDW). RDW was significantly elevated and factors associated with RDW were anemia as well as CV factors associated with elevated heart rate (acutely decompensated chronic heart failure and atrial fibrillation), suggesting sympathetic overactivity.

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INTRODUCTION

Red blood cell (RBC) distribution width (RDW) is calculated as the standard deviation in RBC size divided by the mean corpuscular volume (MCV), and represents an expression of the variation in size of the RBC (anisocytosis) that make up the total population in an individual patient[1]. Emerging evidence suggests that, besides RBC abnormalities, diverse human pathologies have been frequently associated with anisocytosis. In this regard, increased RDW is associated with adverse events and mortality in many cardiovascular diseases (CVDs) such as ischemic cerebrovascular disease, peripheral artery disease, atrial fibrillation (AF), heart failure (HF), and hypertension (HTN)[2,3]. This study evaluated RDW and the impact of coexisting morbidities in elderly patients hospitalized with chronic CVD[4].

MATERIALS AND METHODS

This prospective study included 204 consecutive elderly (> 65 years) patients admitted

quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
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to the Cardiology Department of Larissa University General Hospital (Larissa, Greece) from January 2019 to April 2019. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population. Patients hospitalized for acute CVD (acute coronary syndromes [n = 49], acute *de novo* HF (n = 18), acute pericarditis/myocarditis [n = 15]), primary isolated valvular heart disease (n = 9), sepsis (n = 27), and those with a history of blood transfusions (n = 17) or cancer (n = 25) were excluded. The study complied with the Declaration of Helsinki and the study protocol was approved by the institutional ethical committee. There was no need for written informed consent as the study was observational. All authors had full access to the data, take responsibility for its integrity, contributed to the writing of the manuscript, and agree to this report as written.

Patient evaluation

The evaluation of the patients within 24 h from admission included clinical examination, laboratory blood tests, and echocardiography. Levels of hemoglobin (Hb) and RDW were measured with the use of the Siemens Advia 2120 (Siemens Healthcare Diagnostics, INC, Deerfield, IL, United States). NT-pro B-type natriuretic peptide (NT-proBNP) was measured with the use of Siemens Advia Centaur (Siemens Healthcare Diagnostics), while urea, creatinine, and electrolyte levels with Siemens Dimension (Siemens Healthcare Diagnostics). Echocardiography was performed and reviewed by two independent echocardiographers, with the use of General Electric Vivid 7 machine (GE Healthcare, Horten, Norway). The left ventricular ejection fraction (LVEF) was calculated with the use of two-dimensional echocardiography by implementing the biplane method of disks summation technique[5].

Definitions of coexisting conditions/morbidities

(1) Coronary artery disease (CAD): history of typical angina in subjects with risk factors, history of myocardial infarction, history of hospitalization for angina, history of percutaneous coronary intervention or coronary bypass grafting and accordant medical prescription list; (2) HTN: history of HTN treatment within the past 3 years; (3) Acutely decompensated chronic HF (ADCHF): deterioration of preexisting chronic HF resulting in an unplanned hospitalization; (4) AF: electrocardiographic findings of AF at admission and/or history of treatment for AF; (5) Diabetes mellitus (DM): treatment with anti-hyperglycemic agents including insulin, within the past 3 years; (6) Chronic obstructive pulmonary disease (COPD): history of dyspnea, chronic cough or sputum production, or history of recurrent lower respiratory tract infections in a patient receiving COPD treatment the past 3 years; (7) Anemia: self-reported anemia and relevant treatment within the past 3 years or hemoglobin (Hb) < 130 g/L for men and < 120 g/L for women at admission; (8) Chronic kidney disease (CKD): elevated creatinine (≥ 1.2 mg/dL) in three consecutive measurements in the past 3 years and confirmed at admission; and (9) Sleep apnea: Sleep apnea treatment with continuous positive airway pressure (CPAP) within the past 3 years.

Statistical analyses

Descriptive statistics are presented for the study population. Continuous variables exhibiting a normal distribution are summarized as the mean and standard deviation (SD), whereas continuous variables exhibiting a non-normal distribution are presented as the median and interquartile range (IQR). The distribution of each continuous variable was visually examined through histograms. Categorical variables are presented as frequencies and percentages. A linear regression model was employed to identify factors associated with the elevation of RDW. Univariate analysis was initially carried out to explore the independent association of each variable with RDW. Any such factor subsequently entered a stepwise forward selection procedure to obtain the multivariate model fitting the data best. Factors were added one-at-a-time, starting from the one indicated as the most significant in the univariate analysis, until none yielded any further improvement in the data fit. This was judged using the likelihood ratio test, a frequently used test that compares the change in deviance in nested models, with the level of significance for addition to the model set at 10%.All estimates generated from linear regression analyses were presented along with 95% confidence intervals (CIs) and P values. P values will be reported from two-sided tests at the 5% significance level. All analyses were carried out with STATA 15 (StataCorp LLC; College Station, TX, United States).

RESULTS

Patient characteristics

The characteristics of the patients enrolled in this study are presented in Table 1. Patients were elderly, and approximately half were females. Most patients suffered from HTN and CAD, with ADCHF and AF also being frequently present. The most common non-cardiac morbidities were anemia and CKD followed by DM, COPD, and sleep apnea. The RDW values of the study population appeared to be elevated (mean [SD] = 15.48 [2.15], median [IQR] = 14,9 [2.7]) compared to the upper limit of normal of our institution (14.50%). In total, 121 (59.3%) of patients had RDW > 14.5%.

Univariate regression analysis

The results obtained from the univariate linear regression analysis are presented in Table 2. The presence of ADCHF appeared to be the most important independent factor associated with the elevation of RDW, followed by the presence of AF, anemia, CKD, COPD, increased urea values, reduced LVEF, and a higher age. Other factors found to be significant at the 5% level were the presence of DM, the presence of sleep apnea, and increased C-reactive protein (CRP).

Multivariate model selection

The results obtained from the model selection procedure are presented in Table 3. ADCHF appeared to be the most important factor alone (change in deviance compared to the null model: 62.86, $P < 0.001$), and hence was contained in all sets of models considered for investigation of the best data fit. The presence of AF in the model yielded greater improvement compared to any other factor when included in the model jointly with ADCHF (change in deviance compared to model including ADCHF only: 19.33, $P < 0.001$). Thus, AF was retained in the model alongside ADCHF. Anemia provided the most significant improvement compared to any other factor when included in addition to ADCHF and AF (change in deviance compared to model including ADCHF and AF: 8.35, $P = 0.004$), and hence was retained in the model along with ADCHF and AF. No further improvement was observed when all factors excluded during the selection procedure re-entered the model, one-at-a-time, along with ADCHF, AF, and anemia ($P > 0.15$). Therefore, the best model included ADCHF, AF, and anemia.

Multivariate regression analysis

The results obtained from the multivariate linear regression analysis are presented in Table 4. ADCHF was again the most significant factor associated with RDW, with an average increase of 1.41 noted for patients with ADCHF compared with those without. Furthermore, the RDW was on average 1.19 higher for patients with AF compared to patients without AF, and on average 0.81 higher for anemic patients compared to non-anemic. It is noteworthy that when patients were grouped based on the presence or absence of anemia, ADCHF and AF, heart rate was not increased in those with anemia but was significantly increased in those with ADCHF or AF (Figure 1).

DISCUSSION

In this study that included elderly patients hospitalized with CVD, RDW was significantly elevated. ADCHF was the most significant factor associated with RDW, whereas other important factors were AF and anemia. RDW was significantly higher than the RDW of a subgroup of elderly (*i.e.* 71-85-years-old) ($n = 1479$) of a historical cohort including a total of 8089 individuals (15.48 ± 2.15 *vs* 12.6±0.8, respectively; $P < 0.0001$)[6].

An increased RDW mirrors a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal RBC survival and is used along with other RBC indices to help determine the causes of anemia[7]. A high RDW provides a clue for anisocytosis and/or the presence of two red cell populations, since other RBC indices (*e.g.*, MCV or mean corpuscular hemoglobin concentration [MCH]) reflect average values and may not adequately reflect RBC changes where mixed RBC populations are present (*e.g.*, dimorphic RBC populations in sideroblastic anemia or combined iron deficiency anemia (decreased MCV and MCH) and megaloblastic anemia (increased MCV).

Table 1 Baseline characteristics of the study population

Demographic/clinical	
Age (mean ± SD, yr)	77.50 ± 7.41
Female sex, *n* (%)	94 (46)
Body weight (mean ± SD, kg)	76.28 ± 14.22
Height (mean ± SD, m)	1.66 ± 0.09
Systolic blood pressure (mmHg)	135(34.8)
Diastolic blood pressure (mmHg)	79 (21)
Heart rate (beats/minute)	73.5 (19)
Left ventricular ejection fraction (%) (median, IQR)	53.00 (37.50, 55.00)
Laboratory	
RDW[1] (mean ± SD)	15.48% ± 2.15%
C-reactive protein[2] (mg/L) (median, IQR)	0.48 (0.16, 1.37)
Hemoglobin[3] (mean ± SD, g/dL)	12.25 ± 1.92
Hematocrit[3] (mean ± SD)	37.89% ± 6.04%
White blood cells[3] (K/μL)	8.31 (2.85)
Urea (mg/dL) (median, IQR)	51.70 (38.60, 70.50)
Creatinine[3] (mean ± SD, mg/dL)	1.21 (0.49)
SGOT[4] (IU/L) (median, IQR)	20.15 (16.55, 25.65)
SGPT[4] (IU/L) (median, IQR)	16.75 (11.65, 22.90)
K+[4] (mean ± SD, mmol/L)	4.20 ± 0.56
Na+[1] (mmol/L) (median, IQR)	140.00 (137.50, 142.00)
Non-cardiac conditions/morbidities, *n* (%)	
Diabetes mellitus	68 (33)
Chronic obstructive pulmonary disease	37 (18)
Chronic kidney disease	84 (41)
Sleep apnea	15 (7)
Anemia	85 (42)
Cardiac conditions/morbidities, *n* (%)	
Acutely decompensated chronic heart failure	104 (51)
Coronary artery disease	133 (65)
Hypertension	152 (75)
Atrial fibrillation	97 (47.5)
Medications (discharge), *n* (%)	
Renin-angiotensin-aldosterone system inhibitors	159 (78)
Beta-blockers	145 (71)
Diuretics	137 (67)

[1]Three values missing.
[2]Fifty-four values missing.
[3]Two values missing.
[4]Four values missing. RDW: Red blood cell distribution width; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.

RDW has additionally been used as a prognosticator in diverse pathologies including CVD[8,9]. Many of the conditions for which an increase in RDW was

Table 2 Results obtained from univariate linear regression analysis

Factor	Coefficient	95%CI	*P* value
Age	0.072	(0.033, 0.111)	**< 0.001**
Sex (males *vs* females)	-0.520	(-1.115, 0.075)	0.09
Weight	-0.014	(-0.035, 0.007)	0.18
White blood cell count	0.081	(-0.024, 0.185)	0.13
Urea	0.022	(0.014, 0.030)	< 0.001
C-reactive protein[1]	0.085	(0.001, 0.169)	0.05
Left ventricular ejection fraction	-0.057	(-0.073, -0.038)	< 0.001
Acutely decompensated chronic heart failure	2.220	(1.708, 2.732)	< 0.001
Coronary artery disease	0.039	(-0.573, 0.650)	0.9
Hypertension	-0.519	(-1.203, 0.165)	0.14
Atrial fibrillation	1.862	(1.322, 2.402)	< 0.001
Diabetes mellitus	0.854	(0.230, 1.477)	0.01
Chronic obstructive pulmonary disease	1.569	(0.810, 2.327)	< 0.001
Anemia	1.682	(1.123, 2.242)	< 0.001
Chronic kidney disease	1.590	(1.022, 2.158)	< 0.001
Sleep apnea	1.448	(0.289, 2.606)	0.02

[1]Fifty-four values missing.

observed are associated with systemic inflammation and critical illness, but the exact pathophysiologic mechanisms underlying the association of increase in RDW with morbidity and mortality remains unclear[10]. Given that erythropoietin is a key determinant of the RDW, it has been postulated that any condition affecting erythropoietin activity (*e.g.*, inflammation, primary renal disease, HF, bone marrow failure) may potentially lead to increased RDW values[11-13]. Another consideration could be nutritional imbalance, often present in patients with chronic diseases or critical illness, expressed by micronutrient deficiencies (*e.g.*, iron, vitamin B12, or folate deficiency) that are associated with anisocytosis[14], and excess of macronutrients. On the other hand, higher RDW has been associated with the metabolic syndrome (MS) [15,16]. Proinflammatory cytokines inhibit erythropoietin-induced erythrocyte maturation, which may lead to increased RDW[16]. Macronutrient surplus causes lipotoxicity in healthy non-adipose tissues, and induces tissue damage[17]. Other physiologic determinants that are associated with RDW changes include aging, Black ethnicity, and physical exercise[6,18].

The findings of this study regarding the inflammatory nature of RDW elevation are contradictory. Inflammatory diseases[19] were both included in (*e.g.*, AF and ADCHF) and excluded from (*e.g.*, CKD, and COPD) the final model. Moreover, biomarkers of inflammation were unrelated (white blood cells) or weakly related (CRP) to RDW in univariable analysis and both were not included in the final model. The results of the studies on the relationship between RDW and inflammatory biomarkers have been conflicting. In the study of Lippi and colleagues including 3845 outpatients, when participants were grouped according to RDW quartiles, there were strong, graded increases in erythrocyte sedimentation rate and hsCRP ($P < 0.001$), both parameters being up to 3-fold higher in the fourth *vs* the first quartile[20]. In contrast, Lappe and colleagues observed a significant but meaningless correlation between RDW and high-sensitivity CRP ($r = 0.181$; $P < 0.001$) in 1489 patients with CAD[21].

Inflammatory processes are present during the development and complications of CVD. However, although there is a wealth of information about the role of inflammatory cells and pathways during acute injury and the reparative processes that are subsequently activated, little is known about the contribution of the immune system once the trajectory has been set, and chronic CVD has been established—which clinically represents the majority of patients[22]. The causative role inflammation plays in disease progression is not well defined, and the majority of clinical trials that target

Table 3 Results obtained from the model selection procedure

Explanatory factors of RDW	Change in deviance[1]	*P* value
Models including 1 factor[2]		
Age	12.84	< 0.001
Urea	26.50	< 0.001
C-reactive protein	4.01	0.05
LVEF	30.42	< 0.001
ADCHF	**62.86**	**< 0.001**
Atrial fibrillation	42.01	< 0.001
Diabetes mellitus	7.23	0.007
COPD	16.14	< 0.001
Anemia	32.69	< 0.001
CKD	28.60	< 0.001
Sleep apnea	6.04	0.01
Models including 2 factors[3]		
ADCHF + Age	0.15	0.70
ADCHF + Urea	3.03	0.08
ADCHF + C-reactive protein	0.30	0.59
ADCHF + LVEF	0.06	0.80
ADCHF + Atrial fibrillation	**19.33**	**< 0.001**
ADCHF + Diabetes mellitus	3.08	0.08
ADCHF + COPD	2.39	0.12
ADCHF + Anemia	7.74	0.005
ADCHF + CKD	0.85	0.36
ADCHF + Sleep apnea	0.34	0.56
Models including 3 factors[3]		
ADCHF + Atrial fibrillation + Age	0.08	0.78
ADCHF + Atrial fibrillation + Urea	2.10	0.15
ADCHF + Atrial fibrillation + C-reactive protein	0.54	0.46
ADCHF + Atrial fibrillation + LVEF	0.75	0.39
ADCHF + Atrial fibrillation + Diabetes mellitus	2.30	0.13
ADCHF + Atrial fibrillation + COPD	0.89	0.35
ADCHF + Atrial fibrillation + Anemia	**8.35**	**0.004**
ADCHF + Atrial fibrillation + CKD	0.73	0.39
Models including 4 factors[3]		
ADCHF + Atrial fibrillation + Anemia + Age	0.50	0.48
ADCHF + Atrial fibrillation + Anemia + Urea	1.16	0.28
ADCHF + Atrial fibrillation + Anemia + C-reactive protein	0.34	0.56
ADCHF + Atrial fibrillation + Anemia + LVEF	1.86	0.17
ADCHF + Atrial fibrillation + Anemia + Diabetes mellitus	0.92	0.34
ADCHF + Atrial fibrillation + Anemia + COPD	0.77	0.38
ADCHF + Atrial fibrillation + Anemia + CKD	0.26	0.61

[1]Largest change in deviance indicates the best model in each set (highlighted).
[2]Models were compared to the null model.
[3]Models were compared to those indicated as best in the previous set. ADCHF: Acutely decompensated chronic heart failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction.

Table 4 Results obtained from multivariate linear regression analysis

Factor	Coefficient	95%CI	*P* value
Acutely decompensated chronic heart failure	1.406	(0.830, 1.981)	< 0.001
Atrial fibrillation	1.192	(0.673, 1.711)	< 0.001
Anemia	0.806	(0.256, 1.355)	0.004

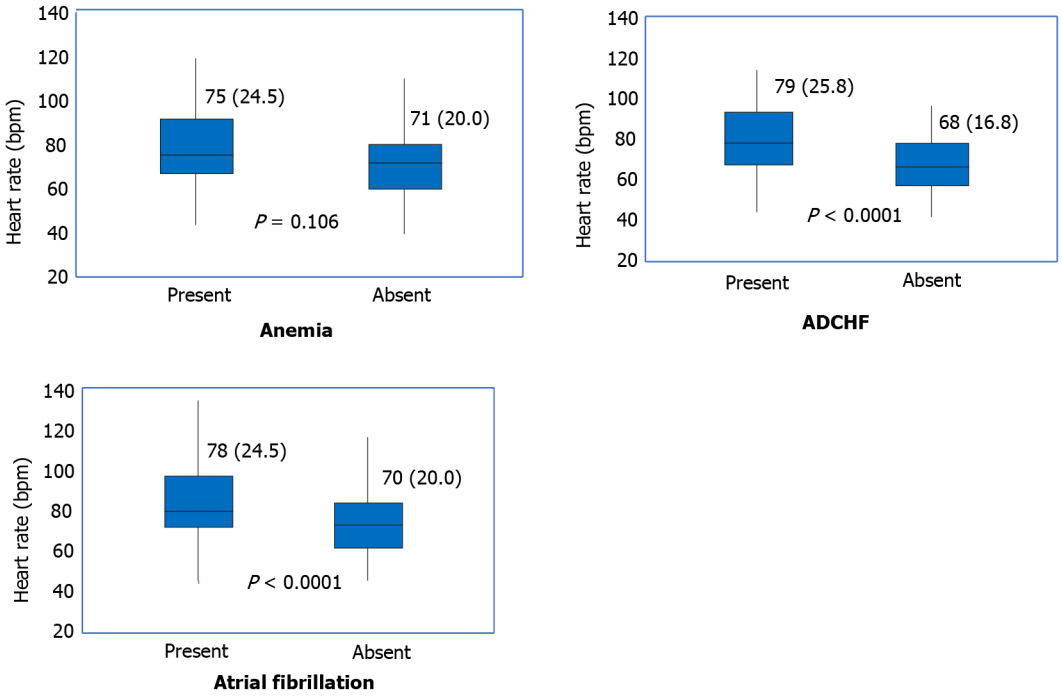


Figure 1 Heart rate in the presence or absence of anemia, acutely decompensated chronic heart failure, and atrial fibrillation. ADCHF: Acutely decompensated chronic heart failure; bpm: Beats per minute.

aspects of inflammation in patients with chronic CVD have largely been negative[23,24]. This may be partly due to the fact that the tools currently used to measure "inflammation" are insufficiently precise and do not provide information about disease site, activity, or discrimination between functionally important activation pathways[23,25].

Anisocytosis can be produced by any factor that increases erythropoiesis. In the present study, in contrast to anemia the two most important non-CV factors inducing anisocytosis, ADCHF and AF were associated with increased heart rate confirming that both are hyper-catecholaminergic states[26,27]. The nervous system emerges as a critical regulatory player of the bone marrow, the primary site of postnatal hematopoiesis and hematopoietic stem cell maintenance, both under homeostatic and pathologic settings, with essential roles in cellular anchorage and egress, stem cell differentiation, and endothelial cell permeability[28,29]. Factors involved in erythropoiesis appear to revolve around the nervous system, and catecholamines seem to be the centerpiece. Several studies support the central role of the sympathetic nervous system (SNS) in the regulation of hematopoiesis[30,31]. Norepinephrine (NE) is delivered to the bone marrow (BM) by the sympathetic nerve in a circadian (diurnal) manner[32]. A close communication exists between the SNS and the BM and dysregulation in this communication may lead to aberrant hematopoietic and immune system responses[33].

This study had several limitations. (1) The study enrolled elderly patients (≥ 65-years-old) and therefore the results should be interpreted with caution in younger populations. As previously mentioned the decision to include only elderly patients was based on the fact that these patients usually suffer from several coexisting morbidities enabling us to study their potential impact on RDW. (2) A control group was lacking to compare RDW. However, a normal range of RDW value of 14.5% representing the upper normal limit is widely accepted[1,6] and RDW was compared with an aged-matched historical control[6]; (3) The cause of anemia was not determined. Iron deficiency anemia is diagnosed in 16.6%–25% of non-hospitalized older adults, 22%–40% of institutionalized older adults, and 15%–65% of hospitalized older adults[34]. Iron deficiency and iron deficiency anemia are common problems in patients with CVD[35]. Therefore, it is reasonable to assume that the study findings were driven by iron deficiency anemia. And (4) By assessing heart rate, we achieved information predominantly on the cardiac sympathetic drive. However, differentiation of sympathetic responses means that no simple test can ever represent each and every sympathetic outflow[36]. Nevertheless, the presence of sympathetic overactivity in ADCHF and AF has been demonstrated in numerous studies.

CONCLUSION

In elderly patients hospitalized with chronic CVD, RDW was elevated and associated both with anemia and factors unrelated to anemia such as ADCHF and AF. It is of interest that ADCHF and AF shared a common characteristic, namely heart rate elevation, which is suggestive of SNS overactivity a well-known regulator of BM. Further studies are necessary to establish the relationship between RDW and SNS.

ARTICLE HIGHLIGHTS

Research background

An increased red blood cell distribution width (RDW) is associated with poor outcomes in patients with several cardiovascular diseases (CVDs).

Research motivation

Data on the pathophysiology of RDW increase in hospitalized patients with CVD are limited.

Research objectives

The current study explored the impact of CV and non-CV coexisting morbidities in elderly patients hospitalized with chronic CVD.

Research methods

This prospective observational study included 204 consecutive elderly (> 65 years) patients admitted to a tertiary university hospital of Greece. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population.

Research results

Factors associated with RDW were anemia, acutely decompensated chronic heart failure (ADCHF), and atrial fibrillation (AF).

Research conclusions

ADCHF and AF shared a common characteristic, namely heart rate elevation, which suggests sympathetic nervous system (SNS) overactivity, a well-known regulator of bone marrow.

Research perspectives

Further studies will establish the relationship between RDW and SNS.

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ORIGINAL ARTICLE

Prospective Study

Effects of exercise training on diastolic and systolic dysfunction in patients with chronic heart failure

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Abstract

BACKGROUND

Chronic heart failure (CHF) is a complex syndrome characterized by a progressive reduction of the left ventricular (LV) contractility, low exercise tolerance, and increased mortality and morbidity. Diastolic dysfunction (DD) of the LV, is a keystone in the pathophysiology of CHF and plays a major role in the progression of most cardiac diseases. Also, it is well estimated that exercise training induces several beneficial effects on patients with CHF.

AIM

To evaluate the impact of a cardiac rehabilitation program on the DD and LV ejection fraction (EF) in patients with CHF.

METHODS

Thirty-two stable patients with CHF (age: 56 ± 10 years, EF: 32% ± 8%, 88% men) participated in an exercise rehabilitation program. They were randomly assigned to aerobic exercise (AER) or combined aerobic and strength training (COM), based on age and peak oxygen uptake, as stratified randomization criteria. Before and

registered with ClinicalTrials.gov (NCT04916184).

Informed consent statement: All study participants provided written consent prior to study enrollment.

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after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography evaluation to evaluate peak oxygen uptake (VO_{2peak}), peak workload (W_{peak}), DD grade, right ventricular systolic pressure (RVSP), and EF.

RESULTS

The whole cohort improved VO_{2peak}, and W_{peak}, as well as DD grade ($P < 0.05$). Overall, 9 patients (28.1%) improved DD grade, while 23 (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.05$). In addition, the whole cohort improved RVSP and EF ($P < 0.05$). Not any between-group differences were observed in the variables assessed ($P > 0.05$).

CONCLUSION

Exercise rehabilitation improves indices of diastolic and systolic dysfunction. Exercise protocol was not observed to affect outcomes. These results need to be further investigated in larger samples.

Key Words: Chronic heart failure; Cardiovascular effects; Cardiac rehabilitation; Aerobic exercise; Strength training; Diastolic dysfunction

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Core Tip: In this study, the exercise training rehabilitation (aerobic exercise with/without strength training) effects on indices of diastolic and systolic cardiac function, were evaluated in stable chronic heart failure patients. Exercise training overall induced benefits on the diastolic dysfunction grade, the ejection fraction of the left ventricle, the right ventricular systolic pressure, as well as aerobic exercise capacity.

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INTRODUCTION

Chronic heart failure (CHF) is a multisystem syndrome, characterized by an abnormality of the cardiac structure or function, condition, which leads to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabo-lizing tissues, despite normal filling pressures[1].

Left ventricular diastolic dysfunction plays an essential role in the pathophysiology of the CHF. The term "diastolic dysfunction" (DD) refers to abnormalities in right or/and left ventricular relaxation[2-5]. Although DD most frequently refers to the context of HF with preserved ejection fraction (EF), due to its central role in its pathophysiology, impaired diastolic function often coexists with systolic dysfunction. HF patients may not accomplish the necessary increase in diastolic relaxation to accommodate the preload increase[1]. Severity of exercise intolerance is associated with left ventricular filling pressure and so the strong relationship between diastolic abnormality and exercise limitation should be underlined[6-8]. It is in that context, that exercise training is currently being extensively evaluated for additional benefits, over the classical medication, in the treatment of DD in patients with CHF[9].

As mentioned before, in patients with CHF, the exercise capacity may be limited by the number of frequently coexisting factors such as decreased contractility, DD, chronotropic incompetence, oxygen metabolism, or skeletal muscle mass disorders. This importance of skeletal muscle dysfunction provides part of the rationale for the use of cardiac rehabilitation[10]. It is well established that exercise training improves functional capacity, quality of life, and clinical outcomes in patients with stable CHF [10,11]. Specifically, in patients with reduced EF, exercise is beneficial in total and HF-

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related hospitalizations and relieves the symptoms of depression. Also, it decreases myocardial oxygen demands for the same level of external work performed, as demonstrated by the product of heart rate × systolic blood pressure, reducing in that way the likelihood of myocardial ischemia[12,13]. In major Cardiology Society Guidelines, exercise training is recommended in all patients with New York Heart Association functional class II to III, no matter of the EF[14-16].

Finally, aerobic regimes have been a major component of exercise rehabilitation to improve cardiorespiratory fitness and disease symptoms[16]. As skeletal muscle abnormalities are an important limitation to exercise intolerance and muscular strength impacts patients' capacities to perform daily tasks, combined regimes of aerobic exercise (AER) and strength training have been employed to induce additional benefit[17,18]. However, there have not been any data on the effects of different regimes on diastolic dysfunction.

The main aim of this study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the EF of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

MATERIALS AND METHODS

Study population and design of the study

The study population consisted of 32 consecutive CHF patients. The demographic, anthropometric, and clinical characteristics of these patients at baseline are described in Table 1. The patients were referred to our hospital's laboratory by HF outpatient clinics, screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations including echocardiography assessment. They randomly assigned to AER (n = 17) or combined aerobic and strength training (COM, n = 15). Randomization process, based on age (50 years as cut-off value) and peak oxygen uptake (16 mL/kg/min as cut-off value) as stratified randomization criteria, was made by a researcher not involved in the rest of the tasks, such as exercise sessions and pre/post evaluations. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

CHF diagnosis was based on history forms, clinical evaluation, and laboratory testing. Patients were considered for inclusion in the study in case they were on stable systolic CHF, under optimal medication for at least 3 mo and had an EF value up to 49%. Exclusion criteria were severe valvulopathy, uncontrolled arterial hypertension, severe chronic obstructive pulmonary disease, severe peripheral angiopathy, neuromuscular diseases and contraindications for CPET. The patients were mainly treated with diuretics, b-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors or sacubitril/valsartan. There were not any changes in treatment regimen during the study.

The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Administration Board and the Ethics Committee of our Hospital. Informed consent was provided by the participants.

Exercise training program

Participants attended supervised exercise sessions at the laboratory three times per week for 12 wk in the early afternoon hours. If any sessions were missed, the duration of the program was extended so that the 36 sessions were accomplished. AER and COM protocols have been previously described in detail[19]. In short, the AER group performed 31 min of interval training (4 × 4–min at 80% VO_{2peak}–5 × 3-min at 50% VO_{2peak}) on a cycle ergometer (Ironman M3 Cycle) followed by balance and coordination exercises. The COM group performed 31 min of AER (in the same way as the AER group) followed by 14 min of strength training (2–3 sets, 10–12 repetitions, 60%-75% of 1 repetition maximum test-knee extension, knee flexion, chest press). Both regimes were of the same total duration.

Cardiopulmonary exercise testing

Participants underwent a ramp incremental CPET on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, United States), before and after completion of the program. Individualized workload increments were estimated according to the equation of Hansen *et al*[20]. Gas exchange was measured

Table 1 Demographic, anthropometric, and clinical characteristics of all chronic heart failure patients at the beginning of the study

Patients, *n*	32
Age[1], yr	56 ± 10
Gender (Males/Females)	30/2
Height[1], cm	178 ± 8
Body mass[1], kg	93 ± 25
BMI[1], kg/m^2	29 ± 6
NYHA class (I/II/III)	3/21/ 8
LVEF[1], %	32 ± 8
VO_{2peak}[1], mL/kg/min	19.4 ± 4.5
Etiology of CHF, *n*	
Ischemic/Dilated/Other cardiomyopathy	20 / 10 / 2

[1]Values are mean ± SD.

BMI: Body mass index; CHF: Chronic heart failure; LVEF: Ejection fraction of the left ventricle; NYHA: New York Heart Association; VO_{2peak}: Peak oxygen uptake.

with the patient breathing through a low resistance valve, with the nose clamped, using an ergospirometry system (Vmax229D; Sensor Medics) calibrated with a known gas mixture before each test. Respiratory indicators (breath-by-breath oxygen uptake [VO_2], carbon dioxide output [VCO_2] and ventilation [V_E]) were measured. Peripheral O_2 saturation was monitored continuously by pulse oximetry. Heart rate and rhythm were monitored by a MAX 1, 12-lead electrocardiographic system (Marquette Electronics, Milwaukee, WI, United States) and blood pressure was measured every 2 min with a mercury sphygmomanometer. All patients were verbally encouraged to exercise to intolerable leg fatigue or dyspnea. CPET variables employed in the study were VO_{2peak} and peak workload (W_{peak}). VO_{2peak} was determined as the average value of VO_2 data measured at the final 20-s period of the exercise phase, and W_{peak} as the corresponding work rate[20].

Echocardiographic measurements

Detailed echocardiography assessment was performed in all patients. A Philips E 33 Doppler analyzer equipped with tissue Doppler imaging (TDI) was used. The period between echocardiography assessment and cardiopulmonary exercise testing was less than 2 wk. Each patient was examined, according to the guidelines of the European Society of Echocardiography (2016 update[21]), in the left lateral and supine position. The EF was calculated using the modified Simpson method from apical two- and four-chambers view (2D and 4D). Analysis of pulsed Doppler mitral flow velocity was attained, and three consecutive cardiac cycles were analyzed and averaged for each patient. Transmitral inflow velocities (E, A, deceleration time of E [DTe] and E/A ratio) were assessed by pulsed-wave Doppler, with the sample volume placed between the mitral leaflet tips in the apical four-chamber view during diastole. When from the Echo–TDI the septal e' was less than 8 and the lateral e' less than 10, the Echo-Doppler transmitral flow was examined. Based on this, three grades of diastolic dysfunction (DD) are described: Grade I (impaired relaxation) is characterized by E/A ratio less than 0.8 and DTe more than 200 ms. Grade II (pseudonormal) is characterized by elevated left atrial pressures. The E/A ratio is 0.8–2 and the DTe is more than 200 ms. Grade III (restrictive pattern), is characterized by a marked decrease in left ventricular compliance (E/A ratio more than 2, DTe less than 160 ms[15]). Another grade, grade 0, refers to normal diastolic function. The E/A ratio was considered as normal if it was 0.78–1.78 and the DTe 150–200 ms. Valsalva maneuver was used to discriminate pseudo normal from true normal pattern. From the apical four-chamber view, a 10 mm^3 sample volume was placed at the septal and lateral mitral annulus, and spectral TDI was recorded, calculating septal e', lateral e' and the mean value (E'). Left atrial volume was measured at end-systole and it was normalized to body surface area (LAVI, mL/m^2). Finally, the right ventricular systolic pressure (RVSP) was calculated using the Bernoulli equation RVSP = 4(V)^2 of peak tricuspid regurgitation velocity (V).

Statistical analyses

Continuous variables were tested for normality of distribution with Shapiro-Wilk test. Within-group differences were assessed with paired sample Student *t*-test or Wilcoxon signed-rank test, based on normality of distribution. Chi-square test was employed to check for between-group differences on categorical variables. Between-group differences of ordinal variables were assessed with Mann-Whitney *U* test. McNemar-Bowker test was also used to check for differences on diastolic dysfunction grade before and after exercise intervention. Time by group interactions were assessed with factorial 2 × 2 analysis of variance. Correlations between variables were tested with Pearson or Spearman coefficient. Continuous variables were presented as mean ± SD. Level of statistical significance *P* was set at 0.05. Statistical computations were made with IBM SPSS 26 statistics.

RESULTS

The whole cohort improved indices of AER capacity, namely VO_{2peak} (from 19.4 ± 4.5 to 21.3 ± 6.0 mL/kg/min, $P = 0.03$) and W_{peak} (from 109 ± 39 to 130 ± 43 watts, $P < 0.01$).

The whole group improved DD, as assessed with grades. Before the exercise program, the number of patients categorized as grade -0, -I, -II, or -III were 1 (3.1%), 18 (56.3%), 10 (31.2%), 3 (9.4%) respectively. After the program, the respective patients were 4 (12.5%), 21 (65.6%), 6 (18.8%), 1 (3.1%). A significant difference was found between total pre- and post-values ($P = 0.01$) (Figure 1A). That was also the case when analysis was performed based on change of DD grade ($P = 0.06$) (Figure 1B). Overall, 9 patients (28.1%) improved DD grade, while 23 ones (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.01$) (Figure 1C). In addition, VO_{2peak}, tended to improve more in patients that also improved grade ($P = 0.09$), while W_{peak} was improved more in these patients ($P = 0.04$) (Figure 2).

The whole sample did not improve any of the other DD variables examined individually. These were E/A ratio (from 1.00 ± 0.64 to 0.88 ± 0.35, $P = 0.27$), LAVI (from 38.70 ± 13.74 to 38.44 ± 17.03 mL/m^2, $P = 0.14$), E' (from 7.74 ± 2.31 to 7.55 ± 1.85 cm/s, $P = 0.62$), E/E' ratio (from 9.15 ± 3.41 to 8.48 ± 3.45, $P = 0.15$), and DTe (from 213.34 ± 41.60 to 212.38 ± 32.99 m/s, $P = 0.59$). In addition, the whole cohort improved RVSP (from 28.92 ± 7.75 to 27.75 ± 6.46 mmHg, $P = 0.05$) and EF (from 32% ± 8% to 36% ± 8%, $P < 0.01$), after completion of the exercise rehabilitation program.

Pre- and post-values of the variables examined in relation to AER and COM groups comparison are presented in Table 2. The AER group improved DD grades ($P = 0.02$) and tended to improve LAVI ($P = 0.10$). The COM group improved RVSP ($P = 0.01$) and tended to improve grades ($P = 0.10$). Both groups improved EF ($P < 0.01$). Not any between-group differences were observed in the variables observed ($P > 0.05$).

DISCUSSION

The exercise rehabilitation effects on parameters of diastolic and systolic dysfunction were explored among CHF patients in this study. Exercise training overall beneficially affected DD stage, RVSP, EF of the left ventricle and AER capacity. Not any differences between the aerobic and combined group were observed.

HF is currently considered a pathophysiological syndrome of multifactorial origin and not just a disease. DD is a common characteristic of the HF patients[22]. Hamlin *et al*[4] showed that CHF patients present with reduced ability to augment the diastolic relaxation, accountable for the inability to accommodate the increase in estimated preload during exercise, resulting in turn in higher filling pressure. Also, HF patients have generally shorter diastolic periods, situation that lead to inability of the myocardium to relax and accept the large volume of blood[23]. The inability to perform exercise without discomfort may be one of the first symptoms experienced by patients with HF and is often the principal reason for seeking medical care[14,24]. Therefore, exercise intolerance is inextricably linked to the diagnosis of HF. Exercise training has been an important means of rehabilitation, with a class IA recommendation on the improvement of functional capacity and symptoms[16]. In line with previous studies[17,25], indices of aerobic capacity as assessed with peak oxygen uptake (VO_{2peak}) and workload (W_{peak}) were also improved in this study. A significant improvement in the DD grades was found in this study. Other diastolic indices, such as E/E', were not found to improve, which may be related to the small sample size.

Table 2 Values of the variables evaluated before and after the exercise training intervention

	Aerobic group		Combined group	
	Pre	Post	Pre	Post
VO_{2peak} (ml/kg/min)	19.0 ± 5.5	22.2 ± 7.8[a]	19.8 ± 3.1	20.3 ± 2.9
W_{peak} (watt)	111 ± 46	129 ± 48[a]	108 ± 31	131 ± 39[a]
E/A	1.15 ± 0.80	1.00 ± 0.41	0.83 ± 0.37	0.74 ± 0.20
LAVI (ml/m^2)	38.83 ± 12.75	37.23 ± 11.78	38.55 ± 15.23	39.81 ± 21.91
E′ (cm/s)	8.00 ± 2.81	7.74 ± 1.97	7.45 ± 1.61	7.33 ± 1.74
E/E′	9.09 ± 4.06	8.76 ± 4.57	9.22 ± 2.63	8.15 ± 1.51
DTe (m/s)	220.65 ± 51.59	213.00 ± 38.08	205.07 ± 25.54	211.67 ± 27.41
RVSP (mmHg)	28.56 ± 7.65	28.23 ± 6.36	29.33 ± 8.10	27.20 ± 6.74[a]
EF (%)	34 ± 8	38 ± 9[a]	29 ± 6	33 ± 6[a]
DD grade 0/I/II/III (*n*)	1/9/4/3	3/10/3/1[a]	0/9/6/0	1/11/3/0

Values are mean ± SD.

[a]$P < 0.05$, significant within-group difference.

DD: Diastolic dysfunction; DTe: Deceleration time of E wave; E': Mean value of the septal and lateral e' of TDI of the mitral annulus; E/A: Ratio of the E and A waves of the transmitral inflow; E/E': Ratio of the E wave to E' wave; EF: Ejection fraction; LAVi: Left atrial volume index; RVSP: Right ventricular systolic pressure; VO_{2peak}: Peak oxygen uptake; W_{peak}: Peak workload.

Belardinelli *et al*[26,27] showed an improvement in DD, after a 2-mo exercise training intervention in HF patients with moderate/severe systolic dysfunction. Similarly, improved LV stiffness[28] and decreased filling pressure[29] have been also reported in other HF trials as a result of exercise training. A meta-analysis of 6 studies, with 144 patients with reduced EF[30], indicated a significant reduction in the ratio E/E' with exercise training. Among them, 3 studies in patients with reduced EF, reported post intervention improvement in all DD grades[31].

The RVSP improvement observed in this study is also in line with previous findings. Mehani *et al*[32] after a 5-mo training program, showed a significant decrease of RVSP by 12.05 mmHg in a group of patients suffering from pulmonary hypertension. Maximal exercise capacity and exercise-triggered symptoms are linked to increased pulmonary capillary pressure and therefore a subsequent increase of left ventricular filling pressure. In this way, filling pressures are directly associated to the LV diastolic function. This point can explain the beneficial reflection of DD improvement on the pulmonary hypertension and the ventilatory limitation of patients with CHF.

In our study, there was not any decrease in the LAVI, an important index in determination of DD. Previous studies showed that left atrial enlargement is an independent marker of adverse outcome in both primary and secondary cardiovascular prevention [33]. Limited data, however, have been reported on the exercise training effects on LAVI in CHF, suggesting conflicting results. Edelmann *et al*[34] reported a significant decrease in LAVI in the training group, while Palau *et al*[35] reported no change in LAVI after interval training. Sandri *et al*[36] also, failed to find a significant change in LA size after 4 wk of training.

A significant improvement in the left ventricular EF (LVEF) was also found in this study. This finding is in line with a recent metanalysis[37], which included trials reporting on LVEF, LV end-diastolic and end-systolic volumes. Overall, AER training improved these parameters. Both continuous and interval regimes were able to induce similar benefits, which may be also affected by the program duration.

Finally, considering the regimes of the exercise applied in this study, overall aerobic and combined regimes improved EF, RVSP, and DD grades. Not any between-group differences were observed. Aerobic training can induce beneficial effects also on skeletal muscles, and continuous aerobic training has been found to reverse partially skeletal myopathy of the HF[38]. Interval exercise training, which was also employed in the present study, can be an effective regime, as it can apply higher exercise stimuli on skeletal muscles *via* a higher exercise intensity[39,40]. Furthermore, strength training has been shown to induce muscle hypertrophy, while the combination of resistance training with aerobic training has the potential to induces greater benefits in

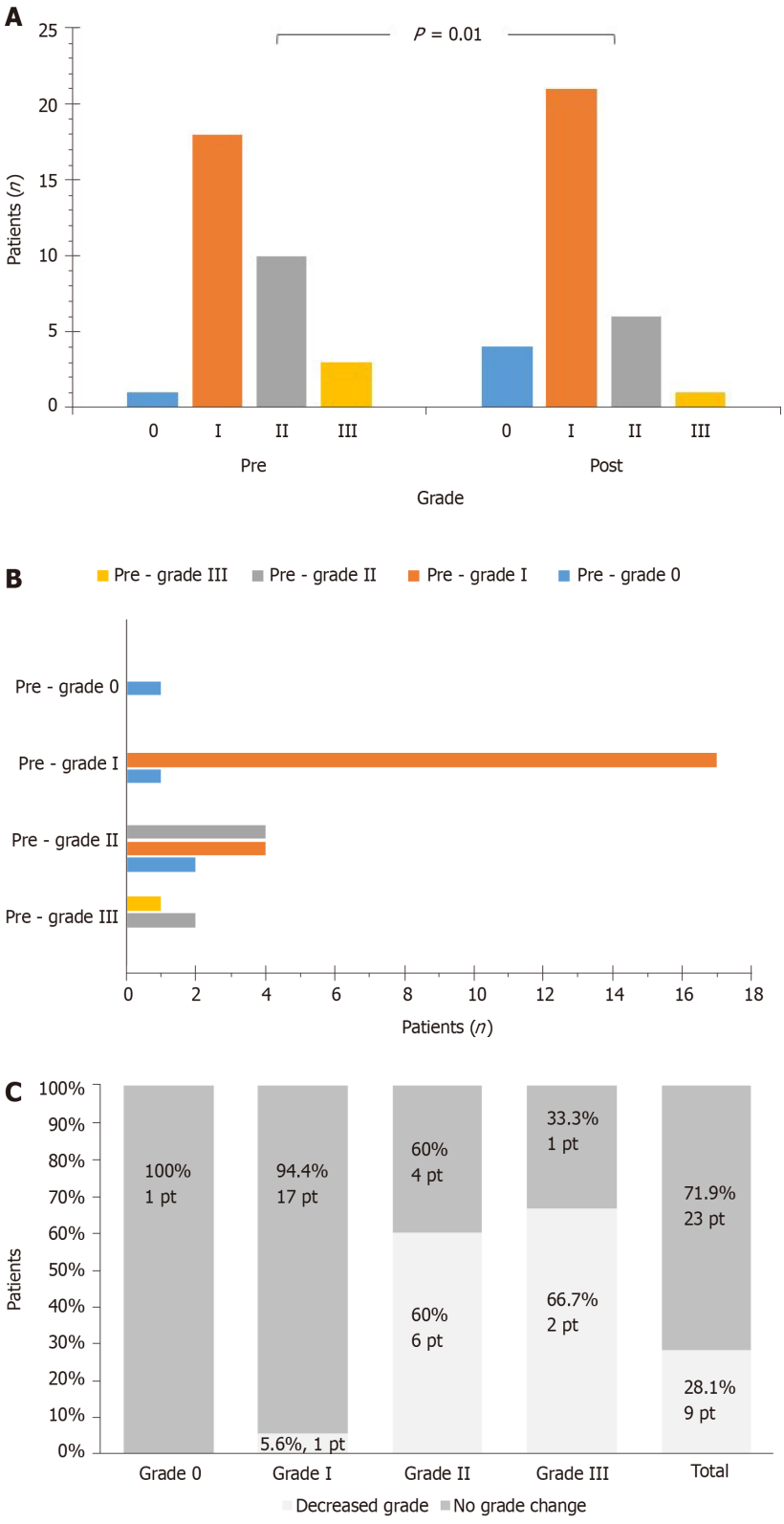


Figure 1 Changes in diastolic dysfunction grades. A: Pre- and post-number of grade-0, -I, -II, -III patients (P = 0.01, as assessed with Wilcoxon signed-rank test); B: Patients' distribution according to pre- and post-level of grade (P = -0.06, as analyzed with McNemar-Bowker test); C: Number of patients that decreased grade or remained at the same grade in relation to baseline grade (P < 0.01, as assessed with χ^2 test).

vascular endothelium[19], muscle strength and aerobic improvement of CHF patients than AER alone[17,18,41]. Interestingly, in a CHF study that employed a combined exercise protocol *vs* control, ventricular stroke volume and left ventricular diastolic indices were improved[28]. The effects of different exercise regimes on the diastolic dysfunction need to be further investigated.

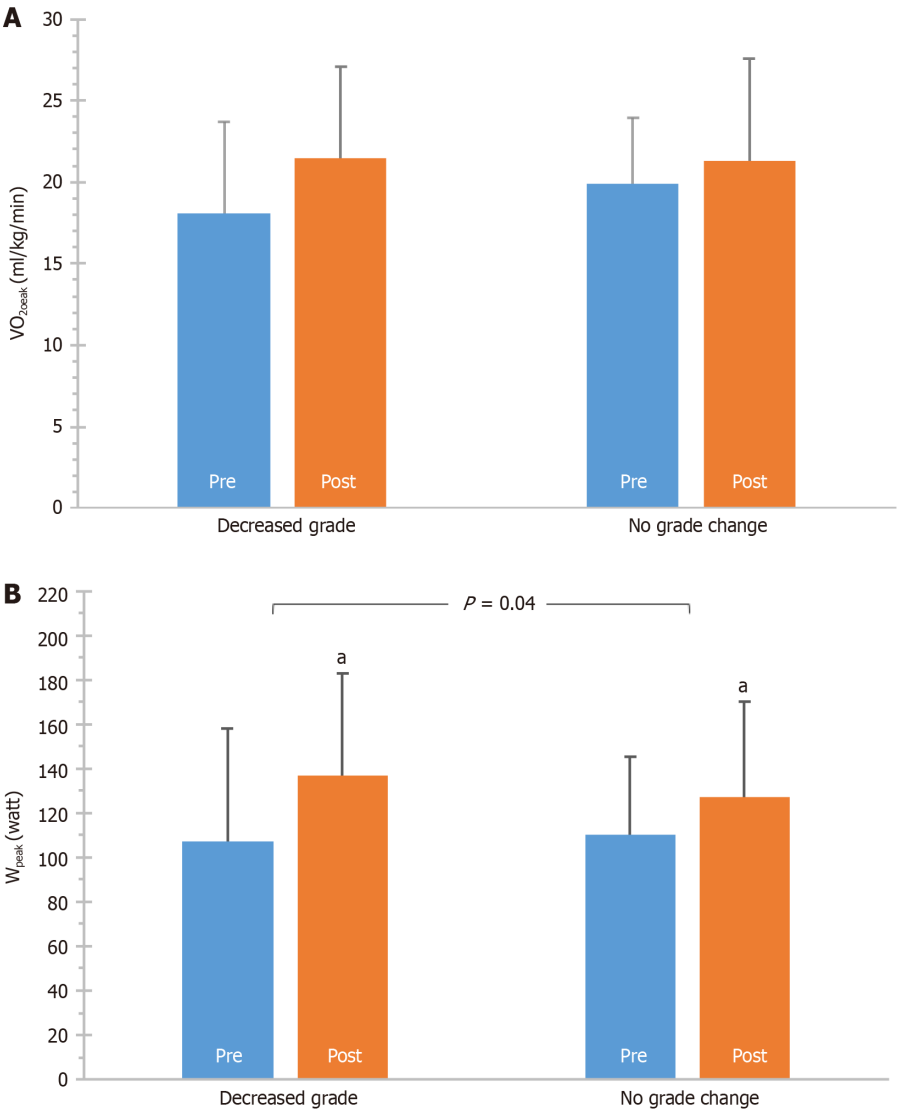


Figure 2 Values of VO_{2peak}(A) and W_{peak}(B) before and after the program for the groups of patients according to DD grade alteration *i.e.* "decreased grade" *vs* "no grade change". $^{a}P < 0.05$, significant within-group difference.

This study had some limitations. First, there is no single non-invasive measure that quantifies the LV diastolic function. Instead, a number of indices are utilized, and current recommendations use a combination of conversional and TDI parameters to determine the diastolic function of the LV[21]. In our study, there was a statistically significant improvement on the DD grades, but other parameters, such as E/A and E/E', were not found to improve. This may be related to the method used to determine the diastolic stage and the sample size. In fact, some results were underpowered to reach definite conclusion. Also, LV diastolic filling patterns as evaluated with transmitral Echo-Doppler are influenced by a variety of factors including valvular insufficiency, myocardium viscoelastic properties, ventricular compliance and loading conditions[21]. However, all patients were under constant medication during the study and all of them had mild degree of mitral regurgitation. Finally, considering that the exercise benefits on CHF have already been well documented, a control group was not employed, and patients randomized in two groups, AER and COM, to explore any potential differences on the diastolic dysfunction.

CONCLUSION

In conclusion, DD plays an essential role in the pathophysiology of the HF syndrome and interventions that improve it can be beneficial in terms of symptoms and outcome. In this study, the effects of an exercise training rehabilitation program (AER with/

without strength training), were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

ARTICLE HIGHLIGHTS

Research background

Diastolic dysfunction (DD) of the left ventricular (LV) is a keystone in the pathophysiology of chronic heart failure (CHF). Exercise training in general induces several beneficial effects in CHF patients, including functional capacity, quality of life and clinical outcomes. In this study, the impact of a rehabilitation program on the DD and the ejection fraction (EF) of the LV is evaluated in patients with CHF and EF < 50%.

Research motivation

Exercise training induces several beneficial effects on CHF patients. However, the effects of exercise training on diastolic DD have not been adequately studied. This is also the case for the effects of different exercise regimes on DD.

Research objectives

The main aim of the study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the ejection fraction (EF) of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

Research methods

In this randomized clinical trial study, 32 patients with CHF were screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations. They randomly assigned to aerobic exercise (AER) or combined aerobic and strength training, by a researcher not involved in the rest of the tasks. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

Research results

Exercise training overall beneficially affected DD grade, right ventricular systolic pressure (RVSP), EF of the LV and AER capacity. No differences between the aerobic and combined group were observed.

Research conclusions

In this study, the effects of an exercise training rehabilitation program (AER with/without strength training) were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

Research perspectives

Future research is warranted to further explore the effects of different exercise training regimes on diastolic dysfunction.

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MINIREVIEWS

Lipid lowering in patients 75 years and older

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Abstract

More than twenty years ago, knowledge about the importance of cholesterol absorption and the potential therapeutic effect of its inhibition led to the discovery and clinical application of the first and only cholesterol absorption inhibitor to date – ezetimibe. Since then, ezetimibe has become a well-recognized player in lipid-lowering therapy. Recent findings of IMPROVE-IT and EWTOPIA 75 imply that elderly patients over the age of 75 years in particular benefit from ezetimibe. This review summarizes the evidence, discusses the possible underlying pathophysiological mechanisms and calls for a change in future dyslipidemia guidelines.

Key Words: Cholesterol; Cholesterol absorption; Cholesterol synthesis; Ezetimibe; Elderly

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Core Tip: The review summarizes the evidence of lipid-lowering therapies in patients 75 years and older, and discusses the possible underlying pathophysiological mechanisms and calls for a change in future dyslipidemia guidelines.

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INTRODUCTION

Aging is a risk factor for cardiovascular morbidity, as the prevalence of atherosclerosis, myocardial infarction, and stroke increases with age[1]. Among all the physiological alterations that occur during the lifespan of a human being, changes in cholesterol metabolism are among the most important. Total cholesterol levels increase beginning from age 18-19 in men and age 20-21 in women and reach their climax at 50-51 and 56-57 years of age, respectively[2]. Although the concentration of endogenously synthesized cholesterol exceeds the amount of exogenous dietary cholesterol in the bloodstream, the inhibition of cholesterol absorption by ezetimibe reduces both low density lipoprotein (LDL)-c levels and the occurrence of cardiovascular events[3-5]. The particular benefit of ezetimibe treatment in regard to hard cardiovascular outcomes in patient populations over 75 years of age was only recently demonstrated in large cardiovascular outcome trials, such as IMPROVE-IT[6] (secondary prevention) and EWTOPIA 75[7] (primary prevention).

CHOLESTEROL METABOLISM

Cholesterol is one of the key components of the cell membrane and a precursor of steroid hormones, bile acids and vitamin D. Plasma cholesterol levels are regulated by three factors: Dietary absorption, endogenous biosynthesis in the liver and bile acids that are reabsorbed in the small intestine. Endogenous cholesterol synthesis begins with the 18-step formation of mevalonate through its conversion by HMG (3-hydroxy-3-methyl-glutaryl-) CoA reductase, which is a target of statin therapy, and ends with the 19-step synthesis of cholesterol from lanosterol. This cascade of reactions occurs in all nucleated cells and is catalyzed by a diversity of enzymes. Late precursors of cholesterol, such as squalene, cholestanol, desmosterol and lathosterol, are traditionally used as cholesterol synthesis markers. Due to its structure, cholesterol cannot be easily transported to tissues. Therefore, it is transported by lipoproteins, which contain triglycerides and cholesterol in their cores and apolipoproteins on their surface. Very low-density lipoprotein is synthesized in the liver and hydrolyzed to LDL in two steps. LDL is the major transporter of cholesterol in the plasma.

In addition to be endogenously synthesized, cholesterol is absorbed from the diet. In the small intestine, esterified cholesterol is converted to free cholesterol, which is absorbed *via* transport and endocytosis by NPC1L1 (Niemann-Pick C1-Like 1). In enterocytes, chylomicrons are formed from cholesterol, phospholipids, and triacylglycerol by apoprotein B48. Chylomicrons are transported *via* the lymphatic system to the bloodstream, where they deliver fatty acids to peripheral tissues and are eventually degraded by the liver. Moreover, nonesterified plant sterols and "excess cholesterol" are excreted back into the small intestine *via* the ATP-binding cassette transporter (ABCG5/G8) heterodimer. This results in large differences between cholesterol and plant sterol concentrations in the bloodstream, with plasma cholesterol levels being approximately 1000-fold higher than plant sterol levels.

PATHOPHYSIOLOGIC ASPECTS OF CHOLESTEROL METABOLISM IN AGING

The increase in LDL-c levels with age can be explained by several factors: A decrease in LDL receptor levels, an increase in the levels of apoB-100 in the liver and serum[8], an increase in cholesterol absorption, and a decrease in bile acid synthesis[9].

Animal studies have demonstrated that the cholesterol absorption rate increases with age[10,11]. According to Duan *et al*[11], cholesterol absorption in older mice (measured by the plasma dual isotope ratio method) is higher than that in younger mice, which is mechanistically explained by an increase in NPC1L1 mRNA expression with aging. Interestingly, the expression of ABCG5/G8, a transporter that pumps plant sterols back into the intestinal lumen and thus decreases plant sterol concentrations in the plasma, is negatively correlated with aging[11].

Another important age-related alteration is a reduction in CYP7A1 expression, an enzyme involved in bile acid synthesis. This leads to a decrease in bile acid synthesis, which in turn results in a lower cholesterol utilization rate[9].

Unfortunately, the number of human studies in this context is very limited. One study reported a positive correlation between cholesterol synthesis marker levels and

aging in a Northern Italian population. In that study, cholesterol absorption marker levels were also elevated in elderly individuals but not in patients with gallstones[12] (Figure 1).

METHODS OF CHOLESTEROL ABSORPTION MEASUREMENT

Methods to quantify cholesterol absorption were established as early as 1960[13,14]. Almost all of the early methods were based on isotope labeling of plasma and fecal probes: Cholesterol balance, single-dose isotopic feeding, dual isotope plasma ratio, continuous isotope feeding, and intestinal perfusion[13]. Another validated method that does not require isotope feeding is the measurement of the ratio of plant sterol levels (campesterol and sitosterol) and cholestanol levels (metabolite of cholesterol), which is performed mainly *via* high-performance liquid chromatography. Plant sterol concentrations have been shown in several studies to be markers of cholesterol absorption[15].

INHIBITION OF CHOLESTEROL ABSORPTION IN ELDERLY INDIVIDUALS

Early studies

A landmark study addressing the importance of cholesterol metabolism in elderly patients was the DEBATE-Study[16]. Strandberg and colleagues conducted a prospective cohort study of home-dwelling elderly individuals to assess the prognostic value of markers of cholesterol metabolism (absorption *vs* synthesis). They found that low cholesterol absorption in individuals older than 75 years of age was associated with fewer cardiovascular events and better survival. In that study, the levels of markers of cholesterol synthesis were negatively associated with cardiovascular outcomes[16]. Strandberg and colleagues speculated that lower cholesterol absorption was associated with better prognosis since these individuals had a lower cholesterol burden during their lifespan. On the other hand, the worse prognosis may have also been due to increased plant sterol absorption. Similar results were reported by our group in elderly patients with aortic stenosis and patients with diabetes mellitus[17,18].

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the liver, thus preventing the formation of mevalonate, which determines the rate of endogenous cholesterol synthesis[19]. Statins reduce LDL-c levels by up to 60% depending on the specific drug and dose (rosuvastatin is the most potent statin, as 40 mg of rosuvastatin reduces LDL-c levels by 55%)[20]. Although statins are the cornerstone of lipid-lowering therapy, target goal attainment with statin monotherapy is often unsatisfactory. In JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin), approximately 10% of the patients showed no change in LDL-c levels, and over 40% had a LDL-c level reduction below 50%[21]. Several loci were identified by genome-wide association studies to be responsible for "nonresponsiveness" to statin therapy[21,22]. On the other hand, ezetimibe treatment is particularly effective in these patients since low endogenous synthesis is associated with high cholesterol absorption[23,24].

The secondary analysis of ALLHAT-LTT demonstrated that statins (pravastatin) conveyed no benefit in a primary prevention setting. Moreover, there was a nonsignificant trend toward increased all-cause mortality in the pravastatin group vs. the placebo group. PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) evaluated hard cardiovascular outcomes in pravastatin- *vs* placebo-treated patients. Pravastatin reduced primary endpoints (a composite of coronary death, nonfatal myocardial infarction, and nonfatal stroke occurrence) after 3 years of follow-up. The subgroup analysis in the study revealed that this effect was stronger among those with established cardiovascular disease than among those without cardiovascular diseases, implying that statins are less effective in a primary prevention setting. However, no significant difference was observed in the interaction test between groups. Moreover, in pravastatin-treated patients, the incidence of newly diagnosed cancer was 25% higher than in the placebo group, although a meta-analysis did not show any significant association with cancer[25].

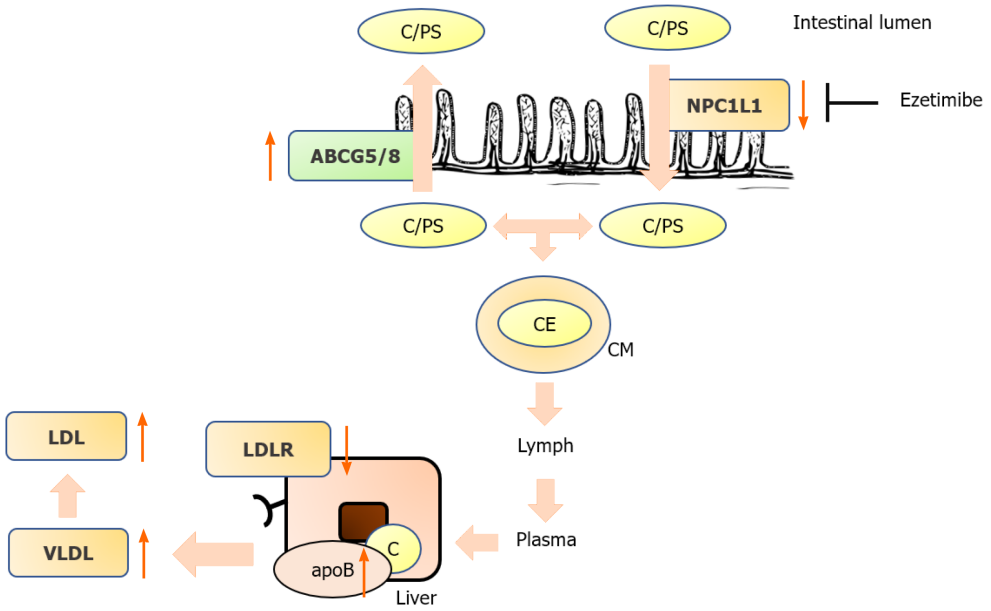


Figure 1 Alteration of cholesterol metabolism during lifetime. Dietary cholesterol is absorbed in the intestinal lumen *via* transport and endocytosis, which is regulated by NPC1L1. NPC1L1 mRNA expression decreases with increasing age. On the other hand, about 50% of dietary cholesterol and about 95% of plant sterols are pumped back into the intestinal lumen by ABCG5/8, which is upregulated in elderly individuals. Cholesterol is packed into the chylomicrons and transported to the liver. Chylomicron remnants are taken up by the low density lipoprotein (LDL)-receptor in the liver. Moreover, endogenous cholesterol is synthesized in the liver. Endogenously synthesized cholesterol is transported to peripheral tissues *via* LDL. The red arrow shows age-related up- or downregulation of different genes/proteins in cholesterol metabolism. C: Cholesterol; PS: Plant sterols, CM: Chylomicrone; LDL: Low density lipoprotein; VLDL: Very low-density lipoprotein; NPC1L1: Niemann-Pick C1-like 1; ABCG5/8-ATP: Binding cassette transporter G5/G8.

Ezetimibe

Ezetimibe targets NPC1L1 in the small intestine, resulting in the inhibition of cholesterol and plant sterol absorption. In humans, ezetimibe also inhibits hepatic NPC1L1 to prevent reabsorption of cholesterol and plant sterols from the bile and increases their excretion. Ezetimibe is metabolized to ezetimibe-glucuronide, which is also a potent inhibitor of NPC1L1. The maximal concentration is reached 1–2 h after oral administration, and it has a terminal half-life of 22 h[3]. Ezetimibe lowers LDL-c levels by approximately 20%[3,4]. PRECISE-IVUS demonstrated that ezetimibe in combination with atorvastatin resulted in greater coronary plaque regression than atorvastatin monotherapy in patients with coronary artery disease[26]. The SHARP trial demonstrated that the combination of statins and ezetimibe reduced LDL-c levels and cardiovascular outcomes in patients with chronic kidney disease[27]. According to the current ESC/EAS guidelines, ezetimibe is recommended as an adjuvant to statin therapy when LDL-c goals cannot be achieved by statin monotherapy[28].

A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S) suggested that patients with high cholesterol absorption and low cholesterol synthesis did not benefit from statins in terms of cardiovascular event reduction[29]. HIJ-Proper, on the other hand, demonstrated that patients with high cholesterol absorption benefited from the addition of ezetimibe in terms of cardiovascular event reduction, whereas patients with low cholesterol absorption did not[30].

IMPROVE-IT secondary analysis – addition of ezetimibe to a statin in elderly patients after acute coronary syndrome

IMPROVE-IT demonstrated for the first time that ezetimibe, a nonstatin drug, reduces LDL-c levels and hard cardiovascular outcomes[5]. In a recent secondary analysis, the outcomes of IMPROVE-IT were analyzed according to age. Interestingly, in patients older than 75 years of age, ezetimibe treatment was much more effective in reducing cardiovascular events. In patients over 75 years of age, the number "needed to treat" was 11, whereas it was 125 in patients younger than 75 years of age[6]. These findings illustrate the preventive capacity of adding a cholesterol absorption inhibitor in elderly individuals over 75 years of age[31].

EWTOPIA 75 – ezetimibe in the primary prevention of cardiovascular disease in elderly individuals

The EWTOPIA 75 study is a prospective, double-blind, placebo-controlled randomized trial that was conducted in Japan and demonstrated the benefit of ezetimibe in elderly patients without a history of coronary artery disease[7]. In this primary prevention trial, ezetimibe reduced both LDL-C levels and hard cardiovascular outcomes. This further adds to the notion that individuals over 75 years of age with elevated cholesterol levels benefit in particular from ezetimibe treatment[32]. This is of particular interest since all statin trials of primary prevention in patients over 75 years of age failed to reduce cardiovascular events[25,33].

Possible role of plant sterols

In a recently published large-scale genetic analysis of over 1 million individuals with and without cardiovascular diseases, Helgadottir and colleagues reported genetic variants of ABCG5/G8 and NPC1L1 that increase plasma plant sterol levels, and plasma cholesterol levels have a greater impact on cardiovascular risk than the levels of other lipid genes that increase only serum cholesterol levels (LDL-c receptor, HMG-CoA-reductase, apoB, *etc*.). Genes that increased non-HDL cholesterol levels by 1 mmol/L and also increased serum plant sterol levels increased cardiovascular risk 2.0-fold. However, genes that increased serum non-HDL cholesterol levels by 1 mmol/L but had no impact on serum plant sterol levels increased cardiovascular risk only 1.5-fold[34]. These findings are important since they demonstrate that plant sterols "per se" are atherogenic. On the basis of these findings, determination of the levels of markers of cholesterol metabolism, such as campesterol, sitosterol and lathosterol, should play a more important role in future cardiovascular risk stratification and a more personalized and individualized treatment approach for hyperlipidemia[24,35]. As early as 2016, we suggested evaluating the ratio of cholesterol synthesis and absorption in IMPROVE-IT[36]. This analysis is under way, as assured by the TIMI Study group, and will provide important mechanistic insights[37].

CONCLUSION

Evidence from animal studies and human trials indicates that cholesterol and plant sterol absorption increase with age. Findings from large-scale prospective, randomized trials on primary and secondary prevention demonstrate that patients over 75 years of age benefit in particular from the addition of a cholesterol absorption inhibitor, such as ezetimibe. Therefore, ezetimibe should be the lipid-lowering drug of choice in patients 75 years and older.

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MINIREVIEWS

Electrocardiographic changes in Emphysema

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Abstract

Chronic obstructive lung disease (COPD), predominantly emphysema, causes several thoracic anatomical and hemodynamic changes which may cause changes in various electrocardiographic parameters. A 12-lead electrocardiogram (ECG), which is often a part of routine evaluation in most clinical settings, may serve as a useful screening modality for diagnosis of COPD or emphysema. Our current article aims to provide a comprehensive review of the electrocardiographic changes encountered in COPD/emphysema utilizing published PubMed and Medline literature database. Several important ECG changes are present in COPD/emphysema and may serve as a good diagnostic tool. Verticalization of P-vector, changes in QRS duration, pattern recognition of precordial R-wave progression and axial shifts can be considered some of the most valuable markers among other changes. In conclusion, 12-lead surface electrocardiogram can serve as a valuable tool for the diagnosis of COPD and/or emphysema. An appropriate knowledge of these ECG changes can not only help in the diagnosis but can also immensely help in an appropriate clinical management of these patients.

Key Words: Emphysema; Chronic obstructive pulmonary disease; Electrocardiogram; P-wave axis; Sensitivity; Specificity

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Core Tip: Chronic obstructive pulmonary disease (COPD) remains a major cause of morbidity and mortality in the United States. With COPD, a timely diagnosis and treatment are crucial to prevent increasing severity. COPD can cause electrocardiographic changes due to factors including lung hyperinflation. These changes can be present on the electrocardiograms of patients without COPD; however, specific parameters not seen in those with COPD will be indicative of other diseases such as congenital heart disease. The present review focuses on the use of 12-lead electrocardiogram with an emphasis on vertical frontal plane P-wave axis, combined with other minor abnormalities, which can aid in the diagnosis of COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition and is ranked among the top five causes of death in the United States[1]. It causes significant obstructive airflow limitation and is associated with chronic oxygen dependence, functional limitation, recurrent hospitalizations as well as increased morbidity. Prompt diagnosis and treatment can prevent worsening of the disease and offer morbidity and mortality benefit. As such, it is important for clinicians to promptly recognize this condition even if the patient is getting evaluated for other reasons.

COPD causes several thoracic anatomical and hemodynamic changes which may produce changes in the different electrocardiographic parameters. Increased airway obstruction, right ventricular afterload, diaphragmatic displacement due to hyperinflation, clockwise rotation of the right heart, and body mass index changes correlated with clockwise rotation of the frontal QRS-vector are some of the underlying factors which play a major role in the electrocardiographic changes observed in patients with COPD[2]. A 12-lead electrocardiogram (ECG), which is often a part of routine evaluation in many clinical settings, can yield useful diagnostic clues and may serve as an initial screening modality as well as aid in further evaluation and management of COPD or emphysema. However, some of the ECG changes observed in patients with known COPD/emphysema may carry an independent prognostic value.

This comprehensive review aims at discussing characteristic electrocardiographic findings in COPD, some of which may offer a high sensitivity and specificity as standalone criteria in the diagnosis of COPD.

LITERATURE RESEARCH/MATERIALS AND METHODS

We searched PubMed and Medline for published articles focusing on COPD, emphysema, and electrocardiography. The search terms used in different combinations, were "chronic obstructive lung disease and ECG changes", "emphysema and ECG changes", "COPD and ECG changes", "COPD and ECG", "COPD and electrocardiogram", "emphysema and electrocardiogram", "emphysema and ECG", "COPD and electrocardiographic changes", and " emphysema and electrocardiographic changes", yielding us 177, 70, 175, 1154, 1098, 535, 549, 50 and 31 articles respectively indexed in PubMed and Medline at the time of writing this publication. These articles were further screened for subject relevancy and used if they were English-language full-text papers. Both review articles and original papers were included. Finally, the data from these articles used for writing of this review paper were those that were most relevant and pertinent to our current subject of discussion.

IMPORTANT ECG PARAMETERS

Emphysema produces a variety of electrocardiographic changes which are discussed in details below. A summary of these changes is enclosed at the end of the manuscript in a tabular format (Table 1).

Frontal plane P-wave axis

The changes in the frontal plane P wave axis are among one of the most important changes produced in the standard 12-lead ECG by emphysema. In most normal adults, the frontal P axis is considered to be within a very narrow range, +45° to +65°[2,3]. Studies from the 1940s and 1950s suggested that in patients with chronic lung disease, the mean frontal P vector was shifted rightward or vertically[2,4]. A study of 50 cases of chronic cor pulmonale found that all but 8 cases had a mean manifest frontal P axis of 60° or more[4]. Spodick and colleagues[2] analyzed ECGs of 79 consecutive hospital admissions for diffuse lung disease (predominantly emphysema) and found that the mean manifest P axis was to the right of +70° in 83% of these cases. A vertical P wave axis (> 60°) in the frontal plane especially in individuals over age 45 years has been considered highly suggestive of emphysema by many studies since then[5-12].

As depicted in Figure 1 and Figure 2, a vertical P vector can be primarily determined by two methods on a standard 12-lead electrocardiogram—P wave amplitude in lead III greater than in lead I (bipolar lead set) and/or a predominantly negative P wave in lead aVL (unipolar lead set)[2,13,14]. Out of these two criteria, the bipolar lead set appears to be more sensitive. A recent study from our group reviewed 100 consecutive ECGs of patients with a known diagnosis of emphysema found the bipolar lead set to be a more sensitive marker of vertical P-wave axis in emphysema than the unipolar lead set (sensitivity 88% *vs* 66% respectively)[13]. This study excluded patients younger than 45 years because a vertical P vector may be a normal finding in these patients[13].

Several studies have investigated the sensitivity and specificity of P vector verticalization as a criterion in screening for emphysema. A large study evaluated ECGs of 600 patients with vertical P avector and compared with age and sex matched control cohort with P-vector of < 60° which demonstrated that the sensitivity and specificity of vertical P-vector in diagnosing emphysema to be 94% and 87% respectively[5]. Other studies have shown comparable results[12,14]. Another study showed that frontal P axis > 80° was the single best criterion (among many other P and QRS criteria) for the separation of patients with and without COPD[15]. When the vertical P axis (> 60°) was combined with a QRS duration of < 75 ms, the specificity increased to 100% at the cost of significant decrease in sensitivity[7]. Similar findings of increased specificity and decreased sensitivity have been noted when vertical P axis was used in conjunction with one of the QRS criteria such as vertical QRS axis, low voltage in Leads V6 and/or Vs, as well as R/S ratio in Leads V5 and/or V6 < 1[15].

In addition to carrying a high sensitivity for screening of emphysema, the degree of P axis verticalization has also been found to strongly correlate with the severity of emphysema[5,8,10]. In a study of 154 patients with chronic bronchitis, and with or without emphysema, P axes > +75° correlated negatively with severity of lung disease measured by forced expiratory volume/vital capacity (FEV1/VC%, r = -0.724, P < 0.05)[8]. Calatayud *et al*[10] showed that the frontal P axis negatively correlated (r = -0.35, P < 0.01) with maximum voluntary ventilation (MVV) in a group of 173 patients with COPD referred for pulmonary function testing. In some recent studies, a significant positive correlation has been observed between the radiographic quantification of severity of emphysema and electrocardiographic P-vector verticalization in patients with established clinical diagnosis of emphysema[5]. In a small retrospective study of 26 patients with emphysema who underwent high resolution computed tomography (CT) scans, the computed tomographic visual score of emphysema and orientation of the P vector had a significant overall positive correlation (r = +0.68, P = 0.0001)[5]. This was particularly strong in patients with predominantly lower lobe emphysema (r = +0.88, P = 0.000, FEV1, and orientation of P vector had almost linear negative correlation in this subgroup (r = -0.92, P < 0.0001). Another study showed significant positive correlations with radiographic percent emphysematous area estimated by high-resolution CT and degree of P vector (r = +0.77, P < 0.0001), a stronger correlation was again found in patients with predominantly lower lobe emphysema.

The mechanisms responsible for verticalization of P vector in emphysema have long been debated. P axis in restrictive lung disease tends to be more horizontal than in obstructive lung disease[6,9]. A series of consecutive patients with pure restrictive and pure obstructive lung disease demonstrated that diaphragmatic levels were

Table 1 Common electrocardiographic changes commonly related to chronic obstructive pulmonary disease/emphysema

Vertical P-wave	P-wave axis > 60°
P-pulmonale	P-amplitude in II, III or aVF ≥ 2.5 mm
	P-amplitude in V1 ≥ 1.5 mm
Right ventricular hypertrophy	R in V1 ≥ 7 mm
	R/S in V1 > 1
	VAT in V1 > 35 ms
Sokolow-Lyon: Right ventricular hypertrophy	R in V1 + S in V5 or V6 > 10.5 mm
Clockwise rotation	R/S ratio in V5 ≤ 1
Low voltage limb leads	QRS (R+S) < 5 mm in I, II, aVF, III (all)
Low voltage precordial leads	QRS < 10 mV in V1–V6 (all)
S1S2S3 pattern	Dominant S in I, II, III (all)1
QS complex	Lead III
Rightward QRS-axis deviation:	> 90°
Short QRS duration	< 75 ms
Elevated resting heart rate (especially during exacerbation)	HR > 80 beats/min

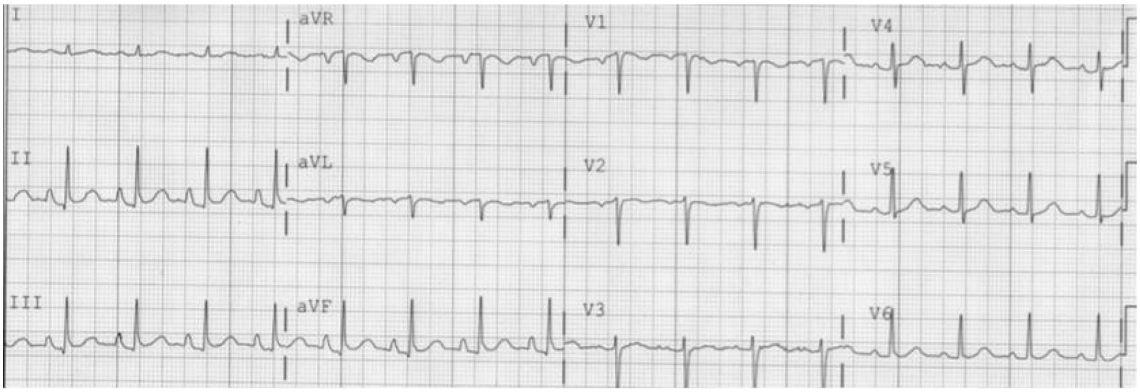


Figure 1 Electrocardiogram showing vertical P wave axis suggested by P wave amplitude in lead III greater than P wave in lead I and a negative P wave in lead aVL. Adapted from Bajaj *et al*[13].

significantly higher in patients with restrictive disease compared with obstructive disease (in the same series, P axes in obstructive disease were predominantly vertical and those in restrictive disease were predominantly horizontal or intermediate)[16]. It was hypothesized that opposite effects on diaphragm level by obstructive disease (low diaphragm) and by restrictive disease (high diaphragm) could explain the axis differences, because the right atrium is attached *via* the inferior vena cava and adjacent pericardium to the right leaf of the diaphragm. Other hypotheses attribute P vector verticalization to the presence of right atrial and right ventricular hypertrophy (RVH) from cor pulmonale.

Hypertension and left ventricular hypertrophy (LVH) represent some clinical scenarios in which a vertical P vector may be observed without the presence of emphysema[2,12]. Conversely, some patients with hypertension and LVH may have leftward P axes in the setting of emphysema[2,12]. Although it could be inferred that LVH may reduce the sensitivity of vertical P axis when used for detection of emphysema, this was refuted in a recent retrospective study[17]. It did not find any statistically significant difference in the mean P vector between emphysema patients with and without echocardiographic evidence of LVH, and concluded that the presence of LVH may not significantly alter the sensitivity of P wave verticalization when used as a sole criterion for the diagnosis of emphysema.

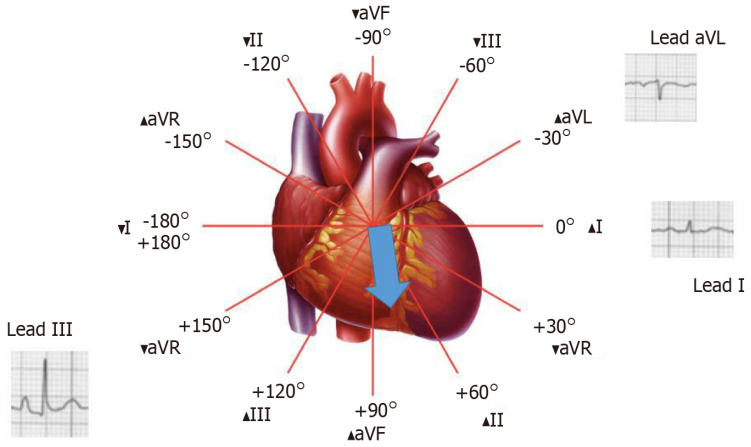


Figure 2 Depiction of vertical P axis in Hexaxial reference system.

It has been noted that many patients with congenital heart disease (CHD) that causes right atrial enlargement, right ventricular enlargement, and right bundle branch block, a vertical P axis may be commonly noted in the absence of emphysema [11]. While most patients with emphysema tend to have posteriorly and superiorly displaced QRS vectors, those with CHD and RVH have anteriorly, rightward, and slightly inferiorly displaced late QRS vectors[11]. The presence of low voltage of QRS (< 0.7 mV in limb leads and V6) and posterior and superior displacement of the mean QRS axis can help differentiate cases of emphysema and CHD with vertical P axis.

Frontal plane P wave amplitude

In addition to changes in the P wave axis, a more vertical position of the heart from diaphragmatic depression in obstructive lung disease can be associated with increased amplitude of P waves in inferior leads (II, III, aVF)[9]. This mechanism has been substantiated by scientific data. "P-pulmonale" is much more common in obstructive lung disease and in fact, it has not been noted at all in cases of restrictive lung disease in some studies[17]. A study of patients with chronic lung disease[18] and P-pulmonale on ECGs who underwent right heart catheterization showed no significant increase in right atrial or pulmonary artery pressures among these patients. In contrast, none of the patients with atrial septal defect or pulmonary hypertension had P-pulmonale on ECG. Given that all the patients with P-pulmonale had low cardio-thoracic ratio on chest radiograph and a considerably depressed diaphragm, the authors concluded that a more vertical position of the heart (particularly right atrium) was the major factor responsible for generation of P-pulmonale in patients with chronic lung disease[18]. Although P-pulmonale is an important finding in the chronic lung disease, it should be noted that there are some important differential diagnoses which should be entertained in cases of P-pulmonale. P-pulmonale may be observed in congenital heart disorders such as tricuspid atresia, rarely some electrolyte derangements and even in left sided cardiac dysfunction probably due to concomitant right atrial strain produced by underlying type-2 or mixed form of pulmonary hypertension[19,20]. It is also plausible that many of these patients in prior studies who had reported P-pulmonale in left heart failure may have previously undocumented co-existing chronic lung disease. It is also to be remembered that P-pulmonale is not necessarily a sign of right atrial enlargement in emphysema, but may be even likely the result of underlying pulmonary hyperinflation, right atrial hypoxia, and transient atrial strain or mechanical load directly resulting from the bronchospasm.

Spodick in his pioneer series of 79 consecutive hospital admissions for diffuse lung disease (almost all had emphysema) noted that classical P-pulmonale and "Gothic" P wave occurred only in cases with frontal P axis of +70° or greater[2]. A classic P-pulmonale refers to P wave amplitude > 2.5 mm in the inferior leads (II, III, aVF), while a "Gothic" P wave[2,4] refers to definite single peaking of P wave of normal amplitude in leads II, III and aVF. A schematic illustration is demonstrated in Figure 3. Although the presence of P-pulmonale and "Gothic" P waves is characteristic of obstructive disease, this finding is much less sensitive as compared to vertical P axis and is found in a little over half of the cases[2,10].

In some studies[9,10], increasing P amplitudes in inferior leads have been associated with decreasing FEV1%[9] and with MVV[11]. Thus, higher P amplitudes in inferior



Figure 3 A schematic illustration of "P-pulmonale" (A), "Gothic" P waves (B) and normal "Cupola" P wave (rounded in contour).

leads may be a marker of decreasing lung function in emphysema, although these inverse correlations were weaker than those with increasing P wave axes.

P wave changes in precordial leads

Initial increased P-wave amplitude in lead V1 may be a sign of right atrial abnormality associated with emphysema. An increased P-terminal force in V1 (V1PTF) is usually a sign of left atrial enlargement[21-23], however an increased V1PTF was also frequently found in patients with cor pulmonale (Figure 4)[24]. Thus, increased V1PTF should be interpreted with caution in patients with known emphysema. A former retrospective study showed that V1PTF correlated with vertical P vectors in patients with emphysema and may be a function of downward right atrial displacement in this population rather than left atrial enlargement[25].

Spodick *et al*[2] noted that 51% cases of diffuse lung disease had biphasic (+/-) P waves in at least V1 and V2 and in some cases as far as V4, 78% of these were associated with vertical P axis of +70° or more. In another series of patients with fibrosing lung disease and COPD, P wave changes in lead V1 were not significantly different between the two groups[9].

Although P-wave indices constitute an important diagnostic criterion in patients with emphysema, the application of such criteria is limited in those patients with emphysema who have atrial arrhythmias including atrial fibrillation. In those patients, other criteria such as QRS voltage, QRS axis and QRS duration changes may be used to supplement the diagnosis of chronic lung disease.

Abnormalities of the PR segment

When compared to normal individuals, increased PR depression in leads II and III has been noted in patients with cor pulmonale in some older studies[4]. It was attributed to abnormal atrial repolarization because these tracings were similar to experimental tracings when atrial muscle was injured. Most such cases also exhibited P waves of high voltage, presumably due to atrial hypertrophy. One study reported strong negative correlation of PR depression of 0.5 mm or more (referred to as Ta waves) with FEV1/VC% in a series comprising of 154 patients with chronic bronchitis[8]. PR interval has been reported to be normal in patients with COPD[4,10].

However, in severe cases where COPD is coupled with pulmonary hypertension, the PR interval may be prolonged. A study examined ECG differences of 142 patients with COPD with or without pulmonary hypertension[26]. Of these, 63% of the patients that had pulmonary hypertension exhibited a longer PR interval than those without pulmonary hypertension. The prolonged PR interval in those patients was also linked to patients having an abnormal mean Papanicolaou (PAP) ≥ 40 mmHg. The combination of a mean PAP ≥ 40 mmHg and a lengthened PR interval has been shown to be a predictor of adverse outcomes for COPD patients with pulmonary hypertension[27].



Figure 4 Note the presence of right ventricular hypertrophy, significant P-terminal force and negative T waves in right precordial leads in this patient with pulmonary hypertension. Adapted from Yanowitz[39].

QRS duration

The ECGs of patients with COPD tend to demonstrate shorter duration of QRS complexes[7,28]. One study in 1970s showed the QRS duration to be shorter in all 12 standard leads in COPD patients when compared to controls (mean 0.061 ± 0.005 s *vs* 0.074 ± 0.003 s, $P < 0.001$)[28]. In another recent study, QRS duration with emphysema was found to be shorter than controls (78 ± 8 *vs* 89 ± 6 ms, $P < 0.01$)[7]. The combination of QRS duration < 75 ms in conjunction with a P axis of > 60° achieved a specificity of 100% for the diagnosis of emphysema, although the sensitivity decreased to 33%[7].

The exact mechanism by which QRS duration becomes shorter in emphysema patients remains elusive, but several hypotheses have been advocated by various authors. Low voltage QRS in emphysema may result in partial loss of the initial and terminal QRS forces which become indistinguishable from baseline, resulting in shorter QRS duration[7,28]. Postmortem investigations in emphysematous patients have suggested diminished left ventricular coronal area and left ventricular cavity, consistent with "left ventricular disuse atrophy"[29]. Some authors have hypothesized that in the absence of significant RVH, a tendency might exist for rapid completion of depolarization in these patients because of "less" left ventricular mass and size[7,25].

QRS axis in horizontal and frontal planes

In emphysema, various changes occur in the anatomic position of the heart. It descends downward due to depression of the diaphragm from hyperinflation of the lungs, assumes a vertical position, rotates clockwise along its longitudinal axis and its apex gets displaced posteriorly[4]. These anatomic changes produce significant changes in the QRS axis in the frontal and horizontal planes. In general, the frontal plane QRS axis tends to be more rightward and the horizontal plane QRS axis tends to be directed more posteriorly (Figure 5 and 6).

Spodick *et al*[2] in his series of 79 consecutive patients with diffuse lung disease noticed that the mean frontal QRS axis was to the right of +70° or indeterminate in almost 50% of the cases, which was quite uncommon for their age group. Among those with relatively leftward QRS axis, many patients had evidence of concomitant left heart disease or congenital chest deformity. In the same study, posterior orientation of the QRS axis in the horizontal plane was evidenced by an S wave of ≥ 2 mm in leads V5 or V6 in 65% of the patients. Moreover, high correlation between posteriorly oriented QRS axis and vertical frontal plane QRS axis as well as vertical frontal plane P axis (> 70°) was noted, indicating that these changes were likely related to emphysema and related anatomic changes in heart position.

Another series of patients with cor pulmonale made several observations regarding QRS changes in such patients[4]. When compared to the normal population, the



Figure 5 Right axis deviation of frontal plane QRS is noted along with P-pulmonale in a patient with pulmonary hypertension. Adapted from Yanowitz[39].

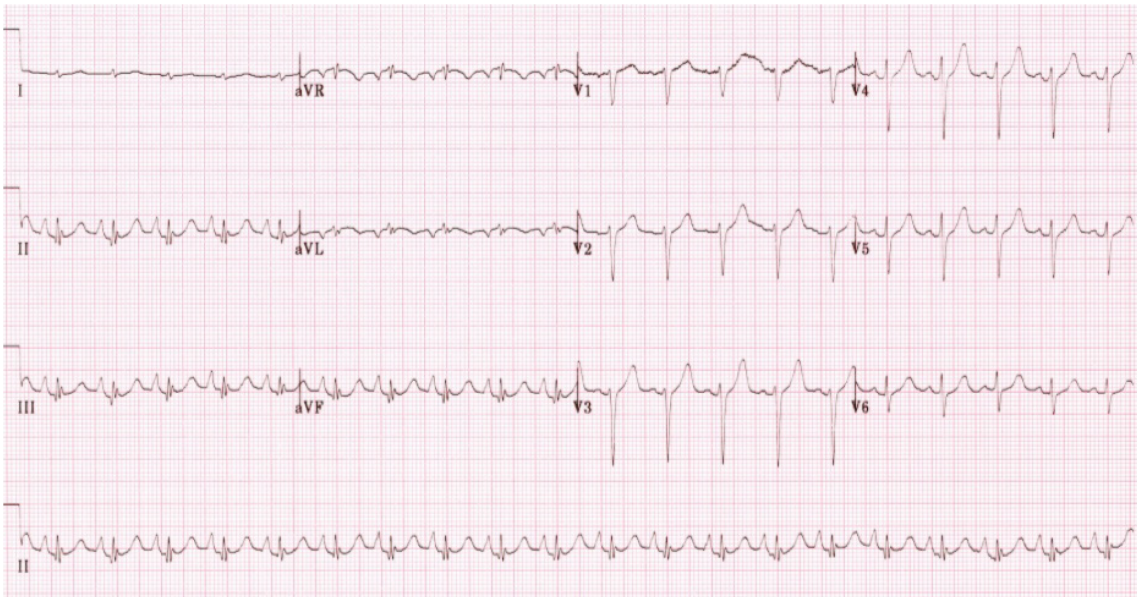


Figure 6 ECG of a patient with chronic lung disease showing precordial QRS changes suggestive of emphysema—poor R wave progression, R < 0.5 mv in lead V6, R/S < 1 in lead V6 and S wave > 5 mm in leads V5-6. Also note—P-pulmonale, lead I sign and negative P in aVL. Adapted from Burns[40].

average voltage of R wave in leads V2-V6 was lower while the average voltage of S wave was higher in leads V3-V6. These changes were attributed to the clockwise rotation of the heart (found to be much more common than in normal hearts in this study and because of frequent finding of left shifting of transitional complexes to leads V5-6). A study from Japan investigated the relationship between shift of transitional zone on precordial leads of electrocardiogram with anatomic rotation of the heart along its long axis by cardiac CT[30]. They measured the left sided angle between interventricular septum and the horizontal axis of the body based on CT and found that the mechanism of clockwise and counterclockwise rotation of the transitional zone could be attributed to the septal angle in about two-thirds of the cases. Relatively higher position of the precordial electrocardiography leads due to vertical heart position was thought to be responsible for clockwise rotation (which typically happens in emphysema) in the remaining cases. This supports the notion that these findings in

precordial leads are related to anatomic changes in heart position.

Poor R wave progression in precordial leads can be found in a variety of clinical conditions other than emphysema. One important differential is an old antero-septal myocardial infarction. One interesting study calculated R/S ratio in all precordial leads in a series of patients with emphysema and previous anteroseptal MI[31]. While the R/S ratio was significantly higher in emphysema from leads V1-V4, the pattern was reversed in leads V5-V6 where it was significantly higher in patients with MI. An R/S ratio > 3.5 in lead V5 was found to be most sensitive (87%), specific (83%) and accurate (85%) in differentiating poor R wave progression because of old anteroseptal myocardial infarction from that due to emphysema. A similar ECG pattern may sometimes be observed in patients with large right sided or tension pneumothorax which should be considered in differential diagnosis as clinically considered relevant [32].

Some other precordial QRS criteria have been studied in relation to emphysema (Figure 6). One study of COPD patients with electrocardiograms and lung function tests determined which QRS complex criteria were most useful in diagnosing COPD [33]. The best QRS criteria were R V6 amplitude of ≤ 0.5 mV and R/S ratio in V6 ≤ 1, which were present five times more in patients in quartile IV (most impaired with COPD) than quartile I. QRS axis greater than 75° or greater than 90° was present twice as often in quartile IV. Although R V6 amplitude of ≤ 0.5 mv and R/S ratio in V6 ≤ 1 were found to have a better discriminatory ratio between quartile IV and I than P axis ≥ 75°, these criteria were not applicable to almost half of the cases due to absence of S wave in V6. Another study found significant negative correlations between S wave ≥ 5 mm in V5-V6 and QRS axis over +75° with FEV1/VC%[8].

QRS amplitude

Some authors have also tried to establish QRS amplitude criteria for diagnosis of emphysema[15]. They studied the reliability of QRS amplitude ≤ 5 mm in limb leads, QRS amplitude ≤ 5 mm in leads V5 and/or V6 and R wave ≤ 7 mm in V5 and ≤ 5 mm in V6. Approximately one-half of the patients were categorized as false positive by these criteria, mostly due to atherosclerotic cardiovascular disease. Other studies did not find QRS amplitude criteria in limb leads to be useful in discriminating between different quartiles of lung function[33]. The average voltage of R+S in precordial leads was normal in cor pulmonale patients in one study[4].

The S1S2S3 syndrome

Older studies found that the average amplitude of R waves was lower while the amplitude of S waves was higher in leads I, II and III among patients with cor pulmonale when compared with normal population[4]. This is in keeping with the higher frequency of right axis deviation of QRS in the frontal plane in patients with emphysema. Some patients may demonstrate the S1-S2-S3 pattern (Figure 7) in leads I, II and III, where the S is of near to or greater magnitude than the R in each of these leads. This is often a normal finding in young individuals and frequently seen in patients with RVH due to other congenital and acquired lesions[34], although appears to have a relatively lower incidence in patients with emphysema (9-22%)[4,15,34,35]. When present, it is usually indicative of severe lung disease[15].

Pseudo left axis deviation / axis illusion phenomenon

Although the majority of patients with chronic lung disease have rightward deviation of frontal QRS axis, some patients may exhibit significant left axis deviation (-80° to -90°) or "indeterminate" axis in the absence of significant left ventricular disease or old myocardial infarction[2,34]. When viewed in the horizontal plane, it becomes apparent that this is due to the posteriorly directed ventricular activation and these axes are in fact not very different from an axis of +80° or +90°, as illustrated in the Figure 8[2]. This has been referred to as "pseudo left axis deviation" because left anterior fascicular block and coronary disease are usually not present[35,36].

"Lead I sign"

The presence of an isoelectric P wave, QRS amplitude < 1.5 mm, and T wave amplitude < 0.5 mm in lead I is usually referred to as "nearly isoelectric lead I" sign, which when present is highly indicative of underlying COPD[15,35,36]. A schematic illustration is provided in Figure 9.

T-wave changes

T wave changes in emphysema have not been extensively studied. One study



Figure 7 S1S2S3 pattern.

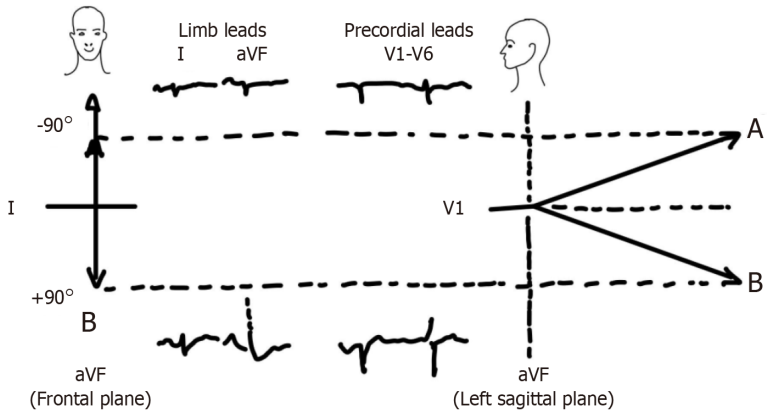


Figure 8 This is a schematic illustration of the axis-illusion phenomenon. A and B are frontal mean QRS axes of -90° and +90° respectively, suggesting a 180° divergence. Their sagittal projections reveal that this is illusory since they are actually much closer in space. Concept adapted from David Spodick's work.

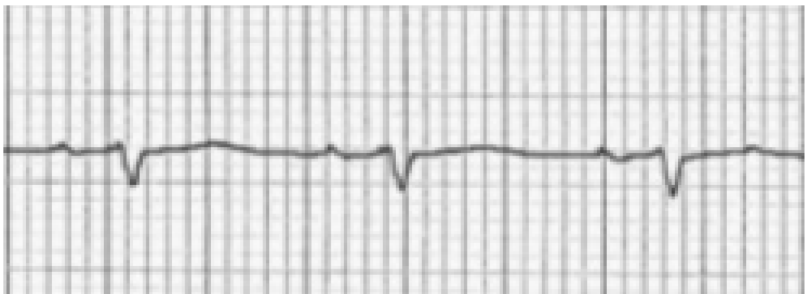


Figure 9 Schematic illustration of Lead I sign in emphysema.

conducted in the 1940s pointed out some T wave changes in a series of patients with cor pulmonale[4]. A negative T wave was found in 59% of cases in lead V1 and in 46% in leads V1 and V2, while it was usually positive in leads V3-V6. These negative T waves (Figure 4) were thought to be related to the position of the heart and not entirely to RVH because of the low incidence of delayed intrinsic deflection

accompanying such negative T waves[4]. In the inferior limb leads, the RS-T segment frequently (66.6%) showed a negative displacement and was rarely positive. In leads III and aVF, diphasic T wave was more often seen (48%) than negative T waves (which can also be seen in normal hearts, 16%), the significance of which was not clear, but could have been related to heart position as well.

RVH

In advanced COPD, the presence of tall right precordial R waves on the ECG are indicators of progression of RVH and pulmonary hypertension[34]. This is especially true if they are accompanied by T wave inversions in the same leads (Figure 4). Also, progression of RVH is typically associated with accentuation of right deviation of frontal plane P and QRS axes, an increased voltage of P wave in the inferior leads (P-pulmonale), small R waves and increased depth of S waves in leads V5 and V6 as well as negativity of T waves in leads V1 and V2[4].

Cardiac arrhythmias in COPD

A recent study showed that heart rate was significantly higher in patients with COPD compared with the healthy age-matched controls[35]. The frequency of arrhythmias in stable patients with COPD has been studied in some patients enrolled in nocturnal oxygen therapy trial group using 24-h ambulatory ECG monitoring[37]. The results suggested that both ventricular and supraventricular premature beats (including bigeminy, multiform premature ventricular contractions, runs of ventricular tachycardia) were frequent in patients with COPD. In addition, sinus tachycardia and supraventricular tachycardia including multifocal atrial tachycardia were noted in 38% and 69% of patients respectively[38]. Interestingly, history of coronary artery disease, increased sinus heart rate and decreased maximum workload were found to be predictors of death, rather than the presence of arrhythmias[38-40]. Multifocal atrial tachycardia may be noted in cases with significant underlying lung disease, particularly during COPD exacerbation[34].

CONCLUSION

The 12-lead ECG can be extremely valuable to the clinician in pointing towards undiagnosed COPD. A vertical frontal plane P wave axis is an extremely helpful electrocardiographic finding of COPD and appears to be highly sensitive and specific when used as a lone criterion for diagnosis. It has also been shown to correlate strongly with the severity of COPD as measured by spirometric and the CT criteria. Other noted abnormalities include increased P wave amplitude in inferior leads (P-pulmonale and Gothic P waves), increased P terminal force in V1, depression of PR segment, short QRS duration, rightward and posterior QRS axis, S1S2S3 sign, lead I sign and signs of RVH. These findings are less sensitive and specific but substantiate the diagnosis when present in conjunction with vertical P wave axis in frontal plane. All these changes appear to result from more vertical orientation of the heart due to depression of the diaphragm as well as clockwise and posterior rotation along its horizontal axis.

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MINIREVIEWS

Artificial intelligence and machine learning in cardiovascular computed tomography

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Abstract

Computed tomography (CT) is emerging as a prominent diagnostic modality in the field of cardiovascular imaging. Artificial intelligence (AI) is making significant strides in the field of information technology, the commercial industry, and health care. Machine learning (ML), a branch of AI, can optimize the performance of CT and augment the assessment of coronary artery disease. These ML platforms can automate multiple tasks, perform calculations, and integrate information from a variety of data sources. In this review article, we explore the ML in CT imaging.

Key Words: Computed tomography; Machine learning; Artificial intelligence; Cardiovascular imaging

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Core Tip: Machine learning (ML), a subset of artificial intelligence, contains multiple algorithms which include supervised, unsupervised, reinforcement and deep learning. These algorithms can greatly augment multiple aspects in computed tomography which

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include automated segmentation, diagnosis, and stratification based on risk. Outputs need to be carefully assessed by the medical team for any potential biases. For the future of computed tomography and cardiovascular imaging, ML algorithms need to be integrated in clinical care.

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INTRODUCTION

In this digital era, distance is no longer a limiting factor and information is emanating from a variety of devices and sources[1]. These technological innovations have considerably transformed our perception, culture, and our daily lifestyles[2]. Similarly, many of these changes have trickled downwards in healthcare and are especially apparent in the field of cardiovascular imaging. Over the last 10 years, the field of computed tomography (CT) has expanded tremendously with significant changes in diagnostic performance and prognostic implications in coronary artery disease[3,4]. Coronary CT angiography (CTA) is now heralded as an established diagnostic modality in the evaluation of coronary artery disease (CAD)[4,5]. With each year, data arising from each imaging scan is increasing exponentially in intricacy and size[6]. As we approach this technological ceiling, the sheer complexity of this information will supersede the analytic capabilities of conventional statistical software[7].

Artificial Intelligence (AI) refers to a set of actions that can mimic human cognitive thinking and decision making[8]. Machine learning (ML), a branch of AI, can extrapolate hidden characteristics or relationships present in vast expanses of data[2]. It can analyze data from a multitude of sources and link the information in user-friendly approaches[9]. In addition, it can automate several processes and perform many calculations[10]. With the application of ML algorithms in CT for cardiology, it can elevate the modality to unprecedented new heights which can improve the quality of patient care. In our review, we evaluate recent advances and progression of ML in cardiac CT over recent years.

BROAD CLASSIFICATION OF ML

ML is an aggregate term which collectively encompasses a wide variety of analytical algorithms[11]. They can be simply divided into supervised learning, unsupervised learning, semi-supervised learning, deep learning and reinforcement learning[12,13] (Figure 1 and Table 1). Supervised learning requires labeled datasets or domains within the dataset to perform analytical actions[14]. Unsupervised learning does not require labels within a dataset and can analyze information in a very independent manner. For discussion purposes, it can be referred to as agnostic[2,15]. Hierarchical clustering, a type of unsupervised learning, can identify and distinguish new phenotypes within various cardiac diseases[2]. It has gained significant traction recently. Semi-supervised learning is a hybrid approach that utilizes properties present within supervised and unsupervised learning[16]. Reinforcement learning uses definitive reward conditions for the ML architecture to perform certain functions. Nevertheless, frequently not used in the field of cardiology[7]. Multiple studies have been documented to show the potential of ML in CT and CTA (Table 2).

Among all the available ML algorithms, deep learning is considered to have the most revolutionary potential[17]. In various sectors of commerce and industry, deep learning is being heavily utilized to unravel information within large troves of data [18]. From voice recognition software in Siri or Alexa to self-driving cars in google, deep learning is garnering significant interest[12]. The architecture of deep learning algorithms is similar to the arrangement of a human neuron[19,20]. It is structured in a series of layers, there is significant communication between the preceding and subsequent layers. It processes information in multiple layers and is more independent

Table 1 Type of machine learning

Types of machine learning	Function	Examples
Supervised learning (55)	Contains labels and outcomes, deduces inferences for prediction purpose	Includes logistic regression, ridge regression, elastic net regression, Bayesian and artificial neural networks
Unsupervised learning (55)	No labels, independently detects significant relationships.	Includes hierarchical clustering, k- means clustering, principal component analysis
Semi-supervised learning (55)	Properties of both supervised and unsupervised learning	Utilized in image and speech recognition
Re-enforcement learning (55)	Utilizes reward function to execute tasks	Utilized in medical imaging, analytics, and prescription selection

Table 2 Machine learning studies in computed tomography

Ref.	ML approach	Brief study description
ML derived CAC assessment		
Al'Aref *et al*[24]	Multiple ML algorithm	To use CAC and clinical factors for CAD prediction
Tesche *et al*[26]	ML algorithm	To compare ML derived CT FFR and CAC in CT
Kay *et al*[27]	ML algorithm	To identify phenotypes of left ventricular hypertrophy in combination with CAC
ML derived CT FFR assessment		
Zhou *et al*[31]	Multiple ML algorithms	To employ CT FFR for myocardial bridge formation prediction
Tang *et al*[32]	ML algorithm	To compare ML CT FFR, CTA and invasive angiography
Coenen *et al*[33]	Supervised learning	To identify CAD
ML derived evaluation of plaque characteristics		
Dey *et al*[34]	ML algorithm	To generate ML derived scores from plaque characteristics
Hell *et al*[35]	ML algorithm	To predict cardiac death from plaque characteristics from CTA
ML derived evaluation of epicardial adipose tissue		
Rodrigues *et al*[38]	ML algorithm	To segment and distinguish between different varieties of EAT
Commandeur *et al*[39]	Deep learning	To quantify EAT in CT
Otaki *et al*[40]	Supervised learning	To assess the relationship between EAT in CT and MFR in PET
Miscellaneous applications of ML in CT		
Baskaran *et al*[41]	Deep learning	To assess automatic and manual assessment of left and right cardiac structure and function
Al'Aref *et al*[42]	Supervised learning	To identify culprit coronary lesions in CT
Beecy *et al*[43]	Deep learning	To detect acute ischemic stroke in CT
Oikonomou *et al*[44]	Supervised learning	To utilize perivascular fat for cardiac risk prediction
Eisenberg *et al*[45]	Deep learning	To evaluate epicardial tissue for MACE events

CT: Computed tomography; CTA: Computed tomography angiography; CAC: Coronary artery calcium; ML: Machine learning; CAD: Coronary artery disease; FFR: Fractional flow reserve; EAT: Epicardial adipose tissue.

compared to other ML algorithms. As the complexity and size of the dataset increase, the performance of the algorithm improves significantly[21,22].

AUGMENTED CORONARY CALCIUM ASSESSMENT

Coronary artery calcium (CAC) measurement is heralded as a fundamental metric in coronary CT because it serves as a pivotal predictor of mortality and cardiac complic-

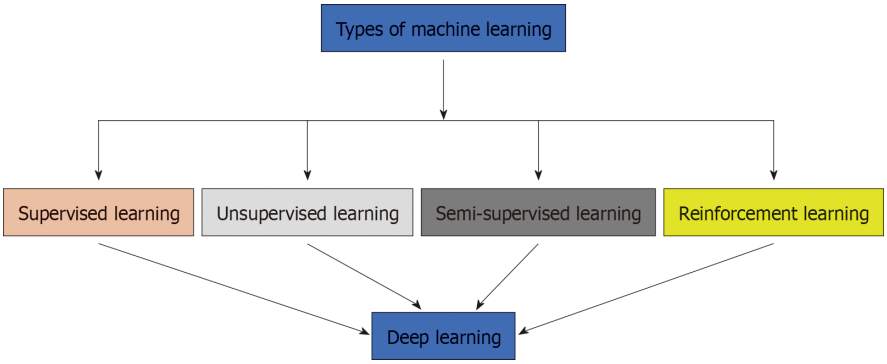


Figure 1 Brief overview of the progression of machine learning.

ations[23]. The Agatston scoring method is the conventional approach utilized to quantify CAC in coronary CT[19]. Furthermore, the CAC plays a diagnostic role in medical management, the CAC scores can be used to stratify patients and monitor medical therapy. However, CAC measurement can be quite tedious due to underlying artifacts, image noise, an abundance of calcifications, interobserver variability, and other factors[24]. The application of ML can significantly elevate the potential of CAC in CT.

Al'Aref *et al*[24] applied an ML architecture incorporating clinical factors in the CONFIRM registry with CAC for calculating the probability of CAD with CTA in a total of 35821 patients. It clearly showcased excellent AUC for ML and (CAC) (0.881) to other conventional approaches in their study [ML independently (0.773), updated Diamond- Forrester Score (0.682) coronary calcium (0.886)]. Hou *et al*[25] assessed the role of supervised ML to evaluate pretest likelihood of CAD in CTA with 6274 individuals. Their ML algorithm demonstrated superior discriminative capacity for CAD occlusion in comparison to traditional scoring metrics such as Modified Diamond Forester scores and CAD consortium score ($P < 0.001$). Tesche *et al*[26] exhibited superior performance of ML derived CT fractional flow reserve (FFR) in comparison to CTA with CAC, substantial distinctions in capability were noted and with propionate increases in Agatston scores ($P < 0.001$). Kay *et al*[27] integrated various algorithmic frameworks with radiomics for identifying new phenotypic characteristics regarding left ventricular hypertrophy (LVH) severity in CT with (CAC) assessment. As a result, ML frameworks are found to be efficacious in identification of LVH.

APPLICATION OF MACHINE LEARNING FOR CT FRACTIONAL FLOW RESERVE

Although CTA enables visual evaluation of a stenotic lesion, it lags behind invasive FFR for assessing the hemodynamic significance of coronary stenosis[28]. Coronary fractional flow reserve (CT-FFR) has become a suitable non-invasive modality for evaluating ischemic heart disease and chest pain[29]. Furthermore, it can perform this task without the requirement of additional medications or imaging. It provides functional and anatomic evaluation, this approach is steadily gaining momentum in CT imaging[30]. ML algorithms can calculate FFR in the absence of computational fluid dynamics and yield additional prognostic information[3]. It can substantially expand the arena of CT-FFR in CT imaging.

Zhou *et al*[31] evaluated CT fractional flow reserve (CT FFR) for estimating myocardial bridge formation by integrating several algorithms. Interestingly, the framework chose properties which contained superior AUC (0.75 ± 0.04) in comparison to clinical attributes (0.53 ± 0.09, $P < 0.0001$), or CT- FFR prosperities (0.62 ± 0.06, $P = 0.0127$). Tang *et al*[32] demonstrated that CT FFR with computational fluid dynamics was superior CTA and invasive angiography for detecting vessel-specific ischemia. This was particularly seen in intermediate lesions ($P < 0.001$ for all). Coenen *et al*[33] demonstrated excellent correlation between ML based CT FFR and deep learning in CAD ($r = 0.997$).

PLAQUE CHARACTERIZATION AND SEGMENTATION IN CAD

ML algorithms can provide additional insight regarding plaque characteristics in CAD and augment our understanding[2]. Dey *et al*[34] utilized a logitboost algorithm to produce an ML-derived risk score from plaque characteristics in CTA for 254 patients. The ML algorithm displayed a higher AUC (0.84) than individual CTA parameters including stenosis (0.76), total plaque volume (0.74), and low likelihood of CAD (P < 0.0006) (0.63). Hell *et al*[35] investigated the role of ML algorithms to predict cardiac death from coronary CTA through the utilization of plaque features in 2748 patients. The non-calcified plaque > 146 mm^3 (P = 0.027), low density non-calcified plaque (P = 0.025), total plaque volume > 179 mm^3, and CDD > 35% in any vessel were significantly associated with elevated risk of future cardiac death.

ML AUGMENTED EVALUATION OF EPICARDIAL AND THORACIC ADIPOSE TISSUE

Cardiac CT is deemed as the gold standard for evaluation of epicardial adipose tissue (EAT) quantification and assessment. EAT is a layer of adipose surrounding the heart and the accompanying coronary arteries. In addition, EAT is significantly linked with various cardiovascular risk factors, atherosclerosis of the coronary arteries, and CAD [36,37]. The application of ML algorithms can automate the quantification of EAT and greatly reduce the time of manual measurements. This can translate into greater clinical implementation in coronary CT.

Rodrigues *et al*[38] applied ML algorithms for segmenting and differentiating types of fat in CT. The ML platform was able to achieve 98.4% mean accuracy and a DICE similarity index of 96.8%. Commandeur *et al*[39] utilized a deep learning algorithm for quantifying EAT in coronary CT. Strong agreement was observed between automatic and expert manual quantification with a mean DICE score coefficient of 0.823 and an excellent correlation of 0.923 with EAT volume. Otaki *et al*[40] utilized a boost ensemble machine learning algorithm for assessing the association of epicardial fat volume from myocardial flow reserve (MFR) in non- contrast CT in positive emission tomography (PET). The ML composite risk score substantially increased risk reclassification of impaired MFR to EAT volume or coronary calcium score (IDI = 0.19 and P = 0.007, IDI = 0.22 and P = 0.002).

MISCELLANEOUS APPLICATIONS OF ML

In CT, ML has been applied in a variety of different situations with overwhelmingly positive results. Baskaran *et al*[41] assessed deep learning for assessing cardiovascular structures for CTA in 166 patients. The ML architecture corroborated in parallel to manual annotation in CTA for left ventricular volume (r = 0.98), right ventricular volume (r = 0.97) (P < 0.05). Al'Aref *et al*[42] utilized ML in CTA to detect precursor culprit lesion from patients with CAD. It exhibited a superior AUC for discriminating lesions in comparison to other ML derived frameworks (P < 0.01). Beecy *et al*[43] on CT for detecting acute ischemic stroke events. Interestingly, their AUC was 0.91 for automatic detection of infarction and had a 93% accuracy with interpretation of experienced physicians. Oikonomou *et al*[44] examined the capability of the random forest ML architecture from the radiomic profile of CTA derived coronary perivascular adipose tissue (PVAT) for identifying cardiac risk. It exceeded traditional risk stratification metrics for MACE prediction (P < 0.001). Eisenberg used deep learning for MACE prediction with EAT and other characteristics. The EAT in CT predicted MACE effectively (HR, 1.35, P < 0.01), inversely with attenuation (0.83, P = 0.01)[45].

BIG DATA UTILIZATION FOR PREDICTION OF OUTCOMES IN CT

Big data has emerged as a valuable resource that provides significant depth and understanding and is instrumental to the growth of ML in clinical medicine (Table 3) [5]. Due to size and magnitude, many important characteristics are often unnoticed by conventional approaches[6,46]. The implementation of AI with these immense expanses of data can yield additional information which can aid in medical management and clinical care.

Table 3 Big data utilization by machine learning in computed tomography

Ref.	ML approach	Number	Brief study description
Motwani *et al*[47]	Supervised Learning	10030	To predict 5-yr mortality from CT
Rosandael *et al*[48]	Supervised Learning	8844	To predict major cardiac events from CT
Han *et al*[49]	ML algorithm	86155	To predict all-cause mortality from CT

CT: Computed tomography; ML: Machine learning.

Motwani *et al*[47] evaluated an ML framework to predict CAD in 10,030 patients for five-year mortality in comparison to traditional cardiac metrics in CT. Interestingly, the ML architecture exhibited a superior AUC (0.79) than CT severity scores (SSS = 0.64, SIS = 0.64, DI = 0.62) for five-year all-cause mortality prediction ($P < 0.0001$). Similarly, van Rosendael *et al*[48] utilized an ML framework in CT with 8844 patients for detecting major cardiovascular events encompassing various attributes in relation to severity scores for CAD prediction. The ML derived AUC (0.771) was significantly higher in CT than conventional scoring parametric systems (0.685-0.701) for anticipating major cardiovascular events, with a notable difference ($P < 0.001$). Han *et al*[49] assessed an ML-derived predictive capacity for all-cause mortality in 86155 patients. Notably, the AUC (0.82) noted to be higher than Framingham risk score and other traditional metrics ($P < 0.05$).

EVOLVING BELIEFS AND FUTURE DIRECTIONS OF ML

It must be emphasized with great importance that cardiovascular disease is heterogeneous in nature[50]. It cannot be perceived as straightforward because disease mechanisms have intricate interactions among molecular, genetic, and environmental factors[22]. The process is very dynamic, it truly reflects the essence of ML algorithms. ML can integrate this information from multiple sources and analyze it in a variety of approaches. This can lead to the development of various genetic markers which can help guide medical management and monitor responses after therapy[6,51]. Furthermore, we can tailor treatment regimens appropriate to the genetic constitutional makeup of an individual, ML algorithms will facilitate the growth of precision medicine[12].

In current times, mobile devices, smartphone apps, and wearable devices are part and parcel of our daily lifestyles[52]. Telemedicine and ML algorithms are clearly intertwined in cardiovascular imaging and CT[1]. The information from these devices can be integrated with various parameters in cardiovascular imaging to yield additional insight regarding various cardiovascular diseases. In many underserved regions of the world, these devices can provide medical care and help direct patients towards appropriate intervention[1,53]. ML algorithms can analyze this information in real-time and help expedite this process[1]. These algorithms can serve as a bridge between different types of technology and cardiovascular imaging.

Although several algorithms have significant potential in computed tomography, deep learning has the most overwhelming potential[54]. It captures information through hierarchical levels of abstraction. As the computational prowess of graphical processing units (GPUs) continue to progressively evolve in conjunction with big data, the relevance of deep learning in computed tomography is becoming imminent. It is very effective in robust tasks such as image classification, image segmentation, and identification of various cardiovascular structures in CT, CTA, and cardiovascular imaging[20]. Furthermore, it does not require extensive training. The accuracy can be achieved by elevating the capability of the network or increasing the training set. This is a stark distinction in comparison to other ML algorithms[55]. Other algorithms entail a significant number of observations, computations, manual labor, and training to achieve optimal efficiency.

Randomized clinical trials (RCTs) are the gold standard in clinical research. The integration of ML algorithms could prove to be exceeding useful if implemented appropriately. Numerous RCTs fail to reach completion due to several factors which could include improper study design, inadequate number of participants, or lack of funding[56]. The integration of ML algorithms during the early or intermediate stage of an RCT could provide an outlook of different outcomes[5]. This information could

be used to restructure the RCT to obtain more successful outcomes. In addition, ML algorithms can enhance the randomization process in RCT[56].

LIMITATIONS OF ML

Though ML algorithms offer a significant promise for the future, it is far from straightforward. Several issues need to be resolved for successful implementation in clinical medicine. The potential of false discovery can occur with small databases, there is not enough information to properly train the algorithm[55]. Unfortunately, AI lacks a moral compass[57]. In addition, several unintentional biases can emerge during the process and could alter interpretation. The "black box" nature has always been an enigmatic property of ML algorithms, this has impeded its adoption in the medical field[2]. Investigators must have a proper research concept and plan before embarking on any ML-related task. As a result, engineers, physicians, and other members of a research team must play an active role in every stage of the ML algorithm[15,58]. Adjustments can be made to the algorithm to deliver clinically relevant information.

For any ML algorithm to thrive and grow, large information or databases is mandatory[15]. Obtaining this information can be complex and tedious. Data needs to be shared among institutions to allow training of the ML model[15]. This might require multiple IRB approvals. Information also needs to be de-identified before it can be shared. Many of these tasks can be time-consuming. Many types of imaging systems are frequently used for storing cardiovascular images. Nevertheless, each institution has their own unique protocols and there are differences in the acquisition process as well[2]. Some form of data standardization is required to facilitate data sharing and ML algorithm growth. If more information can be publicly available, it would be beneficial.

CONCLUSION

ML algorithms will have limitless potential in cardiovascular imaging, this has been evidenced in the field of CT. It will cause multiple paradigm shifts which will have a revolutionary impact in the field of medicine. These frameworks will automate several tasks, perform calculations, and aid as a supplementary tool for medical diagnosis and prognostication. By performing multiple tasks, physicians will have more time to spend with patients and be more focused on proper medical management. ML will serve as a long-lasting bridge between physicians and technology in clinical medicine.

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MINIREVIEWS

Coronavirus and cardiovascular manifestations- getting to the heart of the matter

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Abstract

Coronavirus disease has unarguably been the largest pandemic of recent times. Over 150 million cases have occurred worldwide, and more than 3 million have succumbed to the disease. Cardiac manifestations can have varied presentations from an asymptomatic troponin rise to fulminant myocarditis. The pathogenesis of myocardial damage could be direct or indirect, including inflammation, coronary spasm, plaque rupture, and cytokine storm. Thromboembolism is also an important feature of cardiovascular affliction with both arterial and venous systems being affected. Hence, anticoagulation has also been a matter of debate. Fulminant myocarditis is the most severe form and can lead to circulatory shock with a high mortality. Management of cardiac patients with coronavirus disease 2019 (COVID-19) infection is not considerably different from non-COVID-19 cardiovascular disease, but interaction between cardiovascular drugs and anti-COVID-19 therapy requires careful attention. More recently, vaccines have emerged as a ray of hope for the disease. But simultaneously, there have been reports of thromboembolism following vaccination. In this review, we discuss the various aspects of coronavirus disease affecting of heart and its management.

Key Words: Myocarditis; Cytokine storm; Angiotensin-converting enzymes-2; Acute coronary syndrome; Hypercoagulable state; Vaccine

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Core Tip: Coronavirus affects various parts of cardiovascular (CV) system. Acute coronary syndromes, myocarditis, tachyarrhythmia, heart failure and shock can be the various manifestations. The mechanism of cardiac involvement can be direct or indirect *via* cytokine storm ,inflammation and thromboembolism. Thromboembolism is particularly more common in coronavirus disease (COVID) infection and so is

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bleeding making anticoagulation a daunting task. Management of cardiac manifestations is not very different from a non COVID patient and needs diligent effort due to the need for preventing transmission to health care workers. Undoubtedly, cardiac involvement portends poor prognosis and antecedent cardiovascular disease is abundant among non-survivors. Adequate control of CV risk factors, prompt recognition of symptoms, timely management and early vaccination hold the key to victory against the coronavirus onslaught on the heart. Reports of thromboembolism have also emerged after COVID-19 vaccination but the incidence is rare.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease has evolved into a global pandemic and has affected more than 150 million people worldwide. Unfortunately, more than 3.5 million people have succumbed to the disease till now[1].

Infection with the SARS-CoV-2 virus mainly causes fever (77%–98% of cases), fatigue (52%–75%), and cough (62%–81%). It primarily affects the respiratory system, but its effects on the cardiovascular (CV) system have also been noted. While those with pre-existing CV disease are at an increased risk of mortality, the disease also contributes to CV complications. These may be acute coronary syndrome (ACS), including myocardial infarction (MI), arrhythmias, myocarditis, acute heart failure (HF), cardiogenic shock, and even death[2-4].

CARDIAC INVOLVEMENT IN COVID-19

Cardiac injury is described by the presence of raised cardiac troponins (cTn) in COVID-19. Cardiac biomarkers are elevated in 7%–28% of COVID-19 patients. It can be either due to MI or due to myocardial injury from myocarditis and hemodynamic shock[5-8].

According to the American College of Cardiology (ACC), patients with cTn elevation (myocardial injury) can be classified as (1) Chronic myocardial injury; (2) Acute nonischemic myocardial injury; or (3) Acute myocardial infarction (MI)[9].

An association between ACS is already described for influenza virus and other respiratory viruses. Thus, it is of extreme importance to understand the pathophysiological mechanism of ACS in COVID-19[10,11].

Many patients with COVID-19 present with symptoms mimicking ACS. According to the study of Huang *et al*[4], prevalence of myocardial injury in SARS-CoV-2 is 12%. In another study, cardiac injury is observed in 7.2% overall and 22.2% of intensive care unit (ICU) patients infected with the SARS-COV-2 virus[2].

From a retrospective analysis of 191 COVID-19 pneumonia patients by Zhou *et al* [12], it can inferred that those who develop acute myocardial injury are more likely to die (odd ratio of 21.4, $P < 0.0001$). Thus, myocardial injury is an independent predictor of mortality.

MECHANISM OF CARDIOVASCULAR INVOLVEMENT IN COVID-19

Several mechanisms are postulated to cause CV events in SARS-COV-2 infection (Figure 1). These include a pro-inflammatory state and cytokine storm, which leads to plaque instability in patients with pre-existing CAD. In addition to this, COVID-19 infection induces a prothrombotic state as evidenced by raised D-dimer levels and hypoxemia-related myocardial ischemia due to respiratory failure. All these mechanisms cause myocardial ischemia even in patients without pre-existing CV

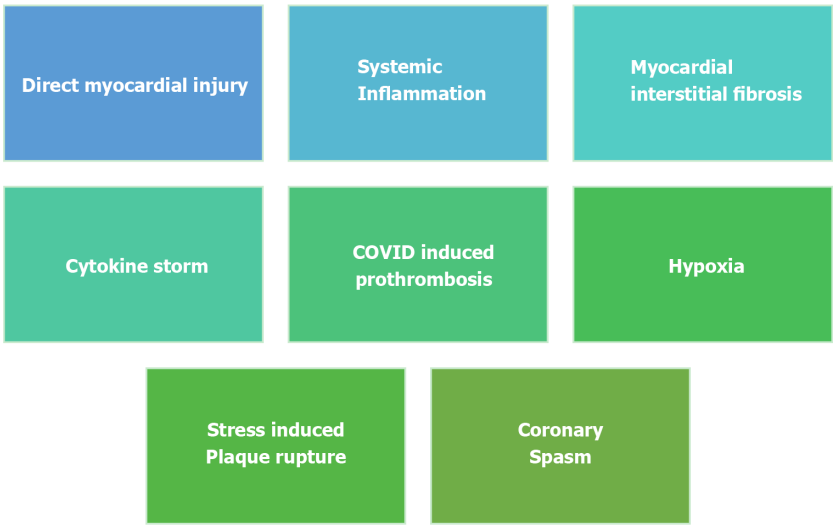


Figure 1 Various mechanisms of myocardial injury associated with coronavirus disease 2019 disease. COVID: Coronavirus disease.

disease[13].

Pro-inflammatory state

In a recently published case of series of COVID-19 patients, Varga *et al*[14] demonstrated evidence of direct viral infection of the endothelial cells. This leads to endothelitis along with micro- and macro-thrombosis in both the arterial and venous circulation. This in addition to the hypercoagulability predisposes to ACS[15].

Cytokine storm

An excessive immune response to SARS-COV 2 virus has been demonstrated in certain patients, which leads to a cytokine storm[4]. In a study of 53 patients with clinically moderate to severe COVID-19 disease, 14 types of cytokines were elevated. Of them, interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein 3 (MCP-3), and interleukin-1 receptor antagonist (IL-1ra), are independently associated with hypoxaemia, disease progression, and death[16]. Cytokine production damages the healthy cells initially in the lungs. Subsequently, it involves other organs, such as the kidney, heart blood vessels, and brain. Due to this hypercytokinemia, there is an increase in hypercoagulability contributing to a 31% increase in incidence of thrombosis. This eventually manifests as ischemic stroke, deep vein thrombosis, acute pulmonary embolism, MI, and systemic arterial embolism[14].

Angiotensin-converting enzymes

The pathophysiology of COVID-19 infection involves binding of the SARS-COV2 virus to the host ACE-2 receptor, which mediates virus entry into the cell. Angiotensin-converting enzymes (ACE)-2 receptors are present in the epithelial cells of the lungs, kidneys, heart, intestines, and blood vessels. ACE is also an important component in the pathophysiology of CAD[17,18].

In COVID-19 infection, there is dysregulation of the rennin-angiotensin-aldosterone system (RAAS)/ ACE-2 *via* the SARS-COV-2 virus, leading to CV involvement[19]. This may be a primary manifestation of COVID-19 or may be secondary to lung involvement, leading to hypoxemia-induced myocardial damage. Patients with pre-existing cardiac disease are especially prone for this. Additionally, the downregulation of ACE-2 with concomitant upregulation of angiotensin II results in RAS overactivation. The ultimate result is loss of the beneficial effects of angiotensin (1-7), aggravating and perpetuating cardiac injury.

Relationship between COVID-19, ACE-2, and hypertension

ACE inhibitors (ACE-I) lead to upregulation of ACE-2 receptors; thus causative role in severe COVID-19 disease is postulated. However, in the study of Guo *et al*[8] in patients with COVID-19, mortality is not impacted by use of ACE-I. In contrast, a retrospective analysis of 1128 hypertensive patients with COVID-19 the inpatient use of ACE-I reduced the all-cause mortality[20]. Thus, patients with pre-existing hypertension who are on ACE-I should continue to take it.

ACS

Decrease in ACS cases

Although COVID-19 has led to an increase in hospitalizations, the amount of ACS admissions has substantially decreased. This decline is more for ST elevation myocardial infarction (STEMI) than for non-ST elevation myocardial infarction (NSTEMI). This finding is observed in multiple countries and is believed to be due to multiple factors. These include hesitance of patients to visit hospitals despite initial symptoms for fear of contracting the COVID-19 infection and confusion regarding symptoms. Other factors include better medication adherence, lower pollution levels, less smoking, and less physical strain[21,22].

In one study, 40% decline in hospital admission for ACS is reported. Another finding of interest is the late presentation for STEMI compared to the pre-COVID-19 era. Fortunately enough, there is no difference in door to balloon time. Mortality rates are also high for STEMI during the COVID-19 pandemic ($P < 0.05$)[23].

Presentation of ACS during COVID-19

In one case series, of 18 patients of ACS with COVID-19, 56% of the patients presented with STEMI and the remaining developed it during the course of illness. ST elevations could be diffuse or focal and there was high prevalence of LV dysfunction in latter. However, obstructive CAD is seen only in a minority of patients, as seen in 6 (33%) out of 9 patients in the study. Of note, all 18 patients had elevated D-dimer levels[24]. In a retrospective single center study by Shi *et al*[25], of 416 patients with COVID-19, prevalence of ACS was 3.6%, and all were NSTEMI.

Management of ACS in COVID-19

According to the latest European Society of Cardiology (ESC) guidelines for management of CAD during the COVID-19 pandemic, primary PCI is the norm if they are in the window period (< 12 h from symptom onset). The primary PCI should be performed with a door to balloon time of 120 min. However, owing to the delay in transfer to a catheterization lab-facilitated hospital during the COVID-19 pandemic, a delay of up to 60 min can be accepted due in many instances. If the delay is more than this and there is no contraindication for thrombolysis, then patient can be thrombolyzed. In any circumstance, treatment should not be delayed ensuring necessary COVID-19 safety precautions[26].

Patients presenting with NSTEMI, should be risk stratified initially depending on the presence of recurrent chest pain, elevation of biomarkers, recurrent ST-T changes, heart failure, and LV dysfunction. COVID-19 testing should be performed as soon as possible regardless of treatment strategy. Patients having very high risk features should undergo immediate invasive management as for STEMI with COVID safety norms. Patients at high risk should be managed in a separate ICU while waiting for the COVID-19 results, and invasive management should be done within 24 h. Patients with intermediate and low risk can undergo non-invasive testing, such as CT coronary angiography, to rule out obstructive CAD. If patients with high risk and intermediate risk NSTEMI are COVID-19 positive, they should be transferred to equipped COVID-19 hospitals for cardiac intervention so that that along with cardiac illness they can also be treated for COVID[26].

MYOCARDITIS

The exact mechanism of myocarditis in COVID-19 is not clear. Some studies suggest high viral load as the possible mechanism. The cytokine storm and inflammatory state in COVID-19 may lead to myocarditis. It is suspected if a COVID-19 patient without pre-existing cardiac disease develops fulminant HF. Echocardiography shows marked depression in LVEF with global hypokinesia, LV dilatation, and pericardial effusion. Patients respond to anti-inflammatory therapy including parenteral glucocorticoids and immunoglobins[26,27].

STRESS-INDUCED CARDIOMYOPATHY

There is a strong relationship between psychosocial stress and cardiomyopathy. In a study published in JAMA, a significant rise in the incidence of stress cardiomyopathy

is observed during the COVID-19 pandemic (incidence proportion: 7.8% of total ACS patients). However, in comparison to the pre-pandemic time, the incidence proportion range is only 1.5%–1.8%. Nevertheless, there is no difference in mortality as compared to that of the pre-pandemic era[28].

CARDIOGENIC SHOCK

All patients presenting with cardiogenic shock or out of hospital arrest, must be considered COVID-19 positive until results are available. Those who are COVID-19 negative should be managed according to the latest guidelines. Patients should be admitted to the ICU, and mechanical circulatory support (MCS) should be provided. For COVID-19-positive patients, ICU admission should be given to those who require ventilatory support, use of MCS should be more restrictive, and health care personnel protection should be the priority[26,29].

HEART FAILURE

Patients with pre-existing cardiovascular disease (CVD) are at increased risk of severe COVID-19 infection. Hypertension and CVD is seen in approximately 17.1% and 16.4% of hospitalized COVID-19 patients as suggested in a meta-analysis of 6 studies and contributes to a 2–3 fold increased risk of mortality[30] (Table 1).

Acute heart failure (HF) can complicate COVID-19 cases. It is diagnosed by the classical signs and symptoms like chest rales, increased jugular venous pressure cardiomegaly, and bilateral pleural effusion. Significant elevation of brain natriuretic peptide (BNP) and NT-pro BNP also suggest HF.

There are various mechanisms responsible for HF in COVID-19, including myocardial ischemia, myocarditis, acute respiratory distress syndrome, acute kidney injury, stress induced cardiomyopathy and arrhythmias. Treatment should be administered according to the standard HF treatment guidelines.

ARRHYTHMIAS

The incidence of cardiac arrhythmias in COVID-19 patients was found to be approximately 16.7% in a single center study of 138 patients. The incidence is higher in seriously ill patients admitted to the ICU[2]. The management of arrhythmias in COVID-19 patients is essentially similar to as in COVID-19-negative patients.

Follow-up and monitoring of patients with implantable intracardiac devices should be done remotely. In COVID patients presenting with atrial arrhythmias, rate-controlling agents should be used in place of anti-arrhythmic therapy. This is because there may be need for the concomitant use of hydroxychloroquine/azithromycin which can lead to QT-c prolongation and torsades de pointes.

In patients presenting with VT/VF, amiodarone is the drug of choice. The implantation of an intracardiac device should be postponed for as long as possible.

For patients with bradyarrhythmias, if pacemaker implantation is required, all the necessary precautions should be taken for protection of health care personnel and to prevent nosocomial infections[26].

PULMONARY EMBOLISM

Strong evidence suggesting the increased risk of pulmonary embolism (PE) in COVID-19 is lacking. Some case reports have suggested that the incidence of pulmonary embolism may be high in hospitalized patients with COVID-19[31,32]. Owing to the high inflammatory state, enhanced hypercoagulability and immobilization, prophylactic anticoagulation should be given to hospitalized patients.

Because patients with COVID-19 pneumonia also have respiratory distress and chest pain, it is possible to miss PE. However, in the case of any unexpected tachycardia, deterioration of respiratory symptoms, and a decrease in blood pressure, PE should be suspected. This is specially important if there are new ECG changes suggestive of PE or there is deep vein thrombosis. Although the D-dimer is not reliable

Table 1 Cardiac involvement in coronavirus disease 2019 patients among various studies

Ref.	Study type	Number of patients	Cardiac involvement	Cardiovascular comorbidities
Wang *et al* [2]	Case series	138	7.2%	Diabetes (10.1%); Hypertension (31.2%); CVD (14.5%); CVA
Huang *et al* [4]	Prospective	41	12%	Hypertension
Guo *et al*[8]	Retrospective	187	27.8%	Hypertension (32.6%); Diabetes (15%); CVD (11.2%); Cardiomyopathy (4.3%)
Zhou *et al* [12]	Retrospective	191	17%	Hypertension (30%); Diabetes (19%); CAD (8%)
Shi *et al*[25]	Descriptive	416	19.7%	Hypertension (30.5%); Diabetes (14.4%); CVA (5.3%); CAD (10.6%)
Yang *et al* [33]	Retrospective, observational study	52	23%	Diabetes (17%); CVD (10%); CVA (13.5%)

CVD: Cardiovascular disease; CVA: Cardiovascular accident.

in COVID-19, it can still be used to rule out PE. In case of high suspicion and normal CT chest despite respiratory worsening, CT pulmonary angiography should be performed. The treatment protocol is similar to as in COVID-19-negative patients[32, 33].

INDICATIONS OF ANTICOAGULATION WITH COVID-19 INFECTION

Parenteral anticoagulants are indicated in all acutely ill hospitalized patients[34].

Dosing of anticoagulation: (1) Moderate disease (standard risk patients): standard weight-adjusted prophylactic dose (*e.g.*, enoxaparin at 40 mg once daily for a 70-kg adult with CrCl > 30 mL/min); (2) Severe and critical disease (high-risk patients requiring invasive ventilation/continuous positive airway pressure (CPAP)/non-invasive ventilation (NIV)/high-flow nasal oxygen): intermediate dose Low Molecular Weight Heparin (enoxaparin at 40 mg two times per day for a 70-kg adult with CrCl > 30 mL/min); (3) Diagnosed/highly suspected macro-thrombosis (PE/DVT): therapeutic dose (enoxaparin at 1 mg/kg with 12 h subcutaneous or 1.5 mg/kg subcutaneously once daily); and (4) Renal insufficiency: Enoxaparin with dose reduction is the preference over other LMWH drugs/fondaparinux. UFH with aPTT monitoring indicated at eGFR < 15 mL/min.

Decisions regarding post discharge prophylactic anticoagulation should be individualized. Based on past and ongoing trials regarding usage of anticoagulants, it can be concluded that patients with moderate to severe disease and fulfilling any one of the below criteria should receive post discharge thromboprophylaxis (Table 2)[34]: (1) Modified IMPROVE venous thromboembolism (VTE) (MIV) score ≥ 4; (2) MIV ≥ 2 with a D-dimer value > 2 times the upper limit of the normal range; (3) Age ≥ 75 years; (4) Age > 60 years with a D-dimer value > 2 times the upper limit of the normal range (ULN); and (5) Age 40–60 years with a D-dimer value > 2 times (ULN) and a history of VTE or with diagnosed malignancy.

PROGNOSTIC IMPLICATION

Many serum biomarkers can be utilized for both diagnosis and prognosis in COVID-19 with cardiovascular affliction (Figure 2). In a study by Liu *et al*[35], C-reactive protein (CRP), lactate dehydrogenase, and D-dimer were elevated in 85.5%, 65.2%, and 65.2% of patients, respectively, in the severe category. In another study, the proportions of patients with increased IL-6, CRP, and procalcitonin levels were significantly higher in the severe COVID-19 group than in mild COVID-19 patients. The Cox proportional hazard model showed that IL-6 and CRP are independent factors in predicting the severity of COVID-19. Based on their analysis, patients with IL-6 > 32.1 pg/mL or CRP > 41.8 mg/L are more likely to have severe complications[36].

Table 2 Modified venous thrombo-embolism score for risk stratification in pulmonary embolism/deep vein thrombosis

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia[1]	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilization > 24 h	1
Age > 60 yr	1

[1]Congenital or acquired.
VTE: Venous thromboembolism; ICU: Intensive care unit; CCU: Coronary care unit.

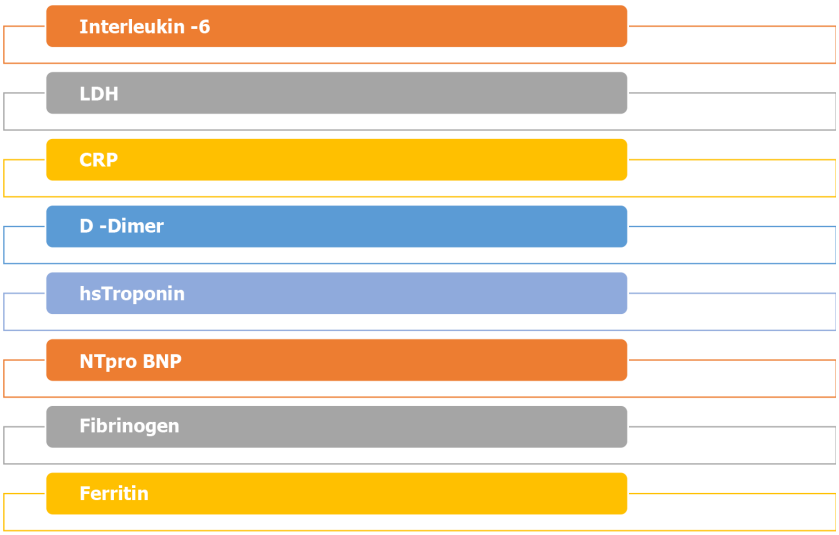


Figure 2 Biomarkers of inflammation/injury commonly utilized for prognostic implications in coronavirus disease 2019 infection. LDH: Lactate dehydrogenase; CRP: C-reactive protein; BNP: Brain natriuretic peptide.

Troponin elevation during a hospital stay enhances the risk of arrhythmias, mechanical ventilation, and indicated a subgroup poised for high mortality[36].

Deranged coagulation parameters (D-dimer, fibrinogen, activated partial thromboplastin time, and prothrombin time) are also predictors of poor prognosis as evidenced in a study from Wuhan[37]. Critically ill patients and deceased patients demonstrate more frequently elevated levels of D-dimer, PT/INR, and lower fibrinogen levels. Interestingly, D-dimer levels also correlated with the CT findings.

COVID-19 VACCINE AND THROMBOEMBOLISM

Vaccination is thought to be the most promising approach for containing or ending the COVID-19 pandemic. The efficacy of the COVID-19 vaccine in preventing COVID-19 infection varies from 50% to 70%, while the efficacy in preventing serious disease is 70–90%. No major safety warnings, other than rare cases of anaphylaxis, are reported in large trials. In February 2021, the first case of prothrombotic syndrome appeared with the AstraZeneca vaccine (COVISHIELD), which is an adenoviral vector-based vaccine. Subsequently, Ad26.COV2.S vaccine (Janssen; Johnson and Johnson) also reported similar issues[38]. Both arterial and VTE are noted with COVID-19 vaccines. However, the distribution is symmetrical for COVISHIELD, while it is skewed in favor of arterial thromboembolism with mRNA vaccines (Pfizer-BioNTech and Moderna) [39]. The underlying mechanism discovered is an immune-mediated thrombotic thrombocytopenia and is similar to that observed with heparin-induced thrombocyt-

openia. The condition starts usually within 1–2 wk after vaccination and is common in young females[40].

The incidence of VTE is 1 case per 100000 exposure. The frequency of COVID-19-related VTE is 14.7% to 17.6%, and the frequency rates of overall arterial thromboembolism is approximately 3.9%[41].Thus, the chances of thromboembolic episodes are far lower as compared to COVID-19 infection itself[]. Thus, the vaccines available are safe and effective.

COVID-19 VACCINE AND ACCELERATED HYPERTENSION

Meylan *et al*[42] reported a case series of 9 patients who developed accelerated hypertension (Stage III) shortly after their vaccinations. However, the majority were being treated for hypertension with drugs beforehand. Anxiety and allergic reactions to vaccine components have been proposed, but in the absence of tachycardia, the former is less likely.

CONCLUSION

The COVID-19 pandemic is producing an adverse impact on health care systems. Studies have demonstrated that this disease not only involves the respiratory system but also multiple organs, including the heart, brain, and kidneys. Cardiovascular involvement is quite common and can be a source of mortality. Thus, there should be a high index of suspicion for cardiac involvement in severe COVID-19 cases, and appropriate measures should be taken. Because the acuteness of pandemic, there is dearth of randomized studies. For patients with primary cardiac presentation, such as ACS, first preference should be given for cardiac management pending a COVID testing. STEMI patients should undergo revascularization either by primary PCI or by thrombolysis according to the window periods and time delays. For NSTEMI patients, treatment should be according to the risk category. For heart failure, arrhythmias, and myocarditis, the standard treatment protocol should be followed.

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ORIGINAL ARTICLE

Observational Study

Elderly patients with non-cardiac admissions and elevated high-sensitivity troponin: the prognostic value of renal function

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Abstract

BACKGROUND

High-sensitivity cardiac troponin (hs-cTn) levels are frequently elevated in elderly patients presenting to the emergency department for non-cardiac events. However, most studies on the role of elevated hs-cTn in elderly populations have investigated the prognostic value of hs-cTn in patients with a specific diagnosis or have assessed the relationship between hs-cTn and comorbidities.

AIM

To investigate the in-hospital prognosis of consecutive elderly patients admitted to the Internal Medicine Department with acute non-cardiac events and increased hs-cTnI levels.

METHODS

In this retrospective study, we selected patients who were aged ≥ 65 years and admitted to the Internal Medicine Department of our hospital between January 2019 and December 2019 for non-cardiac reasons. Eligible patients were those who had hs-cTnI concentrations ≥ 100 ng/L. We investigated the independent predictors of in-hospital mortality by multivariable logistic regression analysis.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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RESULTS

One hundred and forty-six patients (59% female) were selected with an age range from 65 to 100 (mean ± SD: 85.4 ± 7.61) years. The median hs-cTnI value was 284.2 ng/L. For 72 (49%) patients the diagnosis of hospitalization was an infectious disease. The overall in-hospital mortality was 32% (47 patients). Individuals who died did not have higher hs-cTnI levels compared with those who were discharged alive (median: 314.8 *vs* 282.5 ng/L; $P = 0.565$). There was no difference in mortality in patients with infectious *vs* non-infectious disease (29% *vs* 35%). Multivariable analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.000-1.127; $P = 0.048$) and creatinine levels (OR 2.065 per 1 mg/dL increase, 95%CI: 1.383-3.085; $P < 0.001$) were the only independent predictors of death. Mortality was 49% in patients with eGFR < 30 mL/min/1.73 m^2.

CONCLUSION

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons. The presence of severe renal impairment is a marker of extremely high in-hospital mortality.

Key Words: Internal medicine; High sensitivity troponin; Elderly; Non-cardiac admissions; Renal function; Prognosis

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Core Tip: Many reports have shown that there is an association between acute myocardial injury and adverse outcomes in almost every clinical setting. However, data from consecutive elderly patients admitted to Internal Medicine Departments with acute non-cardiac events are limited. We found that these patients are at high risk of in-hospital death and that age and renal dysfunction were the only independent predictors of death. Elderly patients with acute myocardial injury from non-cardiac cause and chronic kidney disease stages IV or V had an extremely high risk (approximate 50%) of in-hospital death.

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INTRODUCTION

Since the introduction of high-sensitive cardiac troponin (hs-cTn) assays, troponin testing has been used in a broad spectrum of patients to detect minor myocardial injury[1,2]. A variety of non-cardiac clinical conditions is accompanied by "troponinemia"[2,3] and many reports have investigated the association between serum hs-cTn concentrations and adverse outcomes in almost every clinical setting[4-6].

Hs-cTn levels increase over time in asymptomatic elderly individuals[7,8]. Moreover, they are frequently elevated in elderly patients presenting to the emergency department for non-cardiac events[9]. However, the 99th centile for the hospital population is not well defined and varies depending on the clinical setting, age and location when the test is requested[9-13]. Most studies on the role of elevated hs-cTn in elderly populations have investigated the prognostic value of hs-cTn in patients with a specific diagnosis or have assessed the relationship between hs-cTn and comorbidities [14-16].

The objective of this study was to investigate: (1) The in-hospital survival of consecutive elderly patients presenting to the emergency department with acute non-cardiac events, elevated hs-cTnI levels and admitted to the Internal Medicine Department; and (2) The independent predictors (*i.e.*, comorbidities) of in-hospital mortality.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective observational study at the University Hospital of Ioannina in Greece. The study protocol conformed to the Declaration of Helsinki and was approved by the institutional ethics committee.

First, we searched the electronic medical records and we selected patients who were aged ≥ 65 years, admitted to the Internal Medicine Department between January 2019 and December 2019, and had hs-TnI levels ≥ 100 ng/L. Then, the paper medical records of the included patients were also reviewed. In our tertiary hospital elderly patients presenting with acute coronary syndromes or other acute cardiac events are admitted exclusively in the Cardiology Department. Additionally, all patients with a final diagnosis of acute myocardial infarction (based on serial troponin measurements, symptoms, and electrocardiogram) after admission were excluded from the study. Patients on hemodialysis or peritoneal dialysis were also excluded.

Demographic, clinical and biochemical data were extracted from patient records. Serum creatinine at presentation was used to calculate the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease study equation [17]. High-sensitivity-cTnI was measured using two-site immunoenzymatic ("sandwich") assay (Beckman Coulter, Inc. Brea, CA, United States). The assay's 99th centile is 19.8 ng/L for men and 11.6 ng/L for women according to the manufacturer. However, troponin concentrations and the 99th percentile upper reference limits (URL) depend on several other factors including age and ethnicity/race[18].

Statistical analysis

Continuous variables were expressed as means ± SD or median (interquartile range) as appropriate. Deviation of continuous variables from the normal distribution was tested using the Shapiro-Wilk test (for a chosen alpha level of 0.05). The student's *t*-test and the Mann-Whitney test were used to compare normally and not normally distributed data, respectively. Only the first hs-cTnI measurement ≥ 100 ng/L of the included patients was considered for the analysis, and log transformation was also used for troponin values (because of non-normal distribution with positive skew). Categorical data were presented as counts and percentages and were compared using the χ^2 or the Fischer's exact test as appropriate. Correlation between continuous variables was determined with the Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of parameters for predicting in-hospital death. We performed binary logistic regression analysis to identify independent predictors of in-hospital death. A P value < 0.05 was considered statistically significant and all tests were two-sided. Statistical analysis was performed with the SPSS/PC (version 22.0, IBM Corp, Armonk, NY, United States) software package.

RESULTS

During the study period (January 2019 to December 2019), 146 patients (59% female) fulfilled our inclusion criteria. Patient age ranged from 65 years to 100 years (median: 87, mean ± SD: 85.4 ± 7.61). There was a substantial burden of comorbidities: 53 (36%) patients had diabetes mellitus, 38 (26%) coronary artery disease, 64 (44%) atrial fibrillation, and 46 (32%) chronic kidney disease (CKD). For 72 (49%) patients the diagnosis of hospitalization was an infectious disease. The second most commonly diagnosis was stroke (15 patients, 10%). Eleven patients (8%) were admitted due to gastrointestinal causes, 8 (5%) due to explained or unexplained falls, 7 (5%) due to pulmonary embolism, 6 (4%) due to severe anemia or pancytopenia, 5 (3%) due to "senility", 4 (3%) due to hypoglycemia or hyperglycemia, 4 (3%) due to cancer, and 14 (10%) due to other causes.

The median hs-cTnI value was 284.25 ng/L (interquartile range 553.4), while the mean was 946.4 (± 2336.07) ng/L. High-sensitivity-cTnI was correlated with creatinine levels (r = 0.169, P = 0.042) and eGFR (r = -0.240, P = 0.004).

The overall in-hospital mortality was 32% (47 patients). Differences between patients who died in-hospital and those who were discharged alive are shown in Table 1. Individuals who died did not have significantly higher hs-cTnI levels (median: 314.8 *vs* 282.5 ng/L; Mann-Whitney U test, P = 0.565). There were no significant differences in mortality according to diagnosis (infectious *vs* non-infectious disease: 29% *vs* 35%), gender (males *vs* females: 35% *vs* 30%), diabetes (30% *vs* 33%), history of

Table 1 Differences between patients who died in-hospital and those who were discharged alive

	Patients who died (*n* = 47)	Discharged alive (*n* = 99)	*P* value
Age (yr), mean ± SD	87.5 ± 5.3	83.4 ± 8.3	0.001
Gender, *n* (%)			0.59
Female	26 (30)	60 (70)	
Male	21 (35)	39 (65)	
History of CAD, *n*	12	26	1
Atrial fibrillation/flutter, *n*	18	46	0.38
Renal function, *n* (%)			
Known history of CKD	24 (52)	22 (48)	0.001
No history of CKD	23 (23)	77 (77)	
Creatinine levels, mg/dL	2.10 (1.03)	1.66 (0.95)	0.008
eGFR (mL/min/1.73 m^2), mean ± SD	35.32 ± 19.85	47.17 ± 24.22	0.002
On antihypertensive therapy, *n*	28	74	0.082
Diabetes Mellitus, *n*	16	37	0.69
On statin therapy, *n*	19	45	0.6
Diagnosis on admission, *n* (%)			0.86
Infectious diseases	21 (31)	46 (69)	
Non-infectious diseases	26 (33)	53 (67)	
CRP (mg/L), mean ± SD	178.16 ± 130.81	154.27 ± 125.30	0.26
hs-TnI (ng/L)			
Median	314.8	282.5	0.57
Log-hsTnI, mean ± SD	2.57 ± 0.57	2.59 ± 0.42	0.89

CAD: Coronary artery disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtrated rate; SD: Standard deviation; CRP: C-reactive protein; hs-cTnI: High sensitive cardiac troponin I; Log: Logarithm 10.

coronary artery disease (32% *vs* 32%), and atrial fibrillation (28% *vs* 35%). Mortality was higher among patients with known CKD (52% *vs* 23%, P = 0.001). Moreover, individuals who died had higher creatinine levels (2.10 ± 1.03 *vs* 1.66 ± 0.95 mg/dL, P = 0.008) and lower eGFR (35.32 ± 19.85 *vs* 47.17 ± 24.22 mL/min/1.73 m^2, P = 0.002). In ROC analysis, the area under the curves was 0.527 for hs-cTnI, and 0.711 for creatinine (Figure 1).

Multivariable analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.00-1.13; P = 0.048) and creatinine levels (OR 2.07 per 1 mg/dL increase, 95%CI: 1.38-3.09; P < 0.001) were the only independent predictors of death. When renal function was estimated as eGFR, it was also a significant independent predictor of mortality (OR 1.04 per 1 mL/min/1.73 m^2 decrease, 95%CI: 1.01-1.06; P = 0.001). Figure 2 shows the percentages of patients who died in-hospital according to the CKD stages. Mortality was 49% in patients with severe CKD (eGFR < 30 mL/min/1.73 m^2).

DISCUSSION

We performed a retrospective investigation of in-hospital mortality in elderly patients admitted to the Internal Medicine Department with non-acute cardiac events and elevated hs-cTnI levels. Our major findings are that (1) these patients were at high risk of in-hospital death; (2) age and renal dysfunction were the only independent predictors of death among the parameters assessed; and (3) patients who died did not have higher hs-cTnI levels compared with those who were discharged alive.

Previous studies have reported that hs-cTnI concentrations and their 99th percentile strongly depend on the characteristics of the population being assessed[7] and that

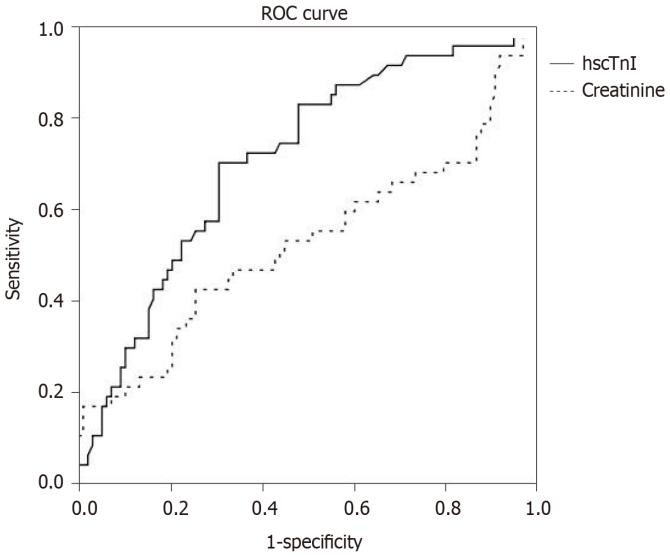


Figure 1 The area under the curves in receiver operating characteristic analysis. ROC: Receiver operating characteristic; hs-cTnI: High-sensitivity cardiac troponin I.

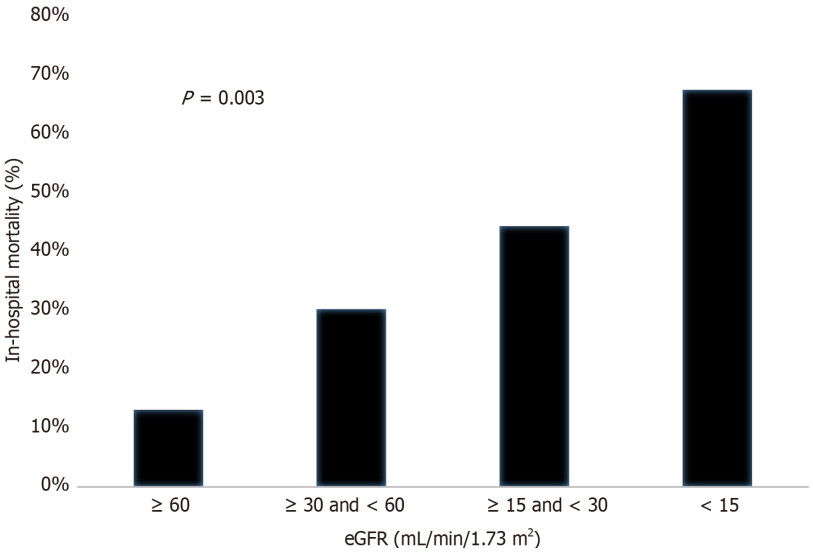


Figure 2 The percentages of patients who died in-hospital according to the chronic kidney disease stages.

more than 20% of elderly inpatients may have hs-TnI levels above URL[11]. Advancing age and decreasing eGFR were shown to be independent predictors of hs-TnI concentration greater than the recommended URL[11]. Moreover, the 99th percentile of elderly inpatients (after excluding participants diagnosed as having acute myocardial infarction) may be 10 times higher than the recommended URL[11]. Eggers *et al*[7] reported the 99th percentile for hs-cTnI near our cut-off value (*i.e.*, 100 ng/L) regarding individuals with age distribution and cardiac history similar to our study group.

The high in-hospital mortality in patients with high troponin levels admitted for non-cardiac causes is in line with previously published studies[5,6,12,19]. The relatively higher mortality in our study could be mainly explained by differences in baseline characteristics of the included patients, since our study population was older, had more frequently a history of CKD and higher creatinine levels (and thus, lower eGFR)[5,6,12,19]. We showed that age and renal function were the only independent predictors of in-hospital mortality in elderly patients admitted with high hs-cTnI levels and non-cardiac causes in the Internal Medicine Department. It is worth noting that the majority of prior research has been conducted in patients with infectious diseases, while in our unselected elderly study group, 50% of the elderly inpatients suffered from other diseases. However, there were no significant differences regarding

mortality according to the cause of admission (infectious *vs* non-infectious disease) and no differences regarding the CRP concentrations between patients who died and patients who were discharged alive.

Our study showed that although elderly patients with non-cardiac events and hs-cTnI ≥ 100 ng/L have a high risk of in-hospital death, individuals who died did not have higher hs-cTnI levels compared with those who were discharged alive. Similarly, Frencken *et al*[5] also showed that troponin release beyond hs-cTnI plasma concentrations of approximate 100 ng/L does not carry an additional mortality risk in patients with sepsis. This non-linear relationship between troponin levels and mortality may be present even in patients with revascularized acute coronary syndromes[12]. The nonlinear relationship with mortality is difficult to explain. It is possible that in patients with non-cardiac acute events, the presence of myocardial injury (and not the extent of injury) maybe a marker of increased mortality. This hypothesis is supported from our ROC analysis, since the area under the curve for hs-cTnI was approximately 0.5, thereby indicating that the level of the troponin (the level of myocardial injury) has no discrimination capacity for further distinguish the risk of in-hospital death.

Cardiac troponin concentrations are often increased in CKD patients[20]. Although the reasons are not clear, higher troponin values in CKD patients are considered to be primarily caused by chronic myocardial injury, and thus troponin release to the circulation, and secondarily by decreased clearance. Miller-Hodges *et al*[21] evaluated hs-TnI testing in patients with suspected acute coronary syndrome with and without renal impairment. They reported that patients with elevated troponin and renal impairment had a greater risk for cardiac events at 1 year. Although previous studies have investigated the prognostic role of troponins in elderly patients[7,8,12], data regarding the evaluation of CKD in elderly patients with non-cardiac admissions and elevated hs-Tn measurements are sparse. We report an extremely high risk of in-hospital death among elderly patients with renal impairment admitted to the hospital for non-cardiac causes with elevated hs-cTnI levels. Elderly inpatients with CKD stages IV or V had a risk of approximate 50% for in-hospital death. This may emphasize the need for more aggressive monitoring and treatment in this group in order to avoid complications and death.

Our study had several limitations. First, all retrospective studies using electronic/paper medical records have inherent methodological problems[22]. Second, we did not use a control group (*e.g.*, patients with "normal" hs-cTnI levels) for comparison purposes. Third, other potential prognostic indices (*e.g.*, brain natriuretic peptides) were available only in a very small number of patients, hence we did not include them in the analysis. Finally, although in almost all the cases cardiology examination was performed, in clinical practice it is often difficult to exclude from the diagnosis an acute coronary syndrome, especially in elderly patients with non-specific symptoms.

CONCLUSION

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons and indicates poor overall prognosis. The presence of severe renal impairment remains as an independent marker of extremely high in-hospital mortality in this selected patient group.

ARTICLE HIGHLIGHTS

Research background

Many reports have shown that there is an association between acute myocardial injury and adverse outcomes in almost every clinical setting.

Research motivation

Data from consecutive elderly patients admitted to the Internal Medicine Department with acute non-cardiac events and acute myocardial injury are limited.

Research objectives

To investigate: (1) The in-hospital survival of consecutive elderly patients presenting to the emergency department with acute non-cardiac events, elevated high-sensitivity

cardiac troponin I (hs-cTnI) levels and admitted to the Internal Medicine Department; and (2) The independent predictors (*i.e.*, comorbidities) of in-hospital mortality.

Research methods

This was a single centre, retrospective, observational study, involving 146 elderly (≥ 65 years) patients (59% female) admitted to the Internal Medicine Department with acute non-cardiac events and elevated hs-cTnI (≥ 100 ng/L).

Research results

Patient age ranged from 65 to 100 (mean ± SD: 85.4 ± 7.61) years. The median hs-cTnI value was 284.2 ng/L. The overall in-hospital mortality was 32% (47 patients). Multivariate analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.000-1.127; $P = 0.048$) and creatinine levels (OR 2.065 per 1 mg/dL increase, 95%CI: 1.383-3.085; $P < 0.001$) were the only independent predictors of death. Mortality was 49% in patients with eGFR < 30 mL/min/1.73 m^2.

Research conclusions

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons and indicates poor overall prognosis. The presence of severe renal impairment remains as an independent marker of extremely high in-hospital mortality in this selected patient group.

Research perspectives

Our results emphasize the need for more aggressive monitoring and treatment in elderly patients with severe renal impairment admitted to the hospital for non-cardiac reasons in order to avoid complications and death.

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ORIGINAL ARTICLE

Prospective Study

Patent hemostasis of radial artery: Comparison of two methods

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Abstract

BACKGROUND

Radial artery obstruction is the most common complication of coronary angiography performed *via* transradial access. Patent hemostasis can significantly reduce the risk of radial artery occlusion. Previous studies utilized sophisticated methods to evaluate radial artery patency. Simplified and easily applicable methods for successful patent hemostasis are currently lacking.

AIM

To determine which method (pulse oximeter *vs* the traditional radial artery palpation) is better to achieve patent hemostasis.

METHODS

This prospective, single center study included 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention between November 2017 and July 2019. Patients less than 18 years old, with a history of radial artery disease, or no palpable artery pulse were excluded from the study. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by palpation of the artery during hemostasis (traditional method). In the second group, radial artery patency was estimated with the use of a pulse oximeter. Two different compression devices were used for hemostasis (air chamber and pressure valve). The primary study endpoint was the achievement of successful patent hemostasis.

RESULTS

The two groups (pulse oximeter *vs* artery palpation) had no significant differences

and approved the final manuscript.

Institutional review board statement: The study protocol was approved by the hospital's ethics review board.

Informed consent statement: Patients participating in the study provided written informed consent.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

Data sharing statement: No additional data are available

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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in age, sex, body mass index, risk factors, or comorbidities except for supraventricular arrhythmias. The percentage of patients with successful patent hemostasis was significantly higher in the pulse oximeter group (82.2% *vs* 68.1%, $P = 0.005$). A lower percentage of patients with spasm was recorded in the pulse oximeter group (9.9% *vs* 19.0%, $P = 0.024$). The incidence of local complications, edema, bleeding, hematoma, vagotonia, or pain did not differ between the two groups. In the multivariate analysis, the use of a pulse oximeter (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and advanced age (OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$), were independently associated with an increased probability of successful patent hemostasis. The type of hemostatic device did not affect patent hemostasis ($P = 0.450$).

CONCLUSION

Patent hemostasis with the use of pulse oximeter is a simple, efficient, and safe method that is worthy of further investigation. Larger randomized studies are required to consider its clinical implications.

Key Words: Radial access; Patent hemostasis; Palpation; Oximeter; Coronary angiography; Radial artery occlusion

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Core Tip: This was a prospective, single center study with 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention. It aimed to evaluate the best method (pulse oximeter *vs* the traditional radial artery palpation) for successful patent hemostasis. The use of a pulse oximeter increased the probability of achieving patent hemostasis compared with artery palpation, and was associated with lower rates of artery spasm. In the multivariate analysis, the use of pulse oximeter and advanced age were independently associated with an increased probability of successful patent hemostasis.

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INTRODUCTION

Transradial access is increasingly used in coronary angiography *vs* transfemoral access as it has several advantages. Transradial access is associated with fewer vascular complications, lower bleeding complications, and reduced mortality in specific high-risk populations[1]. Furthermore, the technique offers earlier mobilization after the procedure, and the patient usually has a shorter hospital stay. The European guidelines for coronary angiography in patients with acute coronary syndrome favor transradial over transfemoral access with a Class IA indication[2,3].

Radial artery obstruction (RAO) is a frequent complication of coronary angiography performed *via* transradial access[4]. RAO may prevent radial artery access for future coronary angiography or as a conduit for coronary artery bypass grafting. At the same time, patients requiring hemodialysis lose an artery that can be used to create an arteriovenous fistula. Therefore, prevention of RAO is of particular clinical importance in patients undergoing coronary angiography *via* transradial access. Experts emphasize the need for the adoption of novel techniques that may reduce the incidence of RAO to less than 5%[5].

Complete obstruction of blood flow in the radial artery during hemostasis is a strong predictor of RAO occurrence[6]. On the contrary, maintaining circulatory anterograde flow in the radial artery during hemostasis, known as patent or nonobstructive hemostasis, reduces the risk of RAO[7,8]. Various methods of patent hemostasis have been described, but there is no current consensus on the optimal

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method. Of note, the application of nonobstructive hemostasis is technically difficult as it requires intense staff mobilization, multiple evaluations of radial artery blood flow, and adjustment of hemostatic pressure in order to maintain patency. That is why patent hemostasis is not fully adopted in most laboratories[9]. The goal of this study was to evaluate a simplified and easily applicable method to achieve patent hemostasis in patients undergoing diagnostic coronary angiography or percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Patient population

A total of 299 consecutive patients undergoing cardiac catheterization between November 2017 and July 2019 and considered eligible for radial access were included in the study. Patients underwent a Barbeau test precatheterization, to assess collateral palmar arch sufficiency. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by artery pulse palpation during hemostasis (traditional method). In the second group, radial artery patency was estimated with the use of a pulse oximeter. Two different compression devices were used for hemostasis, one with an air chamber and another with a pressure valve. The primary study endpoint was the achievement of successful patent hemostasis.

Randomization did not affect coronary angiography, either diagnostic or invasive, and operators were unaware of the patient allocation. RAO was assessed at 24 h and 30 d after the procedure. Patients younger than 18 years of age with a history of radial artery disease or absence of radial artery pulse were excluded from the study. Patients participating in the study provided written informed consent, and the study protocol was approved by the hospital's ethics review board.

Transradial catheterization procedure

Radial artery catheterization was performed using the Seldinger technique. The catheter diameter was 5/6-French.

Conventional hemostasis with radial artery pulse palpation

The introducer sheath was removed immediately after the procedure. The sheath was pulled out by 4 to 5 cm and a hemostatic bandage was applied around the wrist. The bandage was then tightened and the catheter was removed. In group 1, radial artery patency was assessed by radial artery pulse palpation. The bandage remained in place for 4 h and then was slowly removed. A light dressing was applied at the entry site after the procedure.

Patent hemostasis procedure with the aid of pulse oximeter

The sheath was pulled out by 4 to 5 cm and a hemostatic bandage was applied over the entry site. In group 2 a pulse oximeter sensor was placed on the index finger, the bandage was tightened, and the sheath was removed. The ulnar artery was compressed and the hemostatic bandage gradually began to relax. Radial artery patency was confirmed by plethysmographic signal reoccurrence. In case of bleeding before plethysmographic signal appearance, the hemostatic bandage compression was increased. If radial artery flow was confirmed by the oximeter and no bleeding complications occurred, then a bandage remained in place for 4 h. Radial artery patency was assessed on an hourly basis.

Assessment of radial artery patency

Radial artery flow was evaluated with a Barbeau test. The pulse oximeter sensor was placed on the index finger and the plethysmographic signal was observed. Ulnar and radial artery compression led to signal loss. Radial artery pressure was then removed while maintaining ulnar artery compression. Appearance of the plethysmographic signal was proof of radial artery patency, while absence of a signal indicated RAO. The test was performed precatheterization, at 24 h and at 30 d after coronary angiography. Radial artery patency was also assessed at 30 d by vascular ultrasonography with Doppler assessment.

Hemostatic efficacy

Hemorrhagic complications that resulted in blood loss from the puncture site and judged capable of causing hemodynamic instability, blood transfusion, or death were

regarded as significant. Hematomas at the puncture site were considered clinically significant when their diameter exceeded 3 cm.

Statistical analysis

Quantitative variables were expressed as means ± SD or as medians and interquartile range (IQR). Qualitative variables were reported with absolute and relative frequencies. Chi-square and Fisher's exact tests were used to compare proportions. Student's *t*-tests were used to compare mean values that were normally distributed. Mann-Whitney tests were used to compare median values when the distribution was not normal. Logistic regression analyses in a stepwise method (P for entry 0.05, P for removal 0.10) were performed in order to identify factors associated with the presence of specific outcomes. Unadjusted and adjusted odds ratios with 95%CI were computed from the results of the logistic regression analyses. Statistical significance was set at 0.05. The analyses were conducted using SPSS statistical software (version 22.0).

RESULTS

Demographic characteristics and risk factors/comorbidities

Radial artery patency during hemostasis was assessed by artery palpation (control group) in 147 patients (49.2%) and by pulse oximeter sensor in 152 patients (50.8%). The demographic characteristics of the study population are shown in Table 1. The study population consisted mainly of men (75%) with a mean age of 60.8 years. Dyslipidemia was the most common comorbidity followed by hypertension, coronary artery disease, and diabetes mellitus. One out of three patients (35%) had previously undergone PCIs and 6% had previously undergone coronary bypass surgery. The two groups of patients did not have significant differences in their baseline clinical characteristics (Table 1). Patients in the control group had a higher rate of supraventricular arrhythmia, mainly atrial fibrillation (26.5% *vs* 13.2%, $P = 0.004$).

Procedural characteristics

Table 2 shows the procedural characteristics of the two study groups. PCI was performed in 30% of the patients. There were no differences in the number of coronary vessels that received intervention. Half the patients underwent coronary angiography using a 5-french introducer sheath and the other half using a 6-french sheath. The two groups of patients did not differ in several other procedural characteristics (*e.g.*, right or left hand, duration of procedure, radiation time). Patients received similar doses of anticoagulants (heparin) and did not differ in the type of device used for hemostasis (Table 2).

Complications

Table 3 shows the coronary angiography complications. The group of patients in whom the radial artery patency was assessed with the traditional method (artery palpation) had a higher rate of radial artery spasm ($P = 0.024$). The two groups had similar rates of vagotonia, hematoma, bleeding, edema, local complications, and pain.

Patent hemostasis in the study groups

The group of patients whose radial artery patency was assessed using the pulse oximeter achieved significantly higher rates of patent hemostasis than those in the control group, using radial artery palpation (82.2% *vs* 68.1%, $P = 0.005$; Figure 1). The type of hemostatic device (air chamber or pressure valve device) did not affect patent hemostasis ($P = 0.450$). Radial artery flow was restored in a significant percentage of patients at 24 h and at 30 d after coronary angiography (Table 4).

Predictors of patent hemostasis

Multivariate logistic regression analysis revealed that pulse oximeter use (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and patient age (per 1 year increase; OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$) as independent predictors of patent hemostasis (Table 5).

DISCUSSION

The main study findings were: (1) Successful patent hemostasis was significantly more frequent in the pulse oximeter group *vs* the radial artery palpation group; (2) A lower

Table 1 Baseline characteristics of the study population

Baseline characteristics	Control group (conventional hemostasis), *n* = 147	Oximetry – plethysmography group, *n* = 152	*P* value
Age (mean ± SD, yr)	61.5 ± 9.8	60.1 ± 11.6	0.273[1]
Male sex	109 (74.1)	115 (75.7)	0.764[2]
Body mass index (mean ± SD, kg/m^2)			0.343[2]
Normal (18.5-24.9)	31 ± 21.1	35 ± 23	
Overweight (25-29.9)	73 ± 49.7	63 ± 41.4	
Obese (> 30)	43 ± 29.3	54 ± 35.5	
Risk factors/Comorbidities, *n* (%)			
Hypertension	89 (60.5)	92 (60.5)	0.997[2]
Diabetes mellitus	29 (19.7)	40 (26.3)	0.176[2]
Insulin	6 (20.7)	14 (35.0)	0.196[3]
Dyslipidemia	112 (76.2)	114 (75.0)	0.811[2]
Smoking	69 (46.9)	74 (48.7)	0.850[2]
History of coronary artery disease	46 (31.3)	52 (34.2)	0.591[2]
Supraventricular arrhythmia	39 (26.5)	20 (13.2)	0.004[2]
History of interventions, *n* (%)			
Percutaneous coronary intervention	49 (33.3)	56 (36.8)	0.5252
Coronary artery bypass grafting	11 (7.5)	7 (4.6)	0.2963

[1]Student's *t*-test.
[2]Pearson's χ^2.
[3]Fisher's exact test.

percentage of complications (*i.e.* spasm) was recorded in the pulse oximeter group; and (3) Advanced age and the use of a pulse oximeter were independent predictors of successful patent hemostasis.

Many studies have reported the safety and efficacy of performing coronary angiography *via* the transradial access. Transradial access is preferred over transfemoral artery access for percutaneous diagnostic and interventional procedures because it is associated with lower rates of vascular and hemorrhagic complications that lead to transfusions[5,10-12]. A systematic review and meta-analysis including 11707 patients who presented with ST-segment elevation myocardial infarction, reported an association between transradial access and reduction in 30-d mortality (relative risk, 0.72), major bleeding (relative risk, 0.60), and access-site complications (relative risk, 0.40) compared with transfemoral access[11]. Interestingly, the transradial approach has the advantage of a rapid interval to patient mobilization[13].

RAO is a potential complication of coronary angiography using the transradial approach[5,10]. In randomized trials, RAO incidence ranged up to 10%[5]. However, in daily clinical practice RAO frequency is much higher[4,14-16]. Radial artery patency should be routinely checked before discharge of any patient who has undergone coronary angiography *via* transradial access[5]. Radial artery palpation is the most common technique used[17]. However, artery palpation may be misleading as the presence of collateral circulation from palmar arches in the upper extremity is likely to lead to a palpable pulse from the distal stump even in the presence of RAO[5]. RAO is more common at the end of hemostasis and thereafter gradually decreases in the first 24 h and even further in the 30 d after the procedure. In a meta-analysis of 112 studies including 46.631 patients, late revascularization occurred in a significant proportion of patients with RAO[18]. In this study, radial artery flow was restored in a significant percentage of patients at 24 h and at 30 d after coronary angiography.

Measures to reduce RAO incidence include smaller catheters, adequate anticoagulation, the adoption of patent hemostasis strategies with or without ulnar artery compression, and the reduction of hemostasis time to ≤ 120 min[5,16,18-24]. Patent

Table 2 Procedural data of the study population

Procedural data	Control group (conventional hemostasis) (*n* = 147)	Oximetry – plethysmography group (*n* = 152)	*P* value
PCI, *n* (%)	44 (29.9)	58 (38.2)	0.134[1]
Primary PCI, *n* (%)	12 (8.2)	15 (9.9)	0.607[1]
Heparin dose, median (IQR)	5000 (5000-7000)	5000 (5000-7000)	0.113[2]
INR, mean ± SD	1.1 ± 0.3)	1.1 ± 0.3)	0.958[3]
Significant coronary artery lesions, *n* (%)			
Left anterior descending artery	32 (21.8)	36 (23.7)	0.693[1]
Circumflex	10 (6.8)	12 (7.9)	0.718[1]
Right coronary artery	17 (11.6)	20 (13.2)	0.676[1]
Number of vessels[4], *n* (%)			0.707[3]
PCI in 1 vessel (%)	35 (81.4)	50 (87.7)	
PCI >1 vessels (%)	8 (18.6)	7 (12.3)	
Hemostatic device			0.223[1]
Air chamber, *n* (%)	80 (54.4)	72 (47.4)	
Valve with pressure plate, *n* (%)	67 (45.6)	80 (52.6)	
Right hand, *n* (%)	104 (70.7)	115 (75.7)	0.362[1]
Left hand, *n* (%)	43 (29.3)	37 (24.3)	
Puncture attempts, median (IQR)	1 (1-1)	1 (1-1)	0.354[2]
Puncture duration (min), median (IQR)	2.25 (1.42-3.3)	2.22 (1.44-3.37)	0.660[2]
Procedure time (min), median (IQR)	13 (8.4-27.3)	13.8 (9.2-26.9)	0.448[2]
Fluoro time (min), median (IQR)	3.1 (1.3-9.1)	3.4 (1.4-7.7)	0.663[2]
Sheath, *n* (%)			0.257[3]
5F	74 (50.3)	70 (46.1)	
6F	73 (49.7)	79 (52.0)	
7F	0 (0.0)	3 (2.0)	
Patent hemostasis, *n* (%)	94 (68.1)	125 (82.2)	0.005[1]

[1]Pearson's χ^2.
[2]Mann-Whitney test.
[3]Fisher's exact test.
[4]For those who underwent percutaneous coronary intervention.
INR: International normalized ratio; IQR: Interquartile range; PCI: Percutaneous coronary intervention.

hemostasis is the technique of maintaining radial artery forward flow through guided artery compression during hemostasis after coronary angiography[7]. In patients undergoing coronary angiography, complete absence of radial artery flow during hemostatic compression is a strong predictor of RAO[6,24]. On the contrary, maintaining radial artery antegrade flow during hemostasis, known as patent or nonocclusive hemostasis, is an important factor in preventing RAO, but its complexity has limited adoption[5,7,25]. Maintaining radial artery antegrade flow during hemostatic compression constitutes part of the recommended best practice after transradial access for coronary angiography[25].

The best technique to achieve patent hemostasis is a subject of ongoing research. Previous studies utilized relatively sophisticated methods to evaluate radial artery patency. In the landmark prevention of radial artery occlusion-patent hemostasis evaluation trial (the PROPHET study), 436 patients were randomized to undergo either conventional hemostasis or patent hemostasis after diagnostic coronary angiography *via* the transradial approach. Twelve percent of patients who underwent

Table 3 Coronary angiography complications between two hemostatic methods

Coronary angiography complications	Control group (Conventional Hemostasis)	Oximetry – plethysmography group	*P* value
Spasm	28 (19.0)	15 (9.9)	0.024[1]
Vagotonia	24 (16.3)	23 (15.1)	0.777[1]
Hematoma	25 (17.0)	15 (9.9)	0.070[1]
Hematoma diameter, median value (IQR)	0 (0 - 3)	0 (0 - 3)	0.462[2]
Bleeding	7 (4.8)	5 (3.3)	0.517[1]
Edema	26 (17.7)	29 (19.1)	0.756[1]
Local complication	18 (12.2)	24 (15.8)	0.378[1]
Pain	28 (19.0)	22 (14.4)	0.289[1]

[1]Pearson's χ^2.
[2]Mann-Whitney test.
Data are *n* (%)

Table 4 Patent radial artery by patient group

	Control group(conventional hemostasis)	Oximetry-plethysmography group	*P* value[3]
Patent radial artery			
Day 1[1] (*n* = 299)	126 (85.7)	137 (90.1)	0.241
Day 30[1] (*n* = 206)	100 (94.3)	89 (89.0)	0.164
Day 30[2] (*n* = 204)	100 (92.6)	87 (90.6)	0.612

[1]Evaluation with a Barbeau test.
[2]Evaluation with duplex ultrasonography.
[3]Pearson's χ^2.
Data are *n* (%)

Table 5 Predictors of patent hemostasis

	OR (95%CI)	*P* value
Patent hemostasis		
Age (per 1 yr increase)	1.04 (1.01-1.07)	0.006
Control group (reference)		
Oximetry-plethysmography group	2.35 (1.34-4.13)	0.003

conventional hemostasis experienced RAO at 24 h. The corresponding rate for patients in the patent hemostasis group was 5%[7]. The use of an oximetry-plethysmography test was the strongest predictor of achieving patent hemostasis. In the prophylactic hyperperfusion evaluation trial (PROPHET-II), ipsilateral ulnar artery compression during radial artery hemostatic compression increased the rate of patent hemostasis and reduced the incidence of RAO from 3.0% to 0.9%[25]. In the randomized radial compression guided by mean artery pressure *vs* standard compression with a pneumatic device (RACOMAP) trial, a significant reduction in RAO rates from 12.0% to 1.1% was observed in patients following the patent hemostasis protocol compared with traditional arterial obstructive compression[8]. In the RACOMAP trial, nonobstructive hemostasis was performed by compressing the radial artery during hemostasis, guided by the mean blood pressure[8].

In a study by Edris *et al*[26], patent hemostasis was achieved with rapid deflation of the compression band. The technique increased patent hemostasis rates from 40% to 95% and reduced RAO rates from 14.9% to 2.0% without bleeding complications. A study comparing nonobstructive hemostasis to conventional hemostasis reported

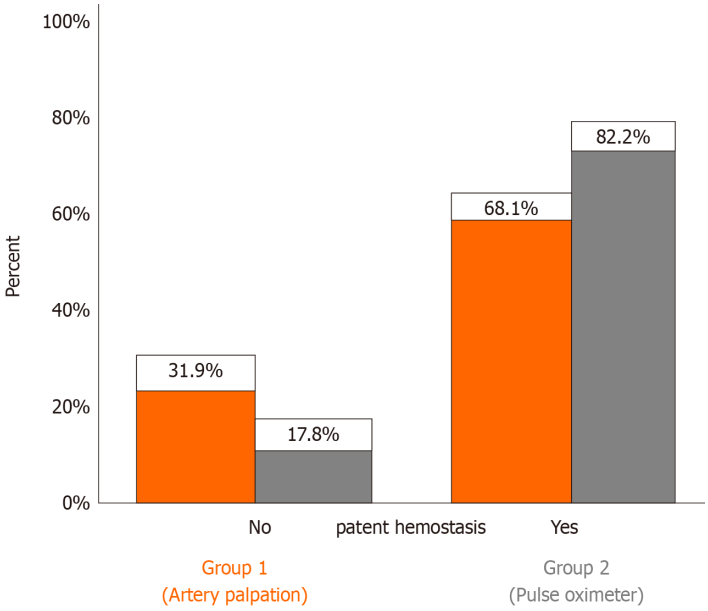


Figure 1 Percentage of patent hemostasis in each study group.

reduced RAO at 24 h in the patent hemostasis group, whereas the difference at 7 d between the two groups was not statistically significant[27]. The result is similar to that observed in this study in which RAO rates at 30 d did not differ between the two groups. The rates of patent hemostasis in this study are similar to those in previous studies (68.1% to 82.2%)[7,24]. Furthermore, in previous studies, nonocclusive hemostasis did not increase bleeding complications compared with conventional hemostasis[7,8]. Plethysmographic evaluation of radial artery flow allows easier achievement of patent hemostasis without adversely affecting the method safety. Similarly, in the present study, no difference was observed in the hemorrhagic events that occurred in the two treatment groups. Interestingly, in the current study, manual compression was not required to achieve hemostasis in the pulse oximeter group. In the PROPHET study manual compression was required in a small percentage of patients (3.6%) to achieve hemostasis[7]. Lastly, the rates of spasm in our study, which were lower in the oximeter *vs* the artery palpation group, were in accord with those reported in the literature[4].

In this study, we observed an association between increased age and successful patent hemostasis. Several speculations can be made regarding that finding. Firstly, radial artery spasm is more frequent in younger than in older patients undergoing PCI *via* radial access and therefore older adults are more likely to have a successful patent hemostasis[28-31]. Secondly, increased arterial stiffness in elderly patients produces a steeper increase in radial artery flow, resulting in reopening of the occlusion in the early period and maintaining vessel patency in the long-term[32]. Lastly, increased arterial stiffness in older patients may preclude the total interruption of flow during manual compression and therefore facilitate patent hemostasis[32].

The current study has several limitations that need to be addressed. Firstly, the study population was not large, but it was comparable to previous studies in the field. Secondly, at 30 d, radial artery patency was assessed with duplex ultrasonography in 204 out of 299 patients. We performed a telephone follow-up of the patients who did not return at 30 d. The three main reasons cited for follow-up interruptions were lack of understanding regarding the necessity of follow-up, social reasons (*e.g.*, distant hometown, financial barriers, relocation) and unawareness of the appointment schedule. Nevertheless, radial artery flow was restored in a significant percentage of patients who presented at follow-up, which is in accord with the current literature. Thirdly, patent hemostasis achieved in the current study by the use of pulse oximetry is relatively more simple than the techniques described in previous studies, and can be more widely implemented in everyday clinical practice.

CONCLUSION

Oximetry-plethysmography is an efficient and safe method to achieve patent hemostasis after coronary angiography *via* transradial access. Larger randomized control trials are urgently needed.

ARTICLE HIGHLIGHTS

Research background

Radial artery obstruction is a frequent complication of coronary angiography performed *via* transradial access. Maintaining circulatory anterograde flow in the radial artery during hemostasis (patent or nonobstructive hemostasis) reduces the risk of radial artery obstruction.

Research motivation

Simplified and easily applicable methods for successful patent hemostasis are currently lacking.

Research objectives

To determine which method, pulse oximeter *vs* the traditional radial artery palpation, is better to achieve patent hemostasis.

Research methods

This a prospective, single center study included 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention between November 2017 and July 2019. The exclusion criteria were: (1) Age of < 18 years; (2) History of radial artery disease; and (3) No palpable arterial pulse. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by palpation of the artery during hemostasis (traditional method). In the second group, radial artery patency was estimated with a pulse oximeter. Two different compression devices were used for hemostasis (air chamber and pressure valve). The primary study endpoint was the successful achievement of patent hemostasis.

Research results

The two groups (pulse oximeter *vs* artery palpation) had no significant differences in age, sex, body mass index, risk factors, or comorbidities except for supraventricular arrhythmias. The percentage of patients with successful patent hemostasis was significantly higher in the pulse oximeter group (82.2% *vs* 68.1%, $P = 0.005$). A lower percentage of patients with spasm was recorded in the pulse oximeter group (9.9% *vs* 19.0%, $P = 0.024$). Multivariate analysis found that the use of pulse oximeter (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and advanced age (OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$), were independently associated with an increased probability of successful patent hemostasis. The type of hemostatic device did not affect patent hemostasis ($P = 0.450$).

Research conclusions

Patent hemostasis with the use of pulse oximeter is a simple, efficient, and safe method, and is worthy of further investigation.

Research perspectives

Larger randomized studies are required to consider its clinical implications.

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META-ANALYSIS

Cardiovascular efficacy and safety of dipeptidyl peptidase-4 inhibitors: A meta-analysis of cardiovascular outcome trials

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Abstract

BACKGROUND

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a generally safe and well tolerated antidiabetic drug class with proven efficacy in type 2 diabetes mellitus (T2DM). Recently, a series of large, randomized controlled trials (RCTs) addressing cardiovascular outcomes with DPP-4 inhibitors have been published.

AIM

To pool data from the aforementioned trials concerning the impact of DPP-4 inhibitors on surrogate cardiovascular efficacy outcomes and on major cardiac arrhythmias.

METHODS

We searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020. We extracted data concerning the following "hard" efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also extracted data regarding the risk for major cardiac arrhythmias, such as atrial fibrillation, atrial flutter, ventricular fibrillation and ventricular tachycardia.

RESULTS

We pooled data from 6 trials in a total of 52520 patients with T2DM assigned either to DPP-4 inhibitor or placebo. DPP-4 inhibitors compared to placebo led to

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a non-significant increase in the risk for fatal and non-fatal myocardial infarction [risk ratio (RR) = 1.02, 95%CI: 0.94-1.11, I^2 = 0%], hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, I^2 = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, I^2 = 0%). DPP-4 inhibitors resulted in a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI: 0.85-1.08, I^2 = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, I^2 = 0%), Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, I^2 = 0%). As far as cardiac arrhythmias are concerned, DPP-4 inhibitors did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, I^2 = 0%), while they were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, I^2 = 0%). DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed cardiac arrhythmias.

CONCLUSION

DPP-4 inhibitors do not seem to confer any significant cardiovascular benefit for patients with T2DM, while they do not seem to be associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. Therefore, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

Key Words: Dipeptidyl peptidase-4 inhibitors; Cardiovascular outcomes; Atrial fibrillation; Atrial flutter; Type 2 diabetes mellitus

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Core Tip: The antidiabetic efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors has already been proven in recently published large randomized controlled trials. The purpose of the present meta-analysis was to clarify the impact of antidiabetic therapy with DPP-4 inhibitors on surrogate cardiovascular outcomes, and to elucidate the effect of these drugs on major cardiac arrhythmias. According to our analysis, this drug class does not significantly affect the risk for any of the addressed cardiovascular outcomes; however, it increases the risk for atrial flutter compared to placebo.

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INTRODUCTION

It is well-established that type 2 diabetes mellitus (T2DM) represents an independent risk factor for the development of cardiovascular disease, which accounts for half of deaths among diabetic patients[1]. Patients with T2DM experience higher incidence of vascular interventions compared to high-risk patients without T2DM or cardiovascular disease at baseline, underscoring the necessity for targeted therapeutic interventions[2]. In addition, development of cardiovascular complications among patients with T2DM boosts medical costs, leading to an unbearable economic burden [3]. Besides major adverse cardiovascular events, patients with T2DM experience an increased risk of heart rhythm disorders, nevertheless the exact mechanisms of arrhythmogenesis in the context of T2DM are still under investigation[4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a safe treatment option with adequate glycemic efficacy in T2DM. However, their cardiovascular efficacy has been

doubted over recent years, after the publication of relevant cardiovascular outcome trials. Previous meta-analyses failed to show any cardiovascular benefit with their use in patients with T2DM[5-7]. Since then, additional randomized controlled trials addressing "hard" cardiovascular outcomes with DPP-4 inhibitors have been published. Therefore, we sought to update and extend these meta-analyses, by incorporating all relevant data from published cardiovascular outcome trials until October 2020. In addition, we planned to assess the effect of DPP-4 inhibitors on major cardiac arrhythmias, since there are no relevant studies published in the literature so far.

MATERIALS AND METHODS

Our meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched PubMed database and grey literature sources form inception to October 2020, in order to identify relevant cardiovascular outcome trials assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in patients with T2DM. Our inclusion criteria were: (1) Randomized controlled trials; (2) Enrollment of patients with T2DM; (3) Enrollment of adult patients; and (4) Assessment of at least one cardiovascular outcome of interest. Our exclusion criteria were: (1) Observational studies; (2) Studies enrolling patients with type 1 diabetes mellitus; and (3) Studies enrolling children or adolescents.

We utilized the following search terms: "DPP-4 inhibitor", "dipeptidyl peptidase-4 inhibitor", "vildagliptin", "sitagliptin", "alogliptin", "linagliptin", "saxagliptin", "omarigliptin", "tenegliptin", "evogliptin", "gliptin", "cardiovascular outcome", "cardiac arrhythmia", "atrial fibrillation" combined with the use of Boolean operators "AND" and "OR". We used both free-text words and MeSH terms. We did not imply any filter regarding study setting, study sample, language or publication date. Unfortunately, we did not registered prospectively our protocol in a publicly available repository.

After de-duplication and assessment of eligible studies at title and abstract level for potential inclusion, two independent reviewers (D.P. and E.T.) extracted the data from the eligible reports, by using a pilot tested, data extraction form. We assessed the following cardiovascular efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also assessed the risk for the following cardiac arrhythmias with DPP-4 inhibitor treatment compared to placebo or active comparator: atrial fibrillation, atrial flutter, atrial tachycardia, ventricular fibrillation, ventricular tachycardia, ventricular extrasystoles, supraventricular tachycardia, sinus node dysfunction, second degree atrioventricular block, complete atrioventricular block.

As we assessed only dichotomous variables, differences were calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0% and 25%, moderate if I^2 was between 25% and 50%, or high if I^2 was greater than 75%[8]. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.

Two independent reviewers (D.P. and A.B.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome[9]. Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (V.V.).

RESULTS

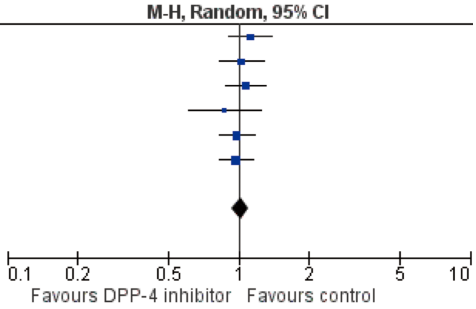
We finally pooled data from six trials in a total of 52520 patients[10-15]. Overall risk of bias was considered as low across all selected trials.

DPP-4 inhibitor treatment did not significantly affect any of the prespecified cardiovascular efficacy outcomes. More specifically, DPP-4 inhibitors compared to control led to a non-significant increase in the risk for fatal and non-fatal myocardial infarction (RR = 1.02, 95%CI: 0.94-1.11, I^2 = 0%), hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, I^2 = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, I^2 = 0%), as shown in Figures 1A, 1C and 1F. In addition, DPP-4 inhibitors produced a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI:

A

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	165	3494	146	3485	14.8%	1.13 [0.91, 1.40]
CAROLINA	153	3023	148	3010	14.5%	1.03 [0.83, 1.28]
EXAMINE	187	2701	173	2679	17.6%	1.07 [0.88, 1.31]
NCT01703208	52	2092	60	2100	5.2%	0.87 [0.60, 1.25]
SAVOR-TIMI 53	234	8240	236	8173	22.1%	0.98 [0.82, 1.18]
TECOS	269	7257	276	7266	25.8%	0.98 [0.83, 1.15]
Total (95% CI)		**26807**		**26713**	**100.0%**	**1.02 [0.94, 1.11]**
Total events	1060		1039			

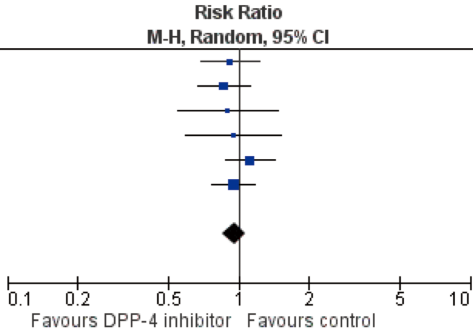
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)



B

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	81	3494	88	3485	15.4%	0.92 [0.68, 1.24]
CAROLINA	104	3023	120	3010	20.7%	0.86 [0.67, 1.12]
EXAMINE	29	2701	32	2679	5.5%	0.90 [0.55, 1.48]
NCT01703208	32	2092	34	2100	6.0%	0.94 [0.59, 1.53]
SAVOR-TIMI 53	135	8240	120	8173	23.0%	1.12 [0.87, 1.42]
TECOS	157	7257	165	7266	29.4%	0.95 [0.77, 1.18]
Total (95% CI)		**26807**		**26713**	**100.0%**	**0.96 [0.85, 1.08]**
Total events	538		559			

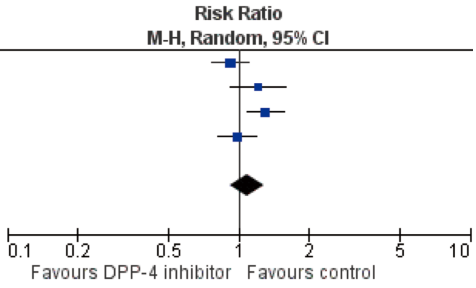
Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)



C

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	209	3494	226	3485	27.1%	0.92 [0.77, 1.11]
CAROLINA	112	3023	92	3010	19.8%	1.21 [0.92, 1.59]
SAVOR-TIMI 53	256	8240	194	8173	26.9%	1.31 [1.09, 1.57]
TECOS	200	7257	202	7266	26.2%	0.99 [0.82, 1.20]
Total (95% CI)		**22014**		**21934**	**100.0%**	**1.09 [0.92, 1.29]**
Total events	777		714			

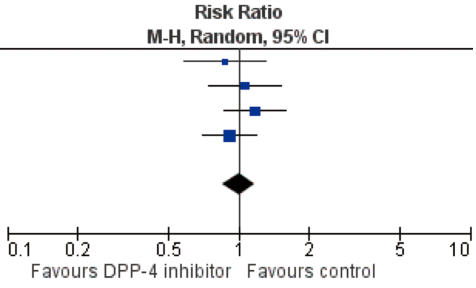
Heterogeneity: Tau² = 0.02; Chi² = 8.53, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 0.99 (P = 0.32)



D

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	42	3494	48	3485	15.3%	0.87 [0.58, 1.32]
CAROLINA	60	3023	56	3010	19.9%	1.07 [0.74, 1.53]
SAVOR-TIMI 53	89	8240	75	8173	27.7%	1.18 [0.87, 1.60]
TECOS	104	7257	114	7266	37.2%	0.91 [0.70, 1.19]
Total (95% CI)		**22014**		**21934**	**100.0%**	**1.00 [0.85, 1.18]**
Total events	295		293			

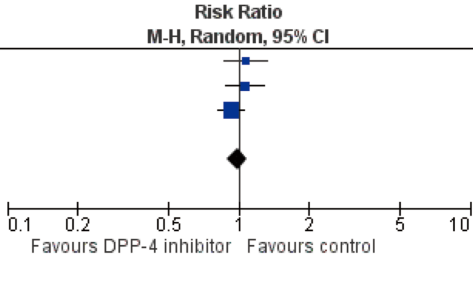
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



E

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	160	3494	149	3485	20.2%	1.07 [0.86, 1.33]
CAROLINA	202	3023	189	3010	26.1%	1.06 [0.88, 1.29]
SAVOR-TIMI 53	395	8240	422	8173	53.7%	0.93 [0.81, 1.06]
Total (95% CI)		**14757**		**14668**	**100.0%**	**0.99 [0.90, 1.09]**
Total events	757		760			

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



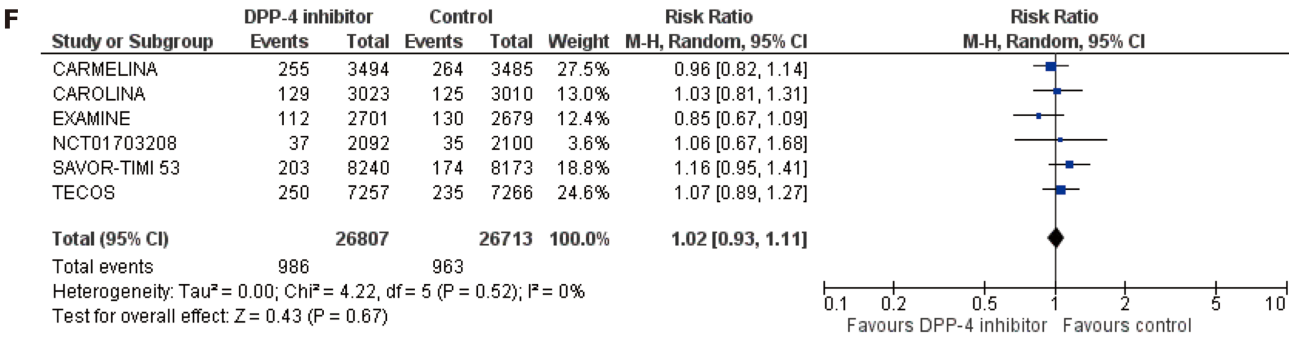


Figure 1 Effect of dipeptidyl peptidase-4 inhibitor treatment compared to control on the risk. A: Fatal and non-fatal myocardial infarction; B: Fatal and non-fatal stroke; C: Hospitalization for heart failure; D: Hospitalization due to unstable angina; E: Hospitalization for coronary revascularization; F: Cardiovascular mortality.

0.85-1.08, I^2 = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, I^2 = 0%), as depicted in Figures 1B and 1E. Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, I^2 = 0%), as shown in Figure 1D.

Regarding the risk for major cardiac arrhythmias, DPP-4 inhibitor treatment did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, I^2 = 0%), as shown in Supplementary Figure 1A. Of note, DPP-4 inhibitors were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, I^2 = 0%), as shown in Supplementary Figure 1B. Finally, DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed major cardiac arrhythmias, as depicted in Supplementary Figures 1C-J.

DISCUSSION

To our knowledge, this is the first meta-analysis of recently published, large, placebo-controlled cardiovascular outcome trials broadly assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in T2DM. Our meta-analysis demonstrates a rather neutral effect of DPP-4 inhibitors on the risk for myocardial infarction, hospitalization for heart failure, stroke, urgent coronary revascularization and cardiovascular death; in parallel, we highlighted the absence of a significant effect of DPP-4 inhibitors on different types of cardiac arrhythmias, except for atrial flutter, for which corresponding risk increased by 52% compared to placebo. Our results are in accordance with previous meta-analyses in the field[6,16]; nevertheless, the impact of DPP-4 inhibitors on the arrhythmic burden across patients with T2DM has not been previously evaluated.

To date, a series of previous reports have indicated some cardioprotective effects of antidiabetic treatment with DPP-4 inhibitors; these generally safe and well-tolerated regimens have been associated with a significant reduction in blood pressure and with a rather low risk for hypoglycemia compared to other categories of antidiabetic drugs, while they do not increase body weight[17,18]. It has also been shown that they reduce arterial stiffness, whereas no significant effect on endothelial function was documented[19]. Additionally, in animal models, DPP-4 inhibitors have been shown to stabilize cardiac electrophysiology by decreasing the total number of premature ventricular contractions and demonstrating an antiapoptotic effect, significantly reducing the infarct size in experimental myocardial ischemia[20,21]. However, the above cardioprotective effects were not clearly translated into clinically significant results in relevant cardiovascular outcome trials and in our meta-analysis, as well.

Of particular interest is the finding of our analysis that DPP-4 inhibitors are associated with a significant increase in the risk for atrial flutter. Underlying pathophysiologic mechanisms remain largely unknown, since there are no relevant published data. However, it is well-established that diabetes mellitus increases the odds for atrial flutter development, almost by two times, as derived from epidemiological data two decades before[22]. In addition, it is known that atrial flutter at baseline is strongly associated with a significant increase in the 10-year risk for myocardial infarction, stroke, heart failure and all-cause death among affected subjects, constituting this arrhythmia as a prognostic marker of future adverse

cardiovascular outcomes[23]. Therefore, the observation that DPP-4 inhibitors actually increase the risk for atrial flutter is of utmost importance that may influence decision-making concerning high-risk patients, such as those suffering from T2DM.

The importance of documenting a neutral effect on a surrogate, prespecified endpoint for a drug class is as important as demonstrating a positive or negative effect, since knowledge about the risk to benefit profile of each different class plays a crucial role in decision-making process in daily clinical routine[24]. Furthermore, considering CVOTs demonstrating significant cardiovascular and renal benefits of other classes of glucose-lowering agents, namely sodium glucose cotransporter-2 inhibitors and glucagon-peptide-1 receptor agonists[25,26], in patients with T2DM, it is important that all such information is incorporated into the clinical guidelines, which have already incorporated these results in their latest recommendations[27,28].

CONCLUSION

In conclusion, DPP-4 inhibitors do not confer any significant cardiovascular benefit for patients with T2DM. In addition, they are not associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. However, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

ARTICLE HIGHLIGHTS

Research background

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a safe and efficacious treatment option in type 2 diabetes mellitus (T2DM).

Research motivation

Recently, several large, cardiovascular-outcome, randomized controlled trials (RCTs) with DPP-4 inhibitors in patients with T2DM have been published, raising some doubts on the cardiovascular efficacy and safety of this drug class.

Research objectives

Herein the authors provide the most updated and broad relevant meta-analysis by pooling data of interest from the available cardiovascular-outcome RCTs, addressing the cardiovascular efficacy and safety of this drug class.

Research methods

The authors searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020.

Research results

Overall, DPP-4 inhibitors seem to have a neutral effect on most surrogate cardiovascular outcome endpoints, such as cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure decompensation, hospitalization for unstable angina or coronary revascularization.

Research conclusions

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

Notably, DPP-4 inhibitors are not associated with a significant effect on the risk for major cardiac arrhythmias, except for atrial flutter, increasing the risk by 52% compared to placebo.

Research perspectives

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

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CASE REPORT

Cardiac involvement in hydrocarbon inhalant toxicity — role of cardiac magnetic resonance imaging: A case report

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Author contributions: Jolly G provided references for and wrote the majority of the introduction, discussion and conclusion sections; Dacosta Davis S, Bitterman L and Saunders A wrote the majority of the case presentation, acquired necessary documentation for submission and completed final formatting of submission documents; Kazbour H supervised the primary medicine team involved in patient care; Kazbour H and Ali S contributed towards revising the manuscript critically for important intellectual content; Parwani P handled supervision, made substantial contribution to the conception of the paper, drafted the first manuscript, provided critical edits to the final manuscript in addition to providing the CMRI imaging, and is the senior and corresponding author of the manuscript.

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Abstract

BACKGROUND

We report a patient who was diagnosed with toxic myopericarditis secondary to hydrocarbon abuse using cardiac magnetic resonance imaging (CMR).

CASE SUMMARY

A 25-year-old male presented to emergency department with chest pain for 3 d. Patient also reported sniffing hydrocarbon containing inhalant for the last 1 year. Labs showed elevated troponin and electrocardiography was suggestive of acute pericarditis. Echocardiogram showed left ventricular (LV) ejection fraction (EF) of 40%. Given patient's troponin elevation and reduced EF, cardiac catheterization was performed which showed normal coronaries. CMR was performed for myocardial infarction with non-obstructive coronary arteries evaluation. CMR showed borderline LV function with edema in mid and apical LV suggestive of myocarditis.

CONCLUSION

CMR can be used to diagnose toxic myopericarditis secondary to hydrocarbon abuse.

Key Words: Myocarditis; Cardiac magnetic resonance imaging; Hydrocarbon abuse; Hydrocarbon inhalant toxicity; Case report

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obtained from the patient for publication of this report and any accompanying images.

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Core Tip: Inhalant abuse has been rampant in the United States population in the last 2 decades. Cardiac manifestations of hydrocarbon inhalant abuse are not well reported. We report a case of myopericarditis in a patient with inhalant abuse. We also describe the role of Cardiac Magnetic Resonance Imaging in diagnosis and treatment of these patients.

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INTRODUCTION

Inhalant abuse has been rampant in the United States population in the last 2 decades [1,2]. Commonly used domestic and industrial items including hair spray, spot remover, PC cleaner and glues have hydrocarbon constituents like dimethyl ether and hydrofluorocarbons. We present our patient who has a longstanding history of huffing dust off, (the propellant cleaner which has difluoroethane as the active hydrocarbon ingredient) who developed myopericarditis with systolic dysfunction. We also discuss the role of Cardiac Magnetic Resonance Imaging in diagnosing and prognosticating in these patients.

CASE PRESENTATION

Chief complaints

Chest pain, nausea and vomiting × 3 d.

History of present illness

A 25-year-old male patient with no prior medical history presented to the emergency department with chest pain, nausea and vomiting × 3 d. He described sharp, intermittent chest pain that is sub sternal, radiating to the back and left arm for last 3 d. His pain is worse upon leaning forward and worse with deep inspiration. He also had multiple episodes of nausea and vomiting with an episode of coffee-ground emesis. Patient reported long-term abuse of hydrocarbon containing inhalant (PC keyboard dust off) for the last 1 year. He used to huff 2 cans of dust off at the same time to achieve a hallucinogenic effect along with marijuana use. One week prior to admission, he reported increased use (10 cans/d).

Personal and family history

History of intracranial aneurysm rupture in father.

Physical examination

The patient's heart rate was 112 bpm, respiratory rate was 15 breaths per minute, blood pressure was 114/73 mmHg and oxygen saturation on room air was 99%. His body mass index (BMI) was 37 kg/m^2. Cardiac examination revealed a regular rate and rhythm, and no jugular venous distention with mild chest wall tenderness. Erythematous, non-scaling lesions were noted on the chest wall, arm and lips. Abdominal examination revealed right upper quadrant and bilateral flank tenderness.

Laboratory examinations

Initial laboratory evaluation showed leukocytosis (WBC-19.6 bil/L), acute kidney injury (Cr-3.4 mg/dL, BUN-54 mg/dL), elevated transaminases (AST-161 U/L, ALT-77 U/L), troponin-1.63 (ng/mL) peaked at 2.06 (ng/mL), CK-3000 ng/mL, CKMB-45 ng/mL. Urine drug screen was positive for cannabinoids. Initial electrocardiography (EKG) showed sinus tachycardia with diffuse inferolateral ST elevation, concerning for acute myopericarditis (Figure 1).

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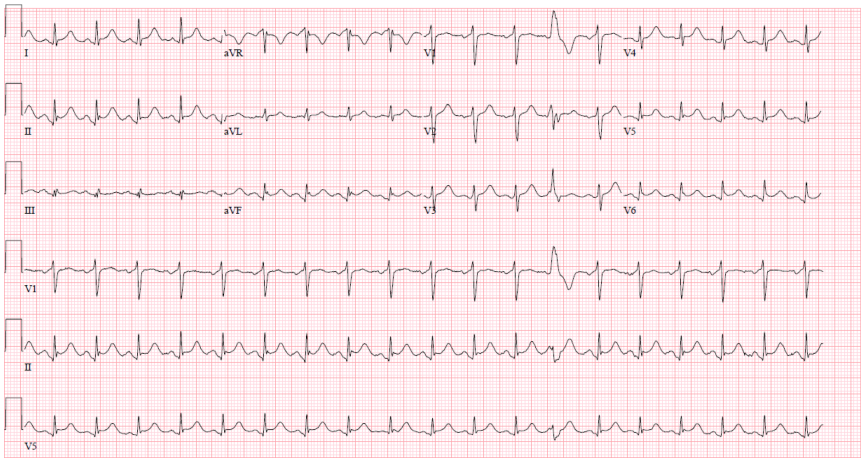


Figure 1 Electrocardiography showing diffuse inferolateral ST elevation without reciprocal ST depression, suggestive of pericarditis.

Imaging examinations

Echocardiogram showed left ventricular (LV) ejection fraction (EF) of 40% to 45% with severe aortic root dilation (5.0 cm) and trivial pericardial effusion. Given patient's elevated troponins, cardiac catheterization was performed. Coronary angiogram showed no evidence of coronary artery disease (Figure 2). Working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) was established and cardiac magnetic resonance imaging (CMR) was performed to evaluate the etiology further.

CMR

CMR showed borderline LV function with edema in the mid and apical LV suggestive of myocardial inflammation (Figure 3A and B). No delayed enhancement was seen in the myocardium or in the pericardium (Figure 4A and B). There was no evidence of pericardial effusion.

FINAL DIAGNOSIS

Based on the clinical presentation and imaging findings, patient was diagnosed with acute toxic myopericarditis secondary to hydrocarbon inhalant abuse. NSTEMI and MINOCA was ruled out based on coronary angiogram and CMR respectively.

TREATMENT

Supportive management for pain control was initially initiated. Once renal function improved, colchicine 0.6 mg b.i.d. was initiated for ongoing chest pain and EKG findings.

OUTCOME AND FOLLOW-UP

Repeat echo obtained 6 wk after the index presentation revealed EF of 60%.

DISCUSSION

Hydrocarbon compounds have been previously reported to have multiple cardiotoxic effects. Cates and Cook[3] reported a case of severe cardiomyopathy complicated by significant reduction in EF (25%) and torsades de pointes in the patient with history of huffing dust off. Interestingly, patient in this case report, recovered normal ventricular function prior to discharge. Samson *et al*[4] reported a similar case of inhalant abuse



Figure 2 Cardiac catheterization projections showing normal coronaries.

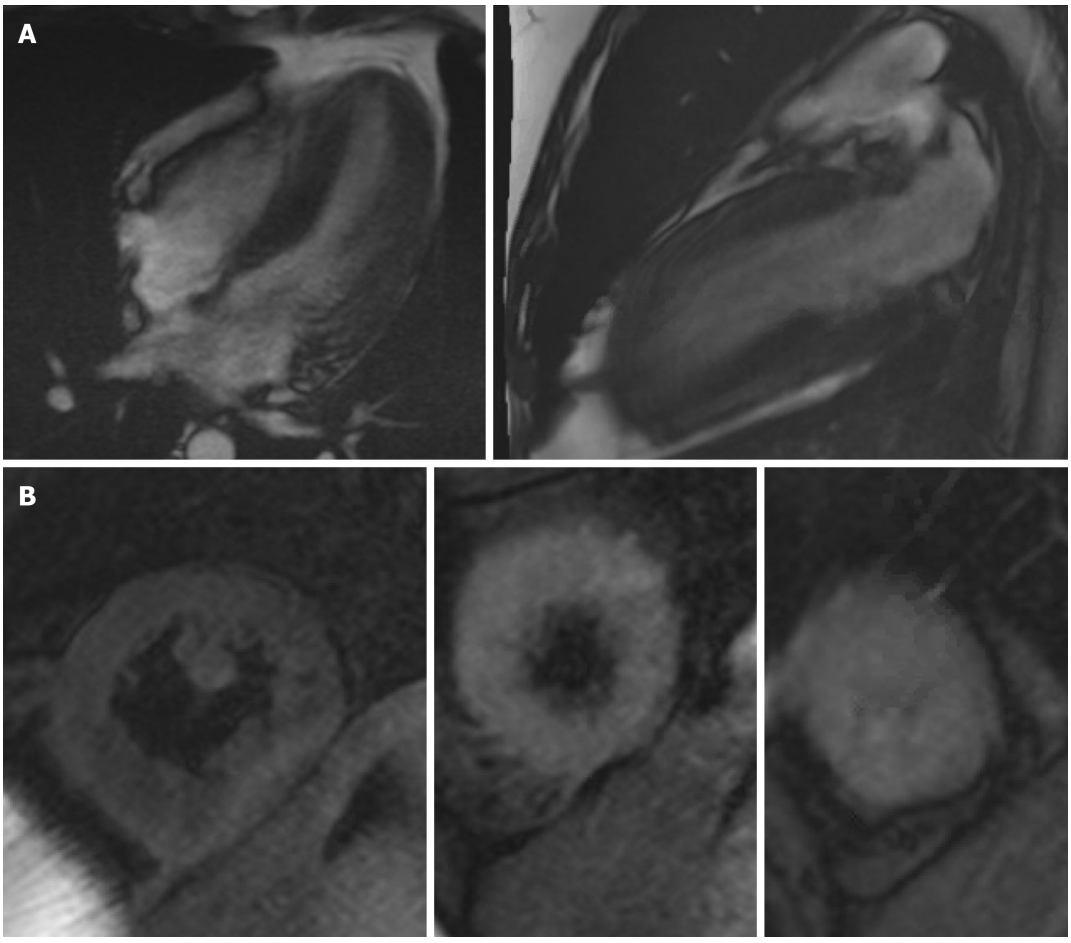


Figure 3 Cardiac magnetic resonance imaging. A: 4 chamber cine, 2 chamber cine showing EF of 40% with global hypokinesis; B: T2 Weighted images showing edema in mid and apical segments.

with severe reduction in EF on presentation, which improved prior to discharge. Cao *et al*[5] reported a case of NSTEMI without significant reduction in EF in a patient with air duster huffing. This patient was noted to have significant hepatic and renal injury, similar to our patient. Life threatening arrhythmias including ventricular fibrillation causing sudden cardiac death has been reported previously[6-8]. Toxic myopericarditis have been previously diagnosed in these patients[2]. Dinsfriend *et al*[2] reported a case of recurrent myopericarditis diagnosed in a patient with inhalant abuse with CMR. CMR showed edema and late gadolinium enhancement (LGE) in base and mid lateral wall and in the mid anterior wall.

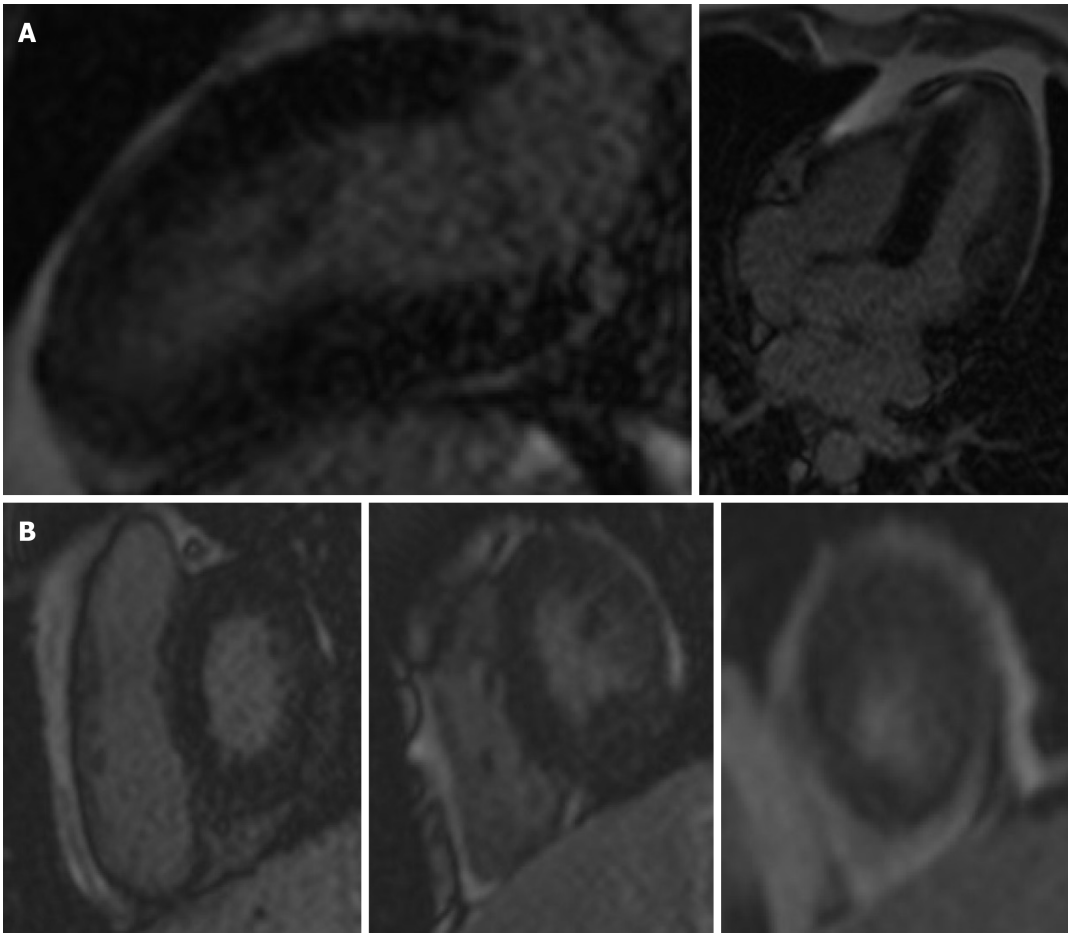


Figure 4 Cardiac magnetic resonance imaging. A: Absence of any late gadolinium enhancement in 4 chamber and 2 chamber; B: Absence of any late gadolinium enhancement in basal, mid and apical left ventricle on short axis.

Myopericarditis refers to an inflammatory process affecting the pericardium and myocardium[9]. Myopericarditis is diagnosed based on clinical features defining pericardial and myocardial involvement. Diagnosis of acute pericarditis involves presence of 2 or more of the 4 criteria: Pleuritic chest pain, pericardial friction rub, suggestive ECG changes (widespread ST segment elevation, PR depression) and new or worsening pericardial effusion[10]. Myocardial involvement is defined by elevated serum cardiac enzymes levels (creatine kinase-MB fraction, or troponin I or T), or new onset of focal or diffuse reduced LV function by echocardiography in the absence of evidence of any other causes[11]. CMR can be utilized to make diagnosis of myopericarditis. CMR diagnosis of myocarditis can be made based on the modified Lake Louise criteria[12]. The three diagnostic targets proposed using this criterion include edema, hyperemia and necrosis or scar. If CMR images indicate 2 out of 3 criteria, there is a high likelihood for acute myocarditis.

We report a case of patient with diffuse ST elevations, chest pain, decreased ejection on CMR in absence of any LGE. Our patient demonstrated early CMR finding in hydrocarbon toxicity manifested predominantly by low EF and edema in absence of LGE. Our patient had BMI of 37 with high low-density lipoprotein and positive family history of CAD. We ruled out coronary artery disease by doing cardiac catheterization however given the modest troponin rise and hydrocarbon toxicity, per recent European Society of Cardiology NSTEMI guidelines and class I recommendation on role of CMR in MINOCA, CMR was performed. CMR was useful in establishing presence of edema without any LGE[13]. This finding although nonspecific, points more towards, myocardial involvement. The absence of LGE provided excellent prognostic information[14]. CMR thus was helpful in diagnosis, prognosis and treatment in this case of inhalant toxicity.

CONCLUSION

Patients with inhalant abuse can have various cardiovascular manifestations. In patients with hydrocarbon toxicity with myocarditis, CMR can provide diagnosis, prognosticate the overall illness and give treatment options.

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OPINION REVIEW

Safety and efficacy of dual antiplatelet therapy after percutaneous coronary interventions in patients with end-stage liver disease

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Abstract

The prevalence of coronary artery disease (CAD) increases in patients with end-stage liver disease, with part of them receiving the percutaneous coronary intervention (PCI) as a treatment option. Dual antiplatelet therapy (DAPT), a standard of care after PCI, could result in catastrophic consequences in this population. Before PCI and the start of DAPT, it is recommended to assess patient bleeding risk. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Furthermore, conventional methods, such as the international normalized ratio, might not be appropriate in assessing individual bleeding risk. The highest bleeding risk among cirrhotic patients has a subgroup with severe thrombocytopenia ($< 50 \times 10^9$/L) and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above $> 50 \times 10^9$/L and prevent variceal bleeding. There is no solid evidence for DAPT in patients with cirrhosis. However, randomized trials investigating short (one month) DAPT duration after PCI with new drug-eluting stents (DES) in a high bleeding risk patient population can be implemented in patients with cirrhosis. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage. Finally, novel methods in assessing CAD severity should be performed to avoid unnecessary PCI and potential risks associated with DAPT. When indicated, PCI should be performed over radial artery using contemporary DES. Complementary medical therapy, such as proton pump inhibitors and beta-blockers, should be prescribed for lower bleeding risk patients. Novel approaches, such as thromboelastography and "preventive"

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upper endoscopies in PCI circumstances, warn clinical confirmation.

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Core Tip: Dual antiplatelet therapy (DAPT) is necessary after a percutaneous coronary intervention (PCI). However, it could result in severe consequences in patients with liver cirrhosis. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Patients with cirrhosis who have the highest bleeding risk are those with severe thrombocytopenia and elevated portal pressure. Despite the lack of solid evidence for DAPT in patients with cirrhosis, trials investigating one month of DAPT duration after PCI can be implemented in cirrhotic patients. Before PCI, functional assessment of coronary artery disease severity should be performed to avoid unnecessary interventions.

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INTRODUCTION

The prevalence of coronary artery disease (CAD) in patients with liver cirrhosis is estimated from 20% to 26%[1-3]. Furthermore, due to the growing incidence of cirrhosis caused by non-alcoholic fatty liver disease, which has overlapping risk factors with the CAD, an even higher prevalence of CAD in patients with cirrhosis can be expected[4,5]. The presence of both comorbidities can limit treatment options for each. For example, a patient can be rejected for surgical heart revascularization due to high operative risk or for the potential liver transplantation (LT) due to unresolved CAD. Percutaneous coronary intervention (PCI) with stent implantation represents a valid treatment option for CAD[6]. Data from the United States report that 1.2% of patients undergoing PCI have cirrhosis[7]. However, dual antiplatelet therapy (DAPT), a standard of care after stent implantation, can have severe consequences in cirrhotic patients with cirrhosis due to elevated bleeding risk.

This article aims to define; do all patients with liver cirrhosis have the same bleeding risk, the evidence behind DAPT in patients with cirrhosis, and what can be done to lower bleeding risk in such patients.

ARE ALL PATIENTS WITH CIRRHOSIS AT THE SAME RISK OF BLEEDING?

In the past, all patients with liver cirrhosis were classified as having high bleeding risk (HBR) due to coagulation abnormalities, thrombocytopenia, and elevated portal pressure-related complications. However, these presumptions are changing with growing evidence that, at least, part of patients with cirrhosis might have a high thrombotic risk[8,9]. Complex alterations in the hemostatic system cause so-called rebalanced hemostasis, meaning that impaired protein synthesis leads to a decreased level of procoagulant factors and anticoagulant factors[10,11]. The international normalized ratio (INR) is often used as a parameter for coagulation cascade competence in cirrhosis, although primarily invented for the warfarin dosing and not for the above mentioned[9]. The potential problem arises from the fact that it measures procoagulant factors but not anticoagulant factors such as protein C and S, which are also depleted in patients with liver cirrhosis[9,12]. Furthermore, it does not measure Factor VIII, whose levels are elevated in cirrhosis patients due to its endothelial

production[13]. Finally, studies that tried to "correct" INR using fresh frozen plasma or activated Factor VII, failed to reduce bleeding events[14-17]. Additionally, fibrinogen measurement has been proposed as a potential alternative to INR for assessing bleeding risk, although its clinical usefulness is yet to be confirmed[9].

The second risk factor for bleeding in patients with cirrhosis is thrombocytopenia, occurring in 64%-84% of patients with cirrhosis or fibrosis[18]. Its cause is multifactorial, with the most important being decreased production due to depressed thrombopoietin levels, splenic sequestration, and increased destruction[9,19-21]. However, a platelet count of > 50 × 10^9/L has been shown to be sufficient to maintain thrombin generation in *in vitro* studies[8,21-23]. This cut level has been recognized by McCarthy *et al*[24] in their opinion paper on management of DAPT in patients with thrombocytopenia, where they advise avoiding PCI in case of thrombocyte count < 50 × 10^9/L. Furthermore, in cirrhotic patients, platelet-induced anticoagulation changes are counterbalanced with the higher activity of endothelium-derived von Willebrand factor[8,9,25].

The third risk factor for bleeding in patients with cirrhosis are complications arising from portal hypertension, primarily esophageal varices[26,27]. The risk of variceal hemorrhage is related to variceal size, the severity of liver dysfunction (Child-Pugh B/C), and the presence of red wale marks on varices[28]. This issue had been recognized in a consensus document from Academic Research Consortium for High Bleeding Risk, in which they defined patients with cirrhosis and portal hypertension as having HBR after PCI[29]. Of note, in the same document, patients with thrombocytopenia (defined as < 100 × 10^9/L), irrespective of etiology, and those with chronic bleeding diathesis are likewise defined as having HBR. Finally, it is essential to emphasize there is no valid bleeding risk score for patients with liver cirrhosis. Most used Child-Pugh and Mayo End-Stage Liver Disease criteria are developed for predicting mortality and not bleeding events, despite having INR as an integrative part of both[30-32]. In summary, based on presented data, patients with the highest bleeding risk are those with severe thrombocytopenia (< 50 × 10^9/L) and those with portal hypertension.

WHAT IS THE CURRENT EVIDENCE REGARDING DAPT AFTER PCI IN PATIENTS WITH CIRRHOSIS?

Historically, due to the concerns for late stent thrombosis after drug-eluting stent (DES) implantation, DAPT was recommended for 12 mo after such procedures. Thus, patients with HBR, including those with liver disease, were excluded from most modern DES trials[29]. Therefore, implantation of a bare-metal stent (BMS) followed by one month of DAPT was recommended in those cases[29]. However, with DES technology advancements and stent thrombosis reduction, randomized trials in HBR patients have been performed. In the LEADERS FREE trial, almost 2500 patients were allocated to modern DES or BMS, followed by one month of DAPT. After one year of follow-up, DES implantation was superior to BMS concerning primary safety endpoint [a composite of cardiac death, myocardial infarction (MI), or stent thrombosis] [9.4% *vs* 12.9%; hazard ratio, 0.71; 95% confidence interval (CI): 0.56-0.91; P < 0.001 for noninferiority and P = 0.005 for superiority] with the lower incidence of clinically driven target lesion revascularization (5.1% *vs* 9.8%; hazard ratio, 0.50; 95%CI: 0.37-0.69; P < 0.001)[33]. Similarly, in ONYX ONE trial, which included 1996 patients, DES implantation was non-inferior to BMS (both with one month of DAPT) after one year of follow-up[34]. Even though both trials investigated patients with HBR, the prevalence of patients with liver disease/cirrhosis was < 1%, too small to extract conclusions in this patient population[33,34].

Several retrospective studies described and investigated outcomes after PCI in patients with liver cirrhosis compared to different patient populations, with only one of them more focused on antiplatelet management[4,7,35-38]. The largest of them was conducted by Wu *et al*[35], which included 914 cirrhotic patients who underwent PCI due to MI and compared them to a four times larger propensity-matched group of patients without cirrhosis. The cirrhosis group had significantly higher 1-year mortality (32.7% *vs* 23.7%, 95%CI: 1.28-1.74) but less recurrent MIs (6.0% *vs* 8.7%, 95%CI: 0.54-0.92). Importantly, cirrhosis group had non-significant increase in major bleeding (3.7% *vs* 2.9%, 95%CI: 0.87-1.23) and significantly increased gastrointestinal bleeding (28.0% *vs* 20.2%, 95%CI: 1.31-1.70). A sub-analysis showed significantly lower mortality and non-significant decreases in recurrent MI in the DAPT subgroup (duration of DAPT had to be > 3 mo) compared to cirrhotic patients on a single

antiplatelet agent. However, patients with a single antiplatelet agent were significantly older with significantly more severe comorbidities (such as heart failure and history of gastrointestinal bleeding), so direct comparison is questionable[35]. After PCI in patients with cirrhosis, worse in-hospital mortality than a historic non-cirrhotic group has also been described by Singh *et al*[7]. In the same study, patients with cirrhosis had worse outcomes if they received BMS instead of DES[7].

The two studies comparing PCI and medical therapy in CAD patients with cirrhosis found no difference in 1-year mortality and a higher bleeding rate[36,37]. Importantly, Krill *et al*[36] described a temporal change in bleeding events. The difference in bleeding was non-significantly different at 30- and 90-d follow-up (although higher in the PCI group) but become significant after 1 and 2 years. That might be associated with higher and extended use of DAPT in the PCI group (63% of patients had DAPT 1 year after PCI)[36]. Similarly, Russo *et al*[4] and Azarbal *et al*[38] described no significant difference in bleeding after PCI than medical therapy, although higher in the PCI group, in shorter follow up of 11 and 1 mo, respectively.

Finally, it is essential to emphasize that the studies mentioned above-included patients up to 2015, with consequent high use of BMS or old generation DES without new DAPT duration protocols.

In conclusion, "hard" evidence for DAPT in patients with liver cirrhosis is scarce. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage.

WHAT ARE POTENTIAL TOOLS THAT COULD BE USED TO ASSESS AND LOWER BLEEDING RISK?

Based on the aforementioned retrospective studies, PCI's usefulness in patients with liver cirrhosis regarding mortality is questionable due to high non-cardiovascular related mortality[36,37,39]. Therefore, appropriate triage of such patients before PCI, and consequent DAPT related bleeding risk, is mandatory. Based on data in the general population, PCI affects prognosis in patients presenting with MI and selected scenarios of a chronic coronary syndrome such as left main or proximal left anterior descending artery disease, a multi-vessel disease with impaired left ventricular systolic function, and a large area of myocardium at risk[6]. In our opinion, PCI is indicated in a patient with cirrhosis who presents with one of the mentioned scenarios if life expectancy, from the hepatological point of view, is reasonably long (one year) or other treatment modalities, such as LT are available. Except for the scenarios mentioned above, PCI of all significant coronary artery stenosis might be indicated before LT. This conclusion is based on retrospective studies that showed worse outcomes after LT in patients with CAD and increased mortality in multi-vessel CAD cases[40-42]. On the other hand, data from several studies indicate no impact of CAD on post-LT survival if CAD is treated appropriately, including PCI when indicated[43, 44]. All presented studies described CAD using plain angiography as the percentage of coronary artery stenosis (usually over 50%). Although this method is valid for CAD definition, more novel and precise methods, such as functional assessment of stenosis, should be done before PCI, especially in borderline stenosis and HBR patients[6]. Therefore, we advise the usage of instantaneous wave-free ratio or a similar method for confirmation of stenosis significance for all coronary artery stenosis estimated to be between 50%-90% as it not only affects prognosis but reduces the number of stents implanted compared to angiogram alone[6,45-47]. In the cases where PCI is indicated, it should be done with third generation DES, preferably with one tested for the short need for DAPT of only one month[6,33,34,48]. Another off-label option would be PCI using drug-coated balloons which has comparable results with modern DES primarily in small CAD (diameter ≤ 2.8 mm) and in HBR patients due to theoretical shorter usage of DAPT and lower risk for thrombosis as no foreign material remains in the artery[49-52]. We advise using the radial artery approach as default vascular access for all left heart catheterization due to better outcomes and lower bleeding risk than transfemoral access[6,53,54]. It also appears to be a safe option in patients with end-stage liver disease based on a single available study[55].

After the PCI, DAPT duration should be shortened in HBR patients, as advised by the guidelines, to three months after elective PCI or six months after PCI in acute coronary syndrome[56]. We also encourage clopidogrel usage compared to more potent P2Y12 inhibitors due to its lower bleeding risk[24,57,58]. A potential drawback of clopidogrel is that it requires activation in the liver[59]. However, a recent study

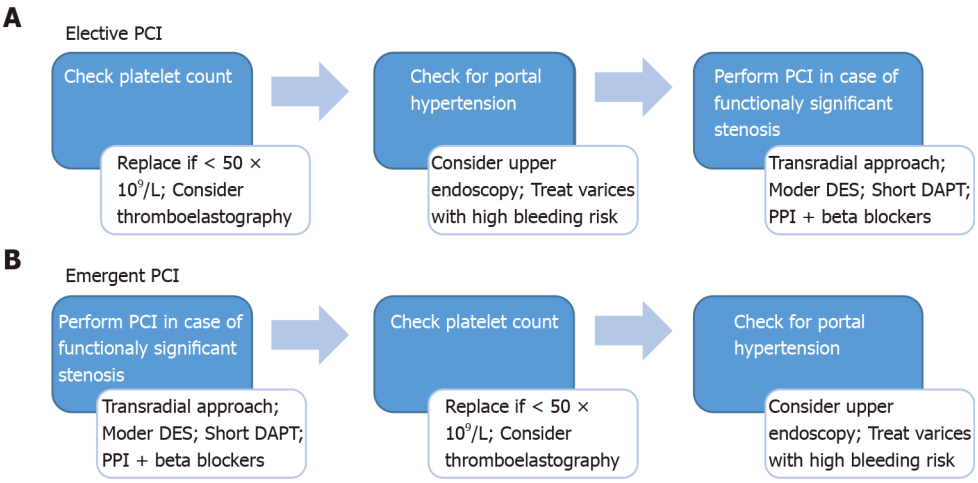


Figure 1 Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings. A and B: In case of elective percutaneous coronary intervention (PCI) (A), platelet count and portal hypertension work up should be performed (and treated) before the PCI. However, in emergent settings (B) above mentioned work up should be performed after the PCI. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy; DES: Drug eluting stent; PPI: Proton pump inhibitor.

described appropriately reduced platelet function after clopidogrel using thromboelastography (TEG), TEG-based platelet mapping, and impedance platelet aggregometry in patients with decompensated cirrhosis[60]. Importantly, no platelet function test has been studied for guiding DAPT in a patient with cirrhosis. On the other hand, TEG has been used to guide blood product use in various scenarios in patients with cirrhosis and impaired coagulation assessed using conventional methods (INR and platelet count)[61]. In randomized trials, TEG compared to conventional methods led to lower blood products use without an increase in bleeding complications in patients with bleeding varices and before invasive procedures[62,63]. Based on mentioned, TEG can theoretically be used to assess hemostatic pathways before administration of DAPT, with more freely DAPT usage in case of preserved hemostasis. However, these presumptions are supposed to be tested in clinical studies before widespread utilization.

Regarding medical therapy for preventing bleeding complications during DAPT, a proton pump inhibitor should be prescribed as it reduces upper gastrointestinal bleeding in patients with cirrhosis[36,64]. It is also most important to administer a maximally tolerated dose of beta-adrenergic blocking agents due to their positive effect on portal hypertension and CAD[28,65]. Lastly, we encourage repeat upper endoscopy in patients with liver cirrhosis before elective PCI or early after urgent PCI to manage varices according to recommendations for primary and secondary prophylaxis of variceal bleeding, as previously proposed[4,28].

In summary, PCI in patients with cirrhosis should be done over trans-radial artery access, using novel DES (with proved safety in short DAPT protocols), in cases when PCI is proved to affect patient prognosis. Along with DAPT, concomitant medical therapy that reduces the risk of bleeding should be administered. Novel approaches, such as TEG or "preventive" upper endoscopies, although promising, warn clinical conformation. Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings is presented in Figure 1.

CONCLUSION

The highest bleeding risk among patients with liver cirrhosis is present in a subgroup of patients with severe thrombocytopenia and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above > 50 × 10^9/L and prevent variceal bleeding. Despite the lack of solid evidence for DAPT in patients with cirrhosis, results from trials investigating shorter DAPT duration after PCI in HBR patient population can be implemented in patients with cirrhosis. Finally, novel methods in the assessment of CAD severity should be performed to avoid unnecessary PCI.

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REVIEW

Cardiac monitoring for patients with palpitations

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Abstract

Palpitations are one of the most common reasons for medical consultation. They tend to worry patients and can affect their quality of life. They are often a symptom associated with cardiac rhythm disorders, although there are other etiologies. For diagnosis, it is essential to be able to reliably correlate the symptoms with an electrocardiographic record allowing the identification or ruling out of a possible rhythm disorder. However, reaching a diagnosis is not always simple, given that they tend to be transitory symptoms and the patient is frequently asymptomatic at the time of assessment. In recent years, electrocardiographic monitoring systems have incorporated many technical improvements that solve several of the 24-h Holter monitor limitations. The objective of this review is to provide an update on the different monitoring methods currently available, remarking their indications and limitations, to help healthcare professionals to appropriately select and use them in the work-up of patients with palpitations.

Key Words: Palpitation; Cardiac monitoring; Electrocardiogram; Loop recorder

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Core Tip: In recent years, electrocardiographic monitoring systems have incorporated many technical improvements that solve several of the 24-h Holter monitor limitations. This review provides an update on the different electrocardiographic cardiac monitoring methods currently available, remarking their indications and limitations, to help healthcare professionals appropriately select and use them in the work-up of patients with palpitations.

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INTRODUCTION

Palpitations are one of the most common reasons for medical consultation and can occur in up to 10% of the population at some point in their lives[1-3]. They tend to worry patients and can affect their quality of life. They are a symptom that is frequently associated with cardiac rhythm disorders, although there are other etiologies[4] (Table 1). In fact, in up to half of the cases, palpitations are not due to a significative arrhythmia[2].

Having an accurate diagnosis is important to determinate the prognosis, to guide treatment and to plan the patient's follow-up. In order to have a diagnosis, it is essential to be able to reliably correlate the symptoms with an electrocardiographic record allowing the identification or ruling out of a possible rhythm disorder. However, reaching a diagnosis is not always simple, given that they tend to be transitory symptoms and the patient is asymptomatic at the time of assessment[1,5].

Electrocardiographic monitoring systems are a first-line tool in assessing these patients. The introduction of the 24-h Holter monitor within 60 s was a true revolution and its use rapidly became widespread[6]. Other than diagnosing palpitations, it has also been an important tool in understanding the physiological cardiac rhythm behavior[7,8] and in the follow-up of patients at risk of cardiovascular disease[8], in syncope work-up[9-12], in risk stratification of certain patients[13-16] or in the detection of silent arrhythmias[8,17-21]. Due to its high availability and probably due to a certain degree of tradition, it is the monitoring system most commonly used by most doctors. However, it has several limitations that reduce its efficiency and diagnostic yield[2,22].

Fortunately, in recent years, in line with the overall technological development that our society has experienced, electrocardiographic monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-h Holter monitor. This evolution of electrocardiogram (ECG) recording systems has occurred in various directions. On the one hand, we have the improvement in the quality and quantity of recordings, such that, at the present time, it is possible to obtain 12-lead ECG traces of excellent quality with increased monitoring time, be it in the form of a continuous recording (which can last up to a month), or in the form of intermittent recordings which can last up to 3 years in the case of implantable recorders[8,23-25]. On the other hand, various recording and analysis algorithms have been developed, which allow for many improvements; for example, the automatic analysis of arrhythmias[18,23]. Remote data transmission systems have also been incorporated with multiple designs able to adapt to each patient's different needs[8,24,26].

Unfortunately, these new devices are still not universally incorporated into daily clinical practice, either because they are not included or reimbursed in the healthcare systems, or due to the inertia of healthcare professionals[27]. In the work-up for palpitations, it is still usual to apply a traditional strategy that is fundamentally based on the use of a 24-h Holter monitor, which has low diagnostic yield on many occasions[2,22]. This lack of yield is due to the fact that the majority of the events to be diagnosed are paroxysmal ones that occur occasionally and unexpectedly. The use of standardized diagnostic protocols with the application of new electrocardiographic monitoring devices has been shown not only to markedly improve the diagnostic yield, but also to

Table 1 Principal cardiac and noncardiac causes of palpitations

	Cardiac and noncardiac causes
Cardiac arrhythmias	Premature contractions (supraventricular or ventricular)
	Supraventricular tachycardia (AF, flutter, AVRNT, *etc.*)
	Ventricular tachycardia
	Severe bradyarrhythmia/AV block
	Pacemaker mediated tachycardia
Structural heart disease	Severe aortic regurgitation
	Hypertrophic cardiomyopathy
	Congenital heart disease with significant shunt
	Mechanical prosthetic valves
Systemic causes	Thyroid dysfunction
	Pheochromocytoma
	Anaemia
	Fever
	Hypoglycaemia
	Arteriovenous fistula
	Autonomic dysfunction
Psychosomatic disorders	Anxiety
	Somatisation disorder
Drugs	Sympathomimetic agents (bronchodilators, antidepressants)
	Vasodilators (hydralazine, doxazosin)
	Recreational: Cocaine, alcohol, amphetamines, cannabis

AVRNT: Atrioventricular nodal re-entry tachycardia; AF: Atrial fibrillation; AV: Atrioventricular.

be clearly cost efficient[2,28-30].

However, it should also be noted that the new devices are not exempt from limitations. Some are related to patient tolerance, either due to the possibility of relative discomfort, the need to wear external devices with electrodes stuck to the skin, or because the implantable devices require a minor surgical procedure, meaning that certain patients may not accept them[8,24,27]. Also, the devices continue to record a significant number of artifacts or rhythmic abnormalities that are not pathological or significant, which inefficiently lengthen the interpretation time of the studies and can even saturate the memory of certain devices. In addition, it should be noted that for a suitable diagnosis to be made, not only is it important to have recorded a quality electrocardiographic trace; the latter must also be properly interpreted in the patient's clinical context, which requires sufficient skill on the part of the healthcare professional interpreting the trace[31].

The objective of this review is to offer an update on the different monitoring methods currently available, their indications and limitations, to help healthcare professionals appropriately select and use them in the work-up of patients with palpitations.

ELECTROCARDOGRAPHIC CARDIAC MONITORING DEVICES

Device classification

The monitoring devices available on the market have differing characteristics. Traditionally, these devices have been classified into three or four groups [24/48-h Holter, external prospective event recorders (PERs), loop recorders (LRs)] based on a series of shared characteristics[8,27] (Table 2). However, thanks to technical develop-

Table 2 Main advantages, limitations, and indications of the most commonly used models of cardiac monitoring devices

	Advantages	Disadvantages	Main indications
24 h Holter	Continuous recording	Discomfort for the patient	Very frequent (daily) symptoms
	12 leads with good correlation with surface ECG	Artefacts	Permanent AF rate monitoring
	Low economic cost	Maximum recording of 24-48 h (low diagnostic yield)	Frequent ventricular premature beats
			Risk stratification of (hypertrophic) cardiomyopathies
Skin patches	Continuous recording of 7–14 d	Single use and greater economic cost	Frequent (weekly) symptoms
	Good tolerability for patients	Analysis by external companies	AF detection in cryptogenic stroke (2 wk)
		Only one lead[1]	
External loop recorders	Loop recording (includes beginning and end of arrhythmic event)	Patient discomfort	Occasional symptoms (monthly)
	4 wk monitoring	Requires education from healthcare professional on how to correctly place the electrodes	AF detection in cryptogenic stroke (2–4 wk)
	High yield and efficiency in the assessment of palpitations		
Implantable loop recorder	Loop recording	Invasiveness and associated complications (infection, bleeding, *etc.*)	Very infrequent symptoms
	Up to 3-yr monitoring (good diagnostic yield)	Individual economic cost	AF detection in at-risk patients (cryptogenic stroke, post-ablation, *etc.*)
	Patient does not have to do anything	Single lead	Syncope
	Remote monitoring		
External event recorders/mobile devices	Easy access for the general population	Single lead[1]	Palpitations work-up
	Possibility of prolonged use (years)	Data management	Population AF screening (not validated)
	Screening for asymptomatic events (AF screening)	Patient has to be involved (not suitable for syncope work-up)	
	Remote monitoring		

[1]There are devices with more leads.

AF: Atrial fibrillation; ECG: Electrocardiogram.

ments in recent years, the devices have gained in functionality and taken on new properties, making it difficult to establish a strict, closed classification. For this reason, some devices will have mixed characteristics between two groups (or will be able to be used in one or other manner according to the patient). Despite this, we should mention some of the most differentiating characteristics allowing a device and specific model to be classified (Figure 1). These characteristics must be considered when indicating the device that best suits each patient.

They may, thus, be classified according to the following.

(1) Monitoring time. There are short recording devices (24–48 h) that are useful for the examination of symptoms that occur every day or frequently; mid-range recording devices (up to 4 wk) and long recording devices (up to 3–4 years)[32]. Due to limitations of data storage, when we increase the monitoring time of the devices, they switch from continuous to intermittent recording, as will be discussed later. To achieve appropriate diagnostic yield in the work-up for palpitations, it is essential to adjust the monitoring time to the frequency of the symptoms. This is, without a doubt, one of the main characteristics when selecting a device.

(2) Recording type. This is another important characteristic to be kept in mind when selecting the most suitable test for each patient type. On the one hand, continuous recording devices such as Holter monitors make a constant ECG recording that can

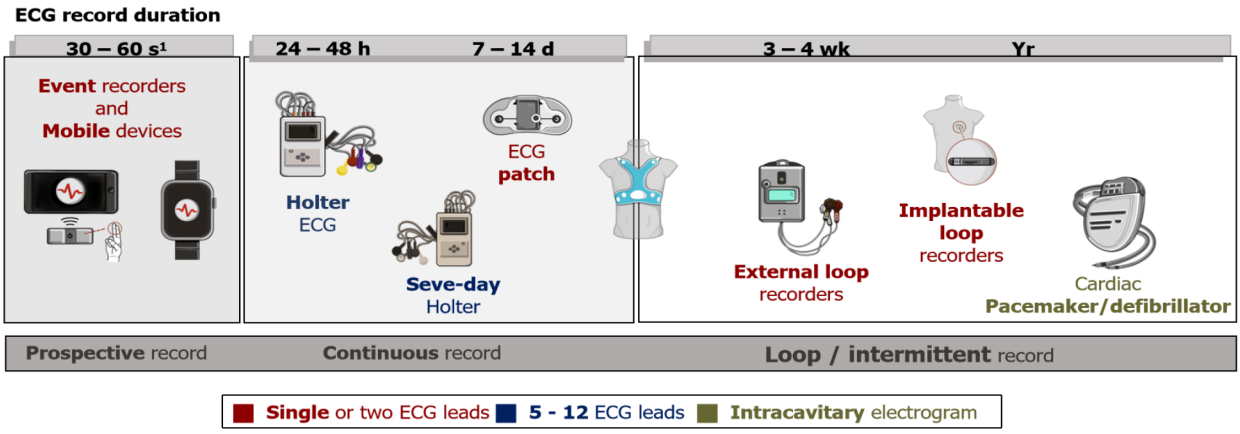


Figure 1 Main electrocardiographic monitoring devices available according to electrocardiogram recording duration and type and number of derivations. [1]While they prospectively register 30–60 s, they may be used repeatedly on a long-term basis. ECG: Electrocardiogram.

later be reviewed in its entirety. Continuous recordings avoid information loss since they do not depend on activation by the patient or on arrhythmia detection algorithms. By contrast, tests using intermittent recording are patient-activated or activate automatically according to different arrhythmia detection algorithms. There are two distinct types of device with this characteristic: Loop recorders [external LRs (ELRs) or implantable LRs (ILRs)] and PERs. The main difference between them is the ability of the LR to record the trace both prospectively and retrospectively, allowing us to obtain the trace from the start of the event (which may be important for the precise diagnosis of certain arrhythmias) (Figure 2). Similarly, LRs have various algorithms allowing for the automatic recording of certain asymptomatic arrhythmias, which prospective recorders do not allow for, since they are only activated by the patient in the event of symptoms (as such, they are also not useful for syncope work-up)[17,32,33]. It should be noted that there are currently certain devices available with continuous recording capacity as well as off-line analysis software with detection algorithms for arrhythmias that present the information in a similar manner to event recorders (although the healthcare professional can review the rest of the recording if this is considered important)[19,34,35].

(3) Number of leads. Recordings range from systems with just one lead to full 12-lead ECGs in the devices with the most leads. It is important to keep in mind that, the greater the number of leads, the more memory the device will use. In addition, there will be a greater number of electrodes to be applied by the patient in order for the recording to be made. As such, as a general rule, the devices allowing for long monitoring times offer a limited number of leads. However, having more than one lead is often useful. For example, on occasion, it allows for the clearing up of doubts as to whether a lead is subject to artifacts (Figure 3) or to better assess the wave morphology, which is important on certain occasions[8,36,37].

(4) Degree of invasiveness. There are implantable and external devices. ILRs require a minor surgical procedure, but once the wound has healed, patients do not usually notice them, and they allow for prolonged monitoring[17,25].

(5) Connectivity. The most up-to-date devices incorporate connectivity systems that allow for remote monitoring. Some can even be linked to smartphones, allowing for the easy sharing and sending of recordings *via* the Internet or Bluetooth[26,32,38,39]. In addition, some applications have algorithms that offer the patient an instantaneous diagnosis of their arrhythmia (although it is recommended that this is ratified by a healthcare professional)[18,40,41].

(6) Automatic algorithms. Different recording and analysis algorithms have been developed in recent years and they have been incorporated into some devices. Most of these algorithms allow for the automatic analysis of arrhythmias such as atrial fibrillation (AF), bradycardia, or asystole, but some of them also allow for the filtering out of noise to try to improve recording quality. There are differences between the algorithms that different brands incorporate into their devices. It is important to evaluate not only the algorithms that they provide, but also their sensitivity and specificity for detecting each type of arrhythmia. All of them should have type I and type II errors, but there may be significant differences depending on the device. Therefore, when selecting a monitoring device, physicians should also consider the accuracy of these algorithms.

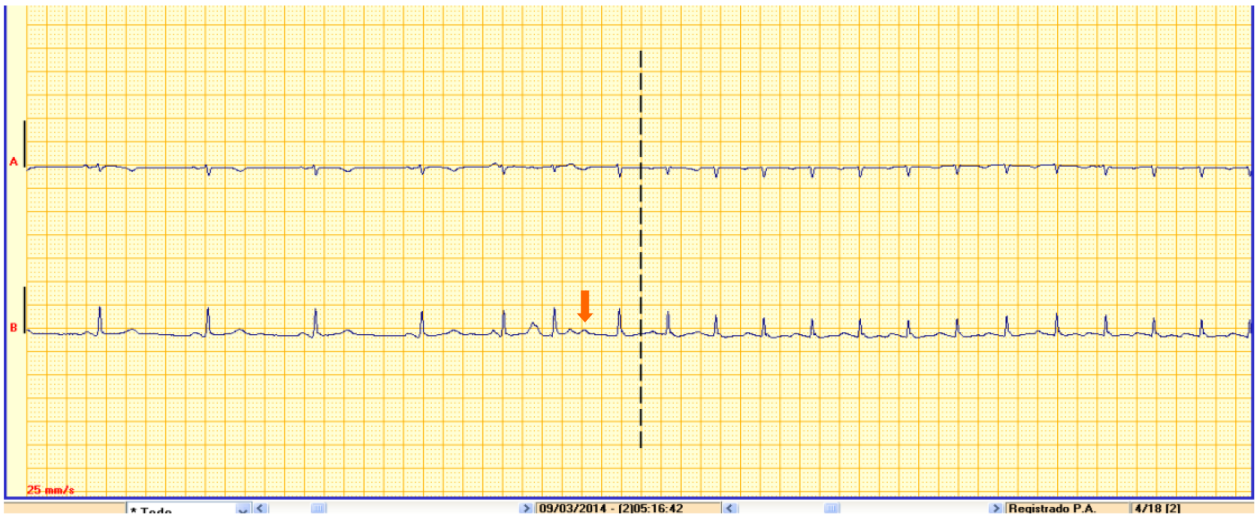


Figure 2 Example of an electrocardiogram trace obtained with an external loop recorders in a patient with palpitations. The beginning of a supraventricular tachycardia (SVT) is observed. A premature atrial beat that conducts with long PR seems to be the trigger of the SVT. This finding is highly suggestive of atrioventricular nodal re-entry tachycardia.

(7) Recording system type used. Initially, most devices used adhesives with electrodes. This is still the most common used format, although others have been developed that can record the cardiac signal, such as patches, belts or vests[8,24]. There are also devices that do not need to be in constant contact with the patient which incorporate electrodes into the recorder's own case, which are brought close to the skin when a recording is desired[42-44].

(8) Availability of other biological signals. In addition to recording the electrocardiographic trace, some devices have sensors that allow other biological signals to be monitored, such as physical activity, bodily position, oxygen saturation and even the presence of apnea[39,45,46].

Main electrocardiographic monitoring devices available

As noted above, there is currently a wide variety of monitoring devices offering a combination of characteristics, which makes it difficult to perform a strict classification. However, it is still useful to differentiate certain major groups (Figure 1 and Table 2), in the knowledge that certain models may have mixed characteristics between two groups or may be used in different ways as appropriate *(e.g.,* there are devices that can function as a 24-h Holter monitor, a continuous 3-wk Holter or a loop recorder) .

Continuous Holter (24/48-h): This takes its name from the cardiologist Norman J. Holter, who developed this technology in 1961. It is currently the most common technique used in clinical practice[47]. Currently, most Holter devices consist of a lightweight recorder with a digital memory card and a series of cutaneous electrodes that obtain a continuous ECG recording. They allow for 24-48-h monitoring time in most cases, although there are devices with recording capacities of up to 7 d.

Originally, the recording was made up of only two or three leads and, still today, many tests are carried out in this way. However, as early as 1966, the first 12-lead Holter monitor was developed with a system of 10 electrodes arranged over the patient's torso. Later on, a simplified five-electrode system was developed (the EASI system) which allowed for the reconstruction of 12 leads with good clinical reliability [48]. Having 12 leads may be especially important when assessing certain arrhythmias, such as the morphology of ventricular extrasystoles or certain repolarization patterns which may only appear in one specific lead. Torso electrodes avoid possible artifacts and discomfort associated with the positioning of the electrodes on the limbs. However, it should be noted that this arrangement attenuates the amplitude of the inferior leads and generates a slight right cardiac axis deviation[48], and some recordings obtained with torso leads cannot be considered completely equivalent to standard ECG leads[8].

After completing the recording, it is transferred into software installed on a computer (and/or a server in the cloud in some of the more advanced devices), which usually allows for an initial automatic analysis identifying the QRS complexes and the

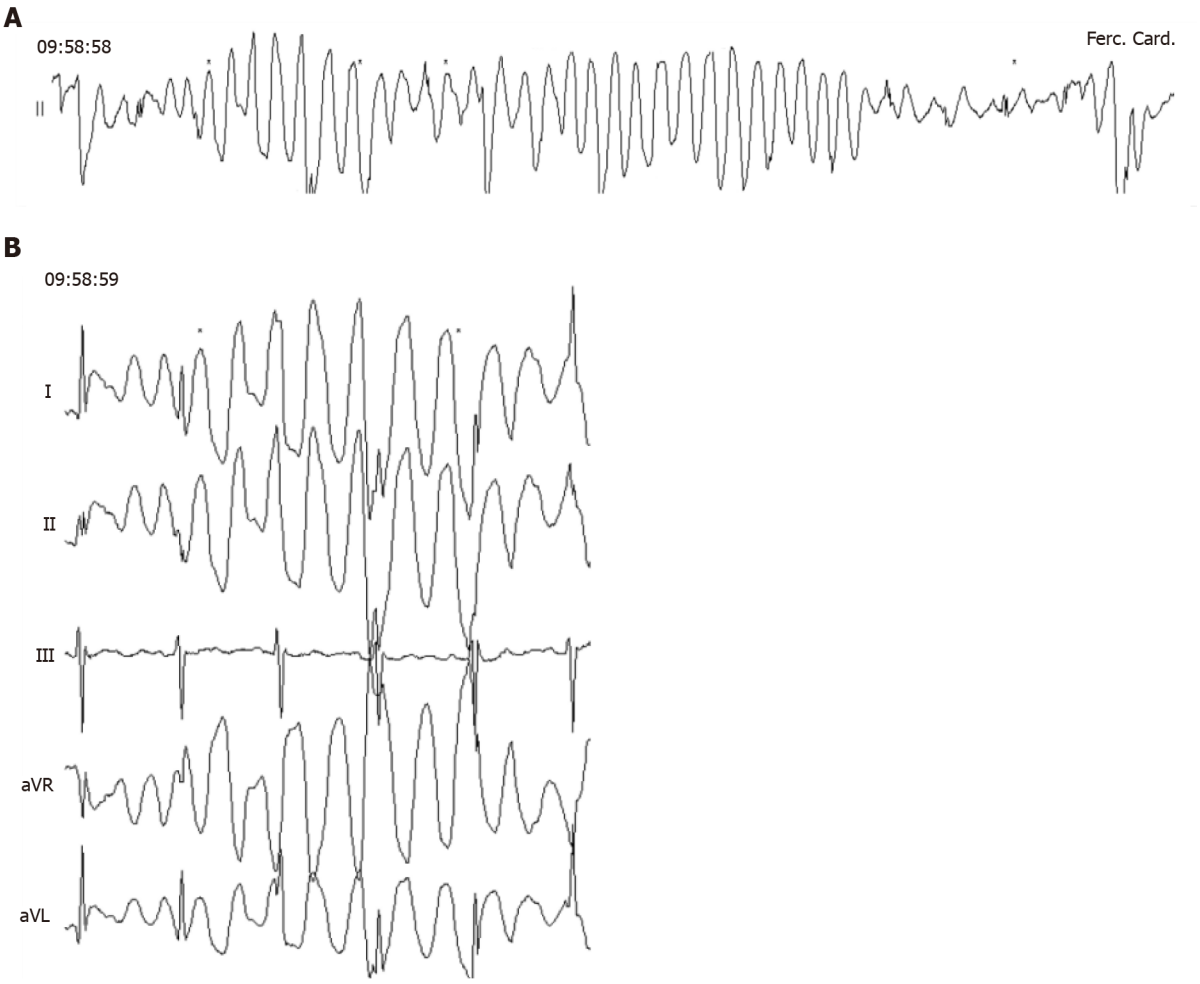


Figure 3 Example of an electrocardiogram tracing obtained with a Holter monitor with single-lead or multiple leads. A: A polymorphic trace is apparent with a single-lead record; B: After checking the other leads, the artifact can be easily identified.

R-R interval to offer values such as maximum/minimum rate, histograms of rate or ST segment analysis. Finally, the healthcare professional must review the data to rule out the presence of possible artifacts and interpret the results of the ECG taking into account the patient's symptom diary[47].

Holter monitors have demonstrated their utility in identifying arrhythmias in patients with palpitations or syncope with different efficacy values in line with the pretest probability of the population studied and the frequency of the symptoms[2,22,28]. In recent years, various case series, including our own[2,32], have shown that the global diagnostic yield of Holter monitors is limited and that, despite the fact that its cost is generally relatively low, its per-diagnosis cost is high[22,27,47]. For example, in a transversal study in usual clinical practice carried out by our group, Holter only offered a diagnostic yield of 3.5% for syncope and 16.5% for palpitations. This yield is even lower when the objective is screening for asymptomatic arrhythmias, such as AF in the context of cryptogenic stroke, where the yield can be < 1%[32].

Among other indications that have been considered, there was risk stratification in certain groups of patients, either through the detection of nonsustained arrhythmias and abnormalities of heart rate variability parameters or dispersion of the QT interval [15,49-53]. However, at the present time, few therapeutic decisions are based on Holter findings, perhaps with the exception of the presence of nonsustained ventricular tachycardia in patients with hypertrophic cardiomyopathy[15], which may be a decisive factor for the implantation of an implantable cardiac defibrillator.

In our opinion, in the work-up for palpitations at the present time, the 24/48-h Holter monitor should only be considered in patients with daily or very frequent symptoms. When this is not the case, there are other tools available that offer not only a greater diagnostic yield, but also better cost efficiency[2,39,54].

Skin patches: These systems, which were developed over the past decade, enjoy a certain degree of popularity in some countries. However, in others, such as Spain, their

use remains marginal. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads for 7–14 d' monitoring. The device itself acquires, amplifies and filters the ECG signal, which is then telematically transmitted for analysis (usually through an external company)[8,24,55].

There are different patch models with different recording characteristics. In some cases, they are similar to a Holter monitor and in others to an ELR. For example, the ZioPatch creates a continuous ECG recording with a single lead that is interpreted *via* an analysis platform. It also has a symptom button on the patch itself[56,57]. Another different example is the NUVANT-Piix. It also has only one lead, but it does not perform a continuous recording; rather, it only records the traces identified as arrhythmias or when the patient experiences symptoms and activates the device with a special magnet[58].

There are studies comparing the efficacy of these new patches with traditional Holter monitors (Table 3), showing good tolerability on the part of patients and a greater diagnostic yield, particularly for the purposes of identifying paroxysmal AF [56,59]. However, these devices have a higher cost and are usually single use[8,56].

In this section, we can also include the so-called "textrodes", which are electrodes included in garments[34]. These devices are currently in a more experimental phase. One of the main problems they entail is the quantity of artifacts due to movement of the fabric. In this regard, studies are being carried out to select the best material and electrode positioning within the fabric[60,61].

Prospective external event recorders (without loop memory) and mobile devices: These tend to be small devices with a couple of electrodes incorporated into them, which allow, when activated by the patient, for a real-time recording of 30–60 s of a single ECG lead[8,24,41,44]. These devices allow for the recording of episodes of palpitations that are sufficiently long for the patient to have time to apply the recorder. However, they have the limitation of not allowing for the recording of the start of the episodes, which is frequently important for diagnosis when it comes to interpreting the mechanism of arrhythmias[32,39] (Figure 2). Similarly, their use is not appropriate for syncope work-up, because if the patient applies the device having recovered from the syncopal episode, in most cases, the possible cause of the syncope will have disappeared[10].

In recent years, these devices have become popular, since they are small devices that do not have to be constantly in contact with the patient and allow for prolonged use (even years, since the batteries can be recharged and they only record when activated), as well as having a relatively low cost. There are currently numerous models from different brands, with various designs. In addition, some of these models link to or are even included as tools belonging to smartphones or smartwatches (such as the Apple Watch), which allows for greater and easier access for the general public[24,40]. Indeed, a significant number of users, especially those of smartwatches, have no medical indication, which may also be controversial[62].

In most models, the recordings are stored in the device itself or in a linked mobile phone. Many incorporate their own algorithms which allow for the identification of certain types of arrhythmia (especially AF), and offer the option of being sent to health centers for interpretation[40,41,44].

Due to their simple use and accessibility, these applications' utility for other indications such as population AF screening (most useful in patients aged > 65 years) [63,64] or also for the detection of cardiac ischemia has been analyzed[65-67], which could facilitate diagnosis in patients who live far away from health centers. New mobile devices are also being developed (they are not yet on the market) which obtain an ECG signal from the patient on an involuntary basis while the devices are being used as normal, which would allow for the intermittent detection of asymptomatic cardiac rhythm disorders[44,63,64,68].

LRs: These allow for more prolonged monitoring, since they do not store a continuous recording[2,49,69]. Even though they continuously monitor the ECG, the device only stores it in its memory for a few minutes before subsequently overwriting it with a newer recording (initially it was an endless circular tape, although the devices are now digital). Only when the device is activated (either *via* manual activation or an automatic arrhythmia detection algorithm), it records on another part of the memory (where it will not be deleted and can be reviewed) the recording from a few minutes before the start of the event until its end. In this way, since several minutes before activation are stored in the device memory, the likelihood of recording the trace at the time of the syncope episode (if it is activated for syncope), or the start of the episode of

Table 3 Summary of relevant studies on diagnostic yield for palpitations according to the different types of devices

Ref.	No. of patients	Study design	Study population	Duration of monitoring	Diagnostic yield	Other findings
Holter 24 h						
Sulfi *et al*[22], 2008	2688	Retrospective cohort	Palpitations and basal sinus rhythm	24 h	16%	Even less diagnostic yield in patients aged < 50 yr
Paudel *et al* [103], 2013	335	Single-center prospective cohort	Palpitations	24 h	75%	40% of patients with ventricular ectopy considered as diagnostic finding (possible selection bias)
ECG patchs						
Barrett *et al*[59], 2014	146	Prospective cohort comparing Patch *vs* 24 h Holter	Palpitations	15 d	60% more diagnostics than 24 h Holter	Over 90% of patients were comfortable with it. Best diagnostic yield during first week
Event recorders						
Narasimha *et al* [104], 2018	38	Prospective cohort comparing Kardia Mobile *vs* ELR (simultaneously)	Palpitations (less often than daily but more than monthly)	14–30 d	89.5% *vs* 68% in ELR group	Better compliance with Kardia Mobile
Hall *et al*[63], 2020	11 studies (> 20000 patients)	Systematic review	AF screening in general population	Heterogeneous	Up to 36% (depending of population's AF burden)	More diagnostic yield in people aged > 65 yr. Approximately 4% of uninterruptable registries
ELR						
Locati *et al*[54], 2016	392 (282 with palpitations)	Prospective cohort	> 2 episodes in last year	4 wk	71.6%	Early recorder use increase diagnostic yield. Diagnostic yield for syncope: 24.5%
Francisco-Pascual *et al*[2], 2019	149 (91 in ELR group)	Prospective ELR cohort compared with historical Holter cohort	> 2 episodes in last year	21 d	86.8%	Holter diagnostic yield: 20.7%. ELR reduce the cost *per* diagnosis
ILR						
Giada *et al*[29], 2007	50 (26 in ILR group)	Prospective cohort comparing ILR with conventional strategy	1 episode *per* month or less (longer than 1 min)	321 d (mean)	73%	Mean time to diagnosis: 279 d. Lower cost *per* diagnosis in ILR group
Padmanabhan *et al*[83], 2019	312 (51 with palpitations)	Prospective cohort of consecutive patients with an ILR implanted	Any indication form monitoring (16.3% due to palpitations)	579 d (mean)	64.7%	38.7% useful in ruling out an arrhythmic cause for symptoms (all indications). 12% AF.

ELR: External loop recorders; AF: Atrial fibrillation; ILR: Implantable loop recorders.

palpitations, is high[2,54,70,71].

At the present time, most LRs can record symptomatic arrhythmias after activation by the patient, usually in the context of symptoms, or silent arrhythmias on an automatic basis[25]. Within this category, we differentiated between external and implantable devices.

(1) ELRs: External event recorders are characterized by a loop memory, which uses cutaneous electrodes to record, be this in the form of independent electrodes or those integrated into a t-shirt. The patients themselves position the electrodes daily[8,25].

Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3–4 wk, although there are reports of more prolonged periods). They are useful for the investigation of symptoms that occur every 2 or 3 wk. It should be noted that palpitations usually occur more frequently than syncopal episodes, hence the diagnostic yield for palpitations is approximately 80% [2], whereas in cases where it is indicated for syncope, it is no greater than 10%[54,72-74] (Table 3).

The quality of the recordings tends to be good, although there may be a not insignificant number of recordings corresponding to an artifact. Another limitation may be patient adherence to the daily positioning of the electrodes, even though this is

generally good, as well as the possibility that the patient may develop an allergy to the electrodes, even though this is rare[54,72].

In the investigation of palpitations, in addition to a high diagnostic yield, it allows for improved cost efficiency in the work-up of these patients[2,73]. A recent study by our group[2] compared the use of ELRs with a conventional Holter strategy in patients with more than two episodes of palpitations *per* year. We were able to demonstrate that investigation in the form of a diagnostic protocol, including that the use of an ELR, had a notably superior diagnostic yield (86% *vs* 21%) and offered a significant reduction in per-diagnosis cost (€375.13 in the ELR group and €5184.75 in the control group ($P < 0.001$). The cost-effectiveness study revealed that the systematic use of ELRs resulted in a cost reduction of €11.30 for each percentage point of increase in diagnostic yield.

Another usual clinical application of these devices is in patients with stroke of unknown etiology. It has been demonstrated that the use of these devices in patients with cryptogenic stroke, compared with the usual strategy of conventional follow-up and 24- or 48-h Holter monitoring, increases the detection rate of silent AF, allowing oral anticoagulation to be started in a greater proportion of patients and at an earlier stage[19,49,75-77].

(2) ILRs: These are small devices that are implanted subcutaneously, usually in the left parasternal region[8,25]. These devices allow for a more prolonged continuous monitoring of up to 3 to 4 years. They offer a single-lead ECG recording. The patient can activate the device when symptoms are experienced using a small remote control or through a smartphone application. Like the external devices, they use automatic arrhythmia detection algorithms[18,33]. The devices available on the market also offer a platform for remote monitoring of the events recorded, sometimes also with data transmission to the patient's mobile[20,26,32].

They have the disadvantage of being minimally invasive, since the latest models have been made significantly smaller. They require a brief surgical procedure for their implantation. There are complications in a small percentage of patients requiring the device to be withdrawn, ranging from local infection/hematoma to intolerance[78,79]. Another limitation is the price of the device, which is significantly greater than that of ELRs[25,29].

In recent years, there has been abundant literature on the diagnostic yield of implantable recording devices. The greatest experience with this kind of device concerns patients with syncope of unknown etiology[10-12], given the long monitoring time that they offer, with diagnostic yield figures around 35%[9,18,30,70]. There are also numerous papers analyzing the role of ILRs in patients with stroke of unknown etiology, and, as with ELRs, it has been shown that the strategy of implanting an ILR leads to a greater and earlier diagnosis rate than following a conventional strategy[49, 80]. They are also used in risk stratification and follow-up of certain patients[13-16,81, 82]

In the field of palpitations, their use has been more limited due to their cost and the availability of noninvasive and cheaper alternatives[83]. The recurrent unexplained palpitations study[29] compared an ILR with a conventional strategy, confirming a notably superior diagnostic yield in the ILR group (73% *vs* 21%). Despite the higher initial cost, the cost *per* diagnosis in the ILR group was lower than in the conventional strategy group (€3056 ± 363 *vs* €6768 ± 6672, $P = 0.012$). However, with the appearance on the market of new ELR devices with good diagnostic yield figures, the use of ILRs is reserved for select cases.

Outpatient telemetry monitoring: These are external monitoring devices similar to Holter monitors or cutaneous patches, but which send a continuous recording *via* telemetry to a central site where the ECG trace can be reviewed in real-time in the event of the onset of symptoms[38,58]. Subsequently, the information can be sent to medical centers with a greater or lesser degree of urgency[8]. Like the skin patches, their use varies according to the region and they are not available in all countries. The most common indication tends to be to monitor for the presence of AF after ablation procedures or to monitor the presence of significant arrhythmias following cardiac surgery or transcatheter aortic valve implantation[8]. Some records have demonstrated the greater efficacy and efficiency of this method compared with conventional Holter monitors[84].

Intracardiac devices: Despite intracardiac devices (pacemakers, defibrillators or resynchronizers) not being indicated for the purpose of monitoring, it should be mentioned that they are also useful for the work-up of patients with palpitations in cases where patients have one of these devices for another indication, since they offer a recording of the intracavitary electrogram during the episode. Many devices have

algorithms that automatically record these events allowing for their subsequent analysis. As such, it is not an ECG recording, but in the case of dual chamber devices, information can be obtained regarding the start of the event and the AV synchrony during tachycardia[85-87].

WORK-UP OF PATIENTS WITH PALPITATIONS

The aim of this section is to provide some clues to help physicians manage patients with palpitations, focusing on the proper use of electrocardiographic monitoring systems. However, it is mandatory to make a brief reference to other important aspects for the evaluation and management of these patients.

Clinical evaluation and risk stratification

The sensation of palpitations is a nonspecific symptom with multiple causes, which are not only cardiological. As such, it is essential to take an appropriate medical history to guide us towards a given suspected diagnosis, allowing us to choose the most suitable tests.

It is important to ask about the patient's medical history (systemic diseases, cardiological history, drug-abuse history, family history of sudden death, *etc.*). Similarly, it is relevant to ask about the characteristics of the palpitations: Are they sustained over time or not, or are they regular (sinus tachycardia, paroxysmal supraventricular tachycardia) or irregular (AF). The triggers (onset at rest or during physical exertion or with stressors) and the presence of certain accompanying characteristics (such as autonomic symptoms, syncope or anginal chest pain) are helpful in identifying at-risk patients requiring admission or more urgent monitoring[1,3].

The physical examination and other easily accessed complementary tests such as electrocardiography can offer specific data but with low sensitivity[1,88]. For example, the presence of a normal ECG does not exclude the presence of causes or arrhythmias, but any pathological findings do greatly increase the likelihood that the cause of the palpitations was cardiological. In up to 27% of patients, the ECG is the key to the diagnosis[88].

Thus, the initial assessment usually includes a detailed clinical history, a focused physical examination, a baseline ECG and usually also a general blood test including thyroid hormones. It is not uncommon in cardiology consultations to also systematically request an echocardiogram to rule out structural heart disease, although this may not be necessary in patients with no other risk factors for heart disease with symptoms highly suggestive of a nonrhythmic origin.

Selection of monitoring type

A key point after risk stratification is appropriately selecting the type of monitoring to be used among all the available devices, in order to achieve optimized diagnostic yield and efficiency in the patient in question.

In the field of palpitations, it is essential to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis[2,6]. This point is worthy of special mention, because it is not uncommon for patients with palpitations to experience different sensations that may correspond to different disorders. For example, it is not unusual for patients to have a sensation of a single palpitation lasting a few seconds almost every day, but to also report occasional episodes of sustained rapid palpitations that start and end suddenly. If, using a Holter monitor, we record an atrial extrasystole and relate this to the single palpitation sensation, we cannot rule out the possibility that these extrasystoles trigger episodes of paroxysmal supraventricular tachycardia (which would explain the second, less frequent, symptom). It would be an error to attribute the entirety of the patient's clinical presentation to the extrasystole, and we should select a monitoring method allowing us to record the less frequent symptom (which is the one suggestive of greater clinical importance). As such, it is essential to take a meticulous history of the symptoms experienced by the patient during monitoring before establishing a certain diagnosis[1,29].

As noted in the previous section, we currently have a wide range of devices at our disposal with significant differentiating characteristics. Various aspects must be considered. The first, and probably the most important, is the frequency with which the symptoms are experienced. The monitoring time must be in line with this frequency. As such, ideally, a 24-h Holter monitor should only be indicated in patients

with frequent and almost daily symptoms[22,48]. If the symptoms are monthly or bimonthly, ELRs have shown excellent diagnostic cost-effectiveness and have certain advantages over other devices[2,54], such as obtaining information regarding the start of the episode. In the event of more infrequent symptoms, at present, external PER are probably the device of choice.

Another important factor is device availability. Many of the new devices are not yet offered as a usual diagnostic tool at healthcare centers or are not covered by insurers. If the patient cannot fund the device, we must choose from among those we have available.

Patient comfort, cost, the accuracy of the automatic algorithms, the possibility of carrying out telemetry monitoring, and the need or otherwise to be able to record the start of the episode are other factors that may influence our decision[8].

Finally, it should be pointed out that, within a specific group of devices, it is important to ensure that the model selected has suitable technical characteristics providing a good quality recording.

Electrophysiological study

Although it is not the reason for this review, it should be mentioned that electrophysiological study (EPS) is an important diagnostic tool in managing patients with palpitations[1,89,90]. In addition to allowing for a precise diagnosis of certain arrhythmias (such as paroxysmal supraventricular tachycardias), it is possible to treat the arrhythmia with ablation during the procedure in those cases where it is indicated [91-93]. It also allows to evaluate other causes of syncope if present[9,10,94,95], and performing risk stratification in patients with structural heart disease[14,71]. Since it is an invasive test, it tends to be considered at the end of the diagnostic process, either in patients with a high probability of significant arrhythmia when the monitoring methods have not allowed for it to be documented, or in patients where, after documenting the clinical arrhythmia, ablation treatment is planned. Nonetheless, it may be indicated at an early stage in patients with recurrent palpitations whose clinical characteristics are highly suggestive of paroxysmal supraventricular tachycardia and who, as such, can benefit from ablation[1,88,89,96].

The diagnostic yield of electrophysiology study is greater in patients with structural heart disease and in those with clinical symptoms highly suggestive of paroxysmal supraventricular tachycardia. For example, in a study carried out by Valles *et al*[90] on patients with sustained palpitations that did not appear on monitoring, the diagnostic yield was 50%. Other papers have reported yields between 40% and 66%[1,89].

In any case, in our opinion, prescribing an electrophysiology study should not preclude the need for electrocardiographic monitoring during the waiting time, be it *via* telemetry monitoring systems if the patient is admitted, or with an external device if not.

Other tests

Exercise-stress testing can be useful and should be considered from the outset when patients report palpitations on exertion[1,97]. Magnetic resonance imaging, coronary computed tomography, specific hormonal studies, *etc*. should be tailored to the patient in line with clinical suspicion and will be necessary in a minority of cases.

Palpitations management work-up summary

Figure 4 summarizes the proposed general algorithm for the management of patients with palpitations of unknown etiology. This algorithm offers an overview of the issue, although it can and should be adapted in specific cases and according to the availability of tests at the center.

The first step in all patients is to perform an initial clinical assessment and stratify the risk (as stated in section ***Clinical evaluation and risk stratification***). In those patients with high-risk criteria and/or priority for EPS, it is necessary to prioritize tests and indicate the study in most cases. During the waiting period, a monitoring system should be maintained (telemetry if the patient is admitted or an ELR if it is an outpatient), because this may provide the diagnosis faster and obtain relevant information for the rest of the work-up.

In cases without risk factors (which form the majority of cases), and without a diagnosis, it is necessary to select a monitoring system, following the indications in section ***Selection of monitoring type***.

Patients without heart disease and with sporadic symptoms not suggestive of an arrhythmic origin may not require further cardiological tests. However, it is not uncommon for the clinical symptoms to continue to generate a high degree of anxiety,

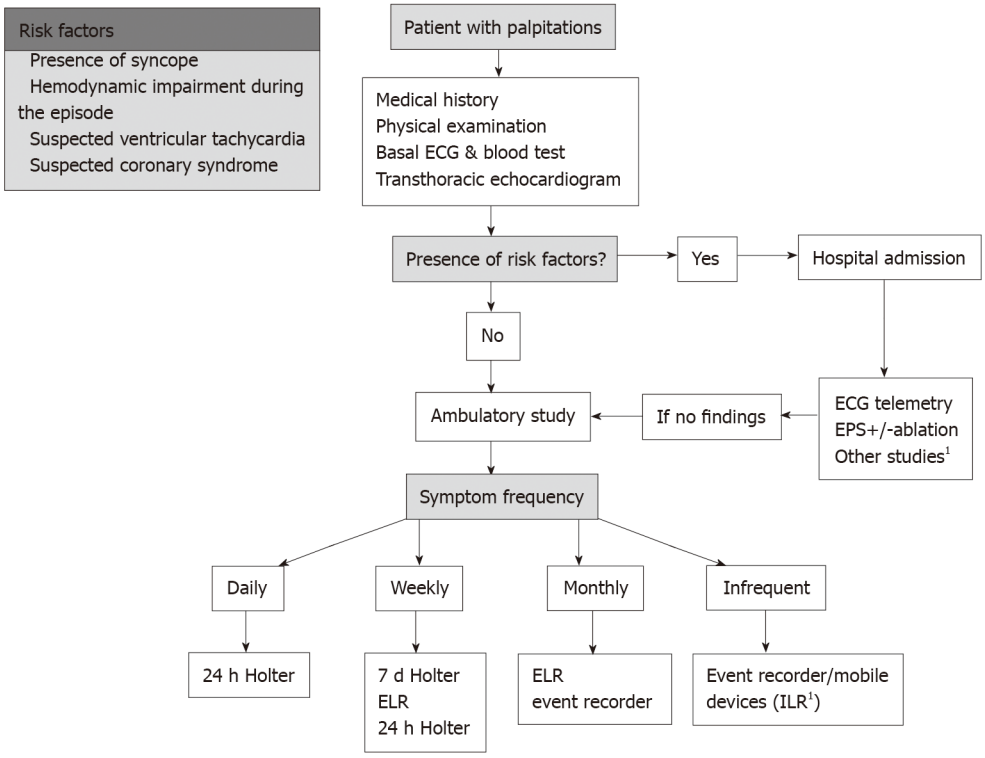


Figure 4 Proposed general algorithm for the management of patients with palpitations of unknown etiology. [1]Consider only in selected patients. ELR: External loop recorder; ILR: Implantable loop recorder; ECG: Electrocardiogram.

hence in some cases we may consider monitoring to ensure there are no arrhythmias, to reassure the patient and to avoid other futile investigations and consultations.

FUTURE PERSPECTIVE

Technological evolution shows no signs of slowing down and it is likely that monitoring devices will continue to be developed at high speed. We expect more widespread use of wearable devices, which incorporate sensors for other vital signs, to open the doors to other indications for monitoring. With regard to electrocardiographic monitoring specifically, we expect further work to be done to improve the current limitations. On the one hand, developing reliable devices that allow for quality external, comfortable, and long-lasting monitoring. On the other hand, the current recorders continue to produce a high number of artifacts and nonsignificant disorders, hence the development of software with algorithms to improve this area will be of clinical utility. The incorporation of artificial intelligence technology allowing for the prediction of future events is another of the most pioneering lines of research[98-102].

Without a doubt, technological development will help us improve the diagnosis and follow-up of patients with palpitations and other cardiac conditions. However, we must be cautious about the increasingly frequent nonmedical use of these devices. We healthcare professionals are faced with the challenge of how to manage, interpret and integrate into the healthcare system all the information that these new devices are providing.

CONCLUSION

Electrocardiographic cardiac monitoring devices are a useful diagnostic tool in confirming or excluding arrhythmias in patients with palpitations. In recent years, electrocardiographic monitoring systems have incorporated many technical improvements and many new devices are now available on the market. To achieve the best diagnostic yield and efficiency, a key point is to properly select the type of monitoring to be used among all available devices. This review provides an update on the different monitoring methods currently available, highlighting their indications

and limitations, to help healthcare professionals to appropriately select and use them in the work-up of patients with palpitations.

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MINIREVIEWS

Cardiovascular magnetic resonance of cardiac tumors and masses

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Abstract

Cardiac masses diagnosis and treatment are a true challenge, although they are infrequently encountered in clinical practice. They encompass a broad set of lesions that include neoplastic (primary and secondary), non-neoplastic masses and pseudomasses. The clinical presentation of cardiac tumors is highly variable and depends on several factors such as size, location, relation with other structures and mobility. The presumptive diagnosis is made based on a preliminary non-invasive diagnostic work-up due to technical difficulties and risks associated with biopsy, which is still the diagnostic gold standard. The findings should always be interpreted in the clinical context to avoid misdiagnosis, particularly in specific conditions (*e.g.*, infective endocarditis or thrombi). The modern multi-modality imaging techniques has a key role not only for the initial assessment and differential diagnosis but also for management and surveillance of the cardiac masses. Cardiovascular magnetic resonance (CMR) allows an optimal non-invasive localization of the lesion, providing multiplanar information on its relation to surrounding structures. Moreover, with the additional feature of tissue characterization, CMR can be highly effective to distinguish pseudomasses

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from masses, as well as benign from malignant lesions, with further differential diagnosis of the latter. Although histopathological assessment is important to make a definitive diagnosis, CMR plays a key role in the diagnosis of suspected cardiac masses with a great impact on patient management. This literature review aims to provide a comprehensive overview of cardiac masses, from clinical and imaging protocol to pathological findings.

Key Words: Cine magnetic resonance imaging; Multiparametric magnetic resonance imaging; Heart neoplasm; Multimodal imaging; Late-gadolinium enhancement; Early gadolinium enhancement

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Core Tip: Cardiovascular magnetic resonance (CMR) allows an optimal non-invasive localization of cardiac masses by providing multiplanar information on its relation to the surrounding structures. Moreover, CMR can be highly effective to distinguish pseudomasses from masses as well as benign from malignant masses. Although histopathological assessment sometimes has an important role to make a definitive diagnosis, CMR is a key modality in the diagnosis of suspected cardiac masses with a great impact on patient management.

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INTRODUCTION

Cardiac masses diagnosis and treatment are a true challenge, although they are infrequently encountered in clinical practice[1]. They encompass a broad set of lesions that include both neoplastic (primary and secondary) and non-neoplastic masses (*e.g.*, thrombi, vegetations, pericardial cysts, mitral annulus calcification or caseous necrosis) and pseudomasses (*e.g.*, lipomatous hypertrophy of the atrial septum, coumadin ridge, Chiari network, Eustachian valve, crista terminalis)[2].

Some of those may be considered as anatomical variants, while some others represent variable prognosis; hence an accurate and early diagnosis is required to allow subsequent assessment of treatment strategy.

The most frequent cardiac masses are non-neoplastic or pseudomasses, which are potentially mimicking cardiac tumors. Cardiac thrombi have a prevalence ranging from 2%-7% in patients with atrial fibrillation or left ventricular dysfunction, while infective endocarditis may be found in 0.8%-3% intensive care unit patients[3-5]. Cardiac tumors are rarer (0.15% prevalence in echocardiographic studies) and mostly benign (90% of surgically-removed masses)[6,7]. Cardiac myxoma is the most frequent benign tumor in adults, while rhabdomyoma and fibroma are the most common in children[8]. However, malignant tumors have been reported to be at least 20 times more common in autopsy studies (1.23%)[9,10]. Sarcomas are the most common primary malignant tumors[11]. Among secondary tumors, the most frequently associated extracardiac neoplasms are lung, lymphoma, breast and esophageal cancer [12].

The clinical presentation of cardiac tumors is highly variable and depends on several factors such as size, location, relation to other surrounding structures and mobility[13]. As a consequence, symptoms may range from incidental detection through routine imaging tests in asymptomatic to exertional dyspnea, cardiogenic shock or sudden cardiac death[10]. Signs and symptoms may be non-specific, such as fever and weight loss, or associated with distal embolization of tumor (stroke or peripheral embolization in case of left-sided mass, pulmonary embolism in case of right-sided mass) or due to direct mass effects (obstruction, coronary artery encasement, pericardial effusion with cardiac tamponade, arrhythmia)[14].

Due to technical difficulties and risks associated with biopsy, which is still the diagnostic gold standard, the presumptive diagnosis is based on a preliminary non-invasive diagnostic work-up[10]. The clinical context should always be considered for the diagnostic work-up, particularly in specific conditions (*e.g.*, infective endocarditis or thrombi). The modern multi-modality imaging techniques have a key role not only for the primary assessment and differential diagnosis but also for management and surveillance of the cardiac masses[15]. Among different techniques, two dimensional-echocardiography is the first level diagnostic test, due to its wide availability and low costs[16]. However, echocardiography may be inconclusive due to limited information about the composition of cardiac mass or pericardial/ myocardial infiltration, limited field of view and variable quality of acoustic window[17].

Cardiovascular magnetic resonance (CMR) is an advanced and highly accurate imaging test capable of providing not only accurate tissue characterization of the mass but also multiplanar information on its relation to surrounding structures, with a higher spatial resolution. Perfusion sequences are useful in the assessment of mass vascularization, while early- (EGE) and late-gadolinium enhancement (LGE) sequences are essential to detect the presence of thrombi and to provide further characterization of the mass[18,19]. Indeed CMR may provide reliable information for the differentiation of malignant from benign tumors[20,21].

This review aims to provide a comprehensive overview of cardiac masses, from exam protocol to pathological findings.

CMR PROTOCOL

A CMR protocol for the study of a suspected cardiac mass should encompass all available sequences for tissue characterization in order to distinguish pseudomasses from cardiac masses (non-neoplastic and neoplastic)[22].

A CMR exam for a suspected cardiac mass can be divided in two parts: The mass localization and its tissue characterization.

The exam should start with an axial steady-state free precession (SSFP) with a balanced T1/T2 effect sequences covering the entire thorax. After that cine-SSFP imaging in long and short axis planes should be performed in order to identify correctly the mass and an additional stack in at least two orthogonal customized imaging planes should be performed to confirm the presence, the location and the extension of the mass (*i.e.* intracavitary, intracardiac or extracardiac). Moreover cine-SSFP sequences allow the assessment of the mass mobility and its attachment points and the hemodynamic impact on cardiac valves[23]. In case of valve involvement, phase-contrast sequences might be performed for quantitative assessment of the hemodynamic effect of the mass[24].

The next step is tissue characterization utilizing all available sequences. "Black-blood" images may also be used to localize a suspected cardiac mass and to provide some information about its tissue composition. Such sequences are generally acquired using a double-inversion recovery fast spin-echo sequence with an initial non slice-selective 180° inversion pulse followed by a slice-selective 180° pulse; a third slice-selective 180° inversion pulse (triple inversion recovery) can be added to obtain fat saturation, resulting in low intensity of fat containing lesions[25,26].

In particular morphologic T1-weighted and T2-weighted, followed by fat-suppressed imaging, should be performed before contrast administration in the same optimal imaging planes identified as above.

Novel T1 and T2 quantitative mapping can provide quantitative information on the studied mass. T1 mapping should be performed before and after the injection of contrast medium to evaluate T1 native, T1 enhanced and extracellular volume[27,28].

A cardiac mass protocol must include contrast-enhanced imaging with first pass perfusion sequences, EGE images, repetition of T1-weighted sequences and LGE sequences.

Perfusion imaging and EGE sequences are used to evaluate the lesion vascularization, the presence of hyperemia near the lesion and for differential diagnosis with thrombus. EGE images are acquired about 3 min after gadolinium injection.

LGE sequences are performed 10-15 min after contrast injection. LGE sequences are fast (or turbo) gradient echo inversion recovery sequences (IR-fast spin-echo)[22,24,29]. The inversion recovery pulse is used to null the signal of normal myocardium in order to maximize the contrast of areas with gadolinium accumulation (edema, increased extracellular space, necrosis). It is crucial to select a proper inversion time (TI). These sequences should be acquired in short axis covering all the ventricles and in

the optimal imaging planes mentioned above both for tissue characterization of the mass and identification of any underlying cardiac pathology.

In summary, to assess each suspected cardiac mass, the protocol must be tailored in terms of the optimal acquisition planes and sequences in order to obtain an accurate tissue characterization.

Table 1 summarizes CMR characteristics of cardiac masses (non-neoplastic and neoplastic).

PSEUDOMASS

Eustachian valve

The eustachian valve, also known as the valve of the inferior vena cava (IVC), is a thin flap-like structure located in the right atrium (RA) at the orifice of IVC that helps direct blood flow through the foramen ovale during embryogenesis. Note that the terms eustachian ridge and eustachian valve are occasionally used interchangeably. However, the eustachian ridge technically refers to the fibrous structure contiguous with the free margin of the eustachian valve[30]. When in doubt, CMR imaging is particularly useful for characterization of the lesion on the basis of its typical location at the inferior cavoatrial junction, lack of enhancement and linear shape.

Crista terminalis

Crista terminalis, or terminal crest, is a horseshoe or twisted C-shaped fibromuscular ridge in the RA. It originates from the atrial septum, extends anteriorly, goes toward the right of the superior vena cava (SVC) orifice, subsequently descends along the posterolateral wall of the RA and turns anteriorly, terminating to the right of the IVC orifice. It is the remnant tissue from the septum spurium, which divides the embryologic primitive RA and sinus venosus[31]. It is an important anatomical landmark in electrophysiology owing to its relation to the sinoatrial node and artery, which should not be injured. Crista terminalis is present in every heart but is not always visualized at imaging. It varies in size, typically 3–6 mm, and is more prominent superiorly. Thrombus is a differential diagnosis (Figure 1), especially in patients with an indwelling right atrial catheter.

Warfarin ridge (coumadin ridge)

The coumadin ridge has been described from echocardiographic studies as a ridge of atrial tissue separating the left atrial appendage (LAA) from the left upper pulmonary vein[32]. It can present as a linear structure or even sometimes as a nodular mass that protrudes into the left atrium (LA). In the past, this structure was often mistaken for thrombus and resulted in patient being prescribed anticoagulation therapy with warfarin (coumadin), from which it derives its name. On cine-SSFP sequences, a prominent coumadin ridge can be identified by its typical location in the roof of the LA adjacent to the left upper pulmonary vein; a particularly prominent ridge can appear as a dark "mass" protruding into the bright left atrial cavity (Figure 2). Thrombus and myxoma are differential diagnosis. As the coumadin ridge is normal cardiac tissue, it should have the same signal intensity as adjacent myocardial tissue on both T1 and T2 -weighted imaging and typically does not show late gadolinium enhancement.

Lipomatous hypertrophy of the interatrial septum

Lipomatous hypertrophy of the interatrial septum (IAS) is a benign condition characterized by mass like deposition of brown fat in the IAS. It results from adipose-cell hyperplasia and has been linked to advanced age and obesity[33]. Classically, there is sparing of the fossa ovalis, resulting in a dumbbell shape of the IAS. Unlike cardiac lipoma, lipomatous hypertrophy of the IAS appears as thickening and is not encapsulated. Lipoma is a differential diagnosis. Fat-suppressed sequences can be used at CMR imaging to characterize this pseudo-lesion; unenhanced chest CT can also help in confirmation of the diagnosis by measuring fat attenuation and demonstrating the dumbbell shape (Figure 3).

Table 1 Cardiovascular magnetic resonance characteristic (location, signal intensity and contrast contrast-enhanced relative to that of adjacent normal myocardium) of benign and malignant cardiac masses

Lesion	Location	T1-WI	T2-WI	Cine-SSFP	Perfusion	EGE	LGE
Non-neoplastic							
Thrombus Acute/subacute	Mural or intraluminal	Iso-Hyper	Iso-Hyper	Iso-hypo	No enhancement	No enhancement	Hypointense border and brighter central zone
Thrombus Chronic	Mural or intraluminal	Hypo	Hypo	Iso-hypo	Rare	No enhancement	Rarely heterogeneous
Pericardial cyst	Right cardiophrenic angle	Hypo	Hyper	Hyper	No enhancement	No enhancement	No enhancement
Mitral annular calcification	Annular fibrous ring of the left atrio-ventricular valve	Hypo	Hypo	Iso-hypo	No enhancement	Peripheral rim of enhancement	Peripheral rim of enhancement
Liquefaction necrosis	Annular fibrous ring of the left atrio-ventricular valve	Mildly Hyper	Mildly Hyper	Iso-hypo	No enhancement	Peripheral rim of enhancement	Peripheral rim of enhancement +/- core enhancement
Neoplastic - Benign							
Myxoma	Left atrium, arising from the interatrial septum	Iso (heterogeneous)	Hyper (heterogeneous)	Hypo	Heterogeneous	Heterogeneous	Heterogeneous
Papillary fibroelastoma	Atrial side of the mitral valve and the aortic surface of the aortic valve leaflet	Iso	Iso	Hypo	Usually not assessable	Mild and homogeneous or no enhancement	Homogeneous or no enhancement
Lipoma	Atrial septum and epicardium, but it may occur anywhere in the heart	Hyper	Hyper (Hypo on STIR images)	Hyper (with black boundary artifact or India ink artifact)	No enhancement	No enhancement	No enhancement
Hemangioma	Every cardiac chamber and also from pericardial space	Iso	Hyper	Hyper	Heterogeneous, intense and prolonged	Homogeneous or heterogeneous	Homogeneous or heterogeneous
Fibroma	Intramural growth in the ventricles (interventricular septum or the ventricular free wall)	Iso	Hypo	Iso-hypo	Mild and homogeneous	Mild and homogeneous	No enhancement or minimal uptake
Rhabdomyoma	Intramyocardial or intracavitary, with intraventricular growth that may cause outflow obstruction	Iso	Mildly Hyper	Iso-hypo	No enhancement or minimal uptake	No enhancement or minimal uptake	No enhancement or minimal uptake
Cardiac teratomas	Intrapericardial (usually compressing superior vena cava and/or right atrium)	Iso or Hypo	Hyper	Iso or Slightly hyper	No enhancement	Mild and heterogeneous	Heterogeneous
Paraganglioma	On the roof of left atrium	Iso-Hypo with "salt and pepper" appearance	Hyper with "salt and pepper" appearance	Hyper	Strong enhancement	Heterogeneous Peripheral	Heterogeneous Peripheral
Neoplastic - malignant: Primary							

cardiac tumor							
Angiosarcoma	Right atrium close to atrio-ventricular sulcus	Iso-Hyper (heterogeneous)	Hyper (heterogeneous)	Iso (heterogeneous)	Strong enhancement	Marked and Heterogeneous	Marked and Heterogeneous
Leiomyosarcoma	Typically involve the left atrium	Iso	Iso-Hyper	Iso	Heterogeneous, intense	Marked and Heterogeneous	Marked and Heterogeneous
Rhabdomyosarcoma	Multiple masses and there is not any predilection in terms of cardiac structures involved	Iso	Iso-Hyper (hyper on STIR images)	Iso	Heterogeneous, intense	Marked and Heterogeneous	Marked and Heterogeneous
Lymphoma	Right chambers, often right ventricle and are associated with pericardial effusion	Hypo-Iso	Mildly Hyper (more evident on STIR images)	Iso	Mild	Heterogeneous	No or progressive mild heterogeneous enhancement
Mesothelioma	Pericardium	Iso	Hyper (heterogeneous)	Iso	Progressive enhancement	Intense enhancement	Intense enhancement
Malignant - Malignant: metastatic disease	Mainly involve myocardium and pericardium	Low (except for Melanoma which is Hyper)	Hyper	Iso	Heterogeneous	Heterogeneous	Heterogeneous

T1-WI: T1-weighted images; T2-WI: T2-weighted images; STIR: Short tau inversion recovery; Cine-SSFP: Cine-steady state free precession; EGE: Early gadolinium enhancement; LGE: Late gadolinium enhancement; Hypo: Hypointense; Iso: Isointense; Hyper: Hyperintense.

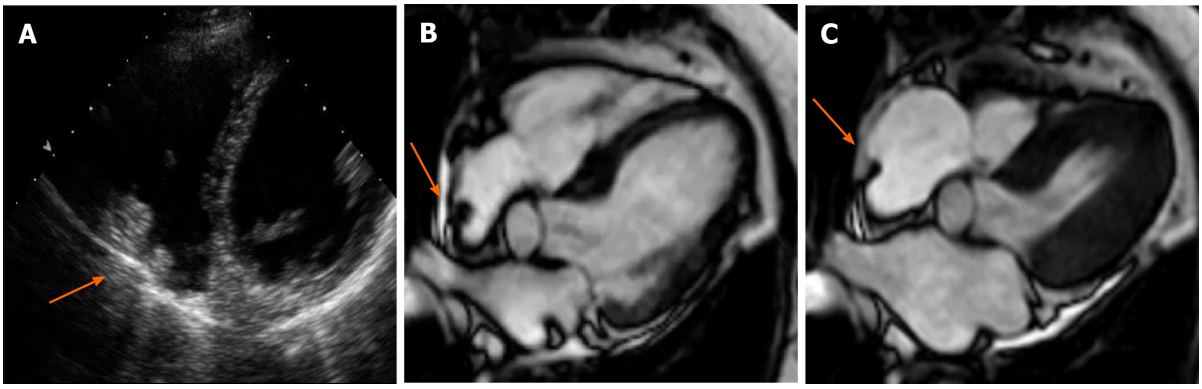


Figure 1 Cardiac mass in a 68-year-old male. Transthoracic echocardiography shows (A) an apparently free mass in the right atrium mimicking a thrombus or a tumor (orange arrow). Cardiovascular magnetic resonance (B, C: 4-chamber cine steady state free precession diastolic and systolic frame respectively) reveals a pseudomass: A hypertrophied crista terminalis (orange arrow) with appearance of right atrial mass on transthoracic echocardiography.

MASS - NON-NEOPLASTIC

Thrombus

Intracardiac thrombi represent the most common cardiac masses, with a prevalence ranging between 2%-25% in normal population and between 3%-50% in patients with atrial fibrillation or left ventricular systolic dysfunction[3,34].

In case of atrial dilation or fibrillation, thrombi are usually located in the posterior wall of the LA or in the LAA. In the left ventricle, the location of thrombi usually relates to presence of regional or global wall motion abnormalities, as seen after myocardial infarction or in cardiomyopathies[35]. When thrombi are found in patients with normal systolic function and contractility, the presence of coagulation disorders should be considered[36]. Occasionally, thrombi can be located in the RA or in vena cava, especially in patients with enlarged right chambers and with central venous lines, and can mimic other masses[37-39].

Identification of a cardiac thrombus is pivotal to start anticoagulation treatment and to prevent systemic or pulmonary embolic events[40]. In most cases, the diagnosis is accidental, and patients are asymptomatic. Generally, thrombi are attached to cardiac walls by a broad base and are immobile. If they are pedunculated and mobile, distin-

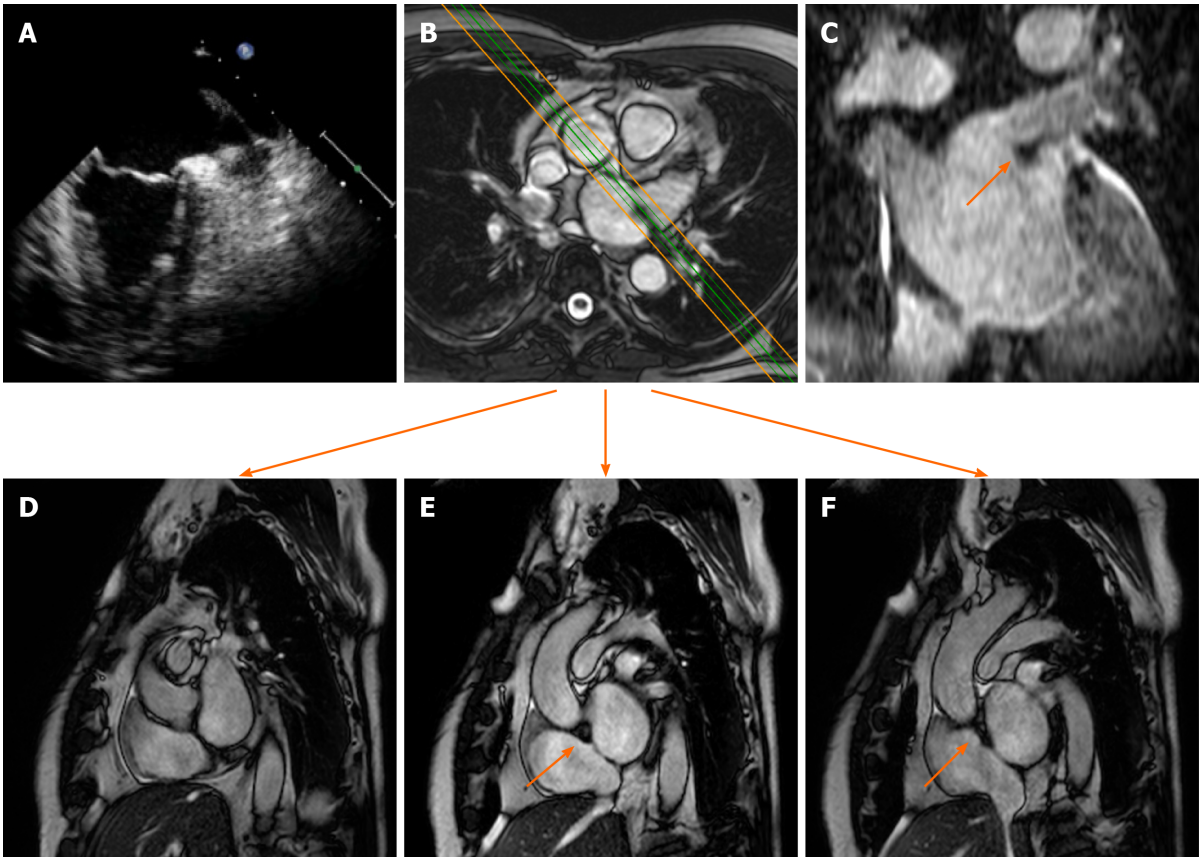


Figure 2 Cardiac mass in a 63-year-old male with atrial fibrillation. Transthoracic echocardiography shows (A) a nodular mass that protrudes into the left atrium at the inlet of the left appendage. The patient underwent 2 mo of oral anticoagulant therapy, and the "mass" did not change. It was therefore requested a cardiovascular magnetic resonance (CMR) (B: axial cine- steady state free precession (SSFP) with the correspondent perpendicular plane oriented according to the green and orange lines and reported in D, E and F), moreover it was performed a three dimensional-steady state free precession SSFP acquisition with an oriented reconstruction (C). Overall the CMR shows the presence of pseudomass (orange arrow), a prominent coumadin ridge in the roof of the left atrium adjacent to the left upper pulmonary vein.

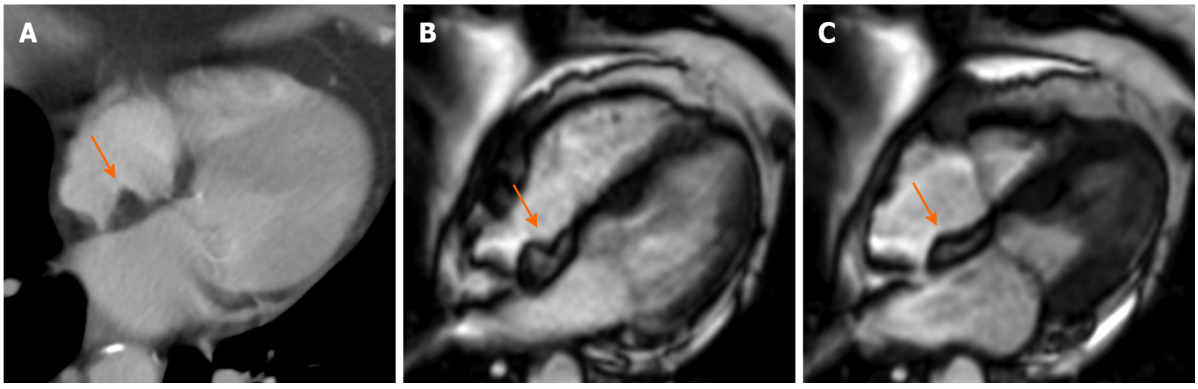


Figure 3 Sixty-five-year-old male patient with a dumbbell-shaped mass along the interatrial septum with negative Hounsfield Unit values on computed tomography scan (A), cardiovascular magnetic resonance cine-steady state free precession images (B and C, diastolic and systolic frame respectively) reveals the chemical shift artifact, also known as "India ink" artifact, typical of structures with adipose content. These findings are in keeping with lipomatous hypertrophy of the interatrial septum (orange arrow).

guishing them from other tumors may be challenging.

CMR has excellent contrast resolution and allows for superior soft tissue characterization. It provides a combined evaluation of morphology, composition and LGE of cardiac masses, with unique advantage of being non-invasive assessment[41,42].

On CMR, thrombi may have different signals, depending on their age and sequence used. Fresh thrombi have a higher signal than myocardium on T1-weighted sequences, and contrast is further accentuated on T2-weighted images, due to high amount of

hemoglobin[35]. After 1-2 wk, they tend to have increased signal on T1-weighted images and decreased on T2-weighted images, due to paramagnetic effect caused by deoxyhemoglobin and methemoglobin in the organizing thrombus[38]. Chronic organized thrombi have low signal either on T1- and T2-sequences, due to loss of water and protons, and they can appear heterogeneous in presence of calcifications (Figure 4).

Differentiation between thrombus and slow-flowing blood on spin-echo sequences may be difficult, due to poor contrast. On the other hand, gradient-echo sequences (or bright-blood imaging) allow for an improved contrast of thrombi from the surrounding blood pool, and clots usually have lower signal compared to normal myocardium[38].

The differentiation between thrombus and myocardium on bright-blood imaging can be difficult when thrombi have similar signal intensity of adjacent myocardium. However, the advantage of bright-blood imaging is represented by cine-CMR, which provides a dynamic evaluation of cardiac motion and blood flow. Balanced SSFP sequences are the most used for cine-CMR in clinical routine for precise detection of mural thrombi[43]. Other sequences that have been successfully used to detect thrombi are phase-contrast sequences with myocardial tagging. Mapping sequences do not provide any T1 or T2 values useful for diagnosis. However, a characteristic pattern of hyperintensity-isointensity-hypointensity has been described for thrombi when TI scout is performed at increasing inversion times, and it may allow to differentiate clots from other cardiac tumors[42].

The method that has shown the best performance for thrombus imaging on CMR is represented by LGE imaging[4]. This technique allows for a straightforward diagnosis, even in case of small thrombi, and independently of their location. Moreover, the presence of thrombus enhancement may also help to differentiate between subacute and chronic clots. In fact, subacute thrombi present homogeneously low-signal, without late enhancement, and can manifest magnetic susceptibility artifacts. In contrast, organized thrombi have intermediate signal and can be heterogeneous due to multiple areas of late enhancement, hindering a prompt differentiation from other cardiac masses[44].

Pericardial cyst

Pericardial cysts account for approximately 7% of all mediastinal masses and 33% of all mediastinal cysts, with an incidence of 1/100000. They are mostly congenital lesions, and commonly located in the right (51%–70%) or left cardiophrenic angles (28%–38%)[45-47]. The cyst walls consist of a single layer of mesothelial cells, and they are usually filled with clear fluid. On CMR they have low signal on T1-weighted sequences and high signal on T2-weighted images[48,49]. There is not fluid enhancement on LGE imaging, but enhancing walls or intracystic septations may be observed (Figure 5). CMR ability to discriminate these lesions from other mediastinal masses allows to avoid further invasive diagnostic procedures, since most patients are usually asymptomatic.

Symptoms may occur when cysts impinge upon or erodes into adjacent structures. In case of cardiac compression, patients may present with retrosternal pain or congestive heart failure symptoms, especially if the right side of the heart is involved. Treatment is usually conservative and CMR is particularly helpful to assess stability of the lesion. When pericardial cysts do not enlarge and patients are asymptomatic, a continued surveillance is the favored option. In contrast, when cysts enlarge and patients present symptoms, surgery may be indicated, mainly to prevent compressive effects and life-threatening complications[50].

Mitral annular calcification and liquefaction necrosis

Calcification of the mitral annulus is the result of a chronic non-inflammatory process, which is characterized by calcium deposition in the annular fibrous ring of the left atrio-ventricular valve[51].

It is more frequent in older patients, and it is related to altered metabolism of calcium phosphate and to chronic renal disease. Mitral annular calcification may present as an immobile mass, generally located in the inferior or inferolateral portion of the mitral anulus. In severe cases it may involve the whole annulus and compress the adjacent myocardium. Usually, it is composed by a calcified core enclosed by a fibrotic envelope. On CMR, it is typically characterized by low signal on T1- and T2-weighted sequences, without enhancement after intravenous injection of gadolinium. However, the fibrotic envelope may show a peripheral rim of enhancement on LGE imaging[51] (Figure 6). Rarely, this lesion can evolve to liquefaction necrosis (or caseous calcification). In this case, the core contains a mixture of cholesterol, fatty

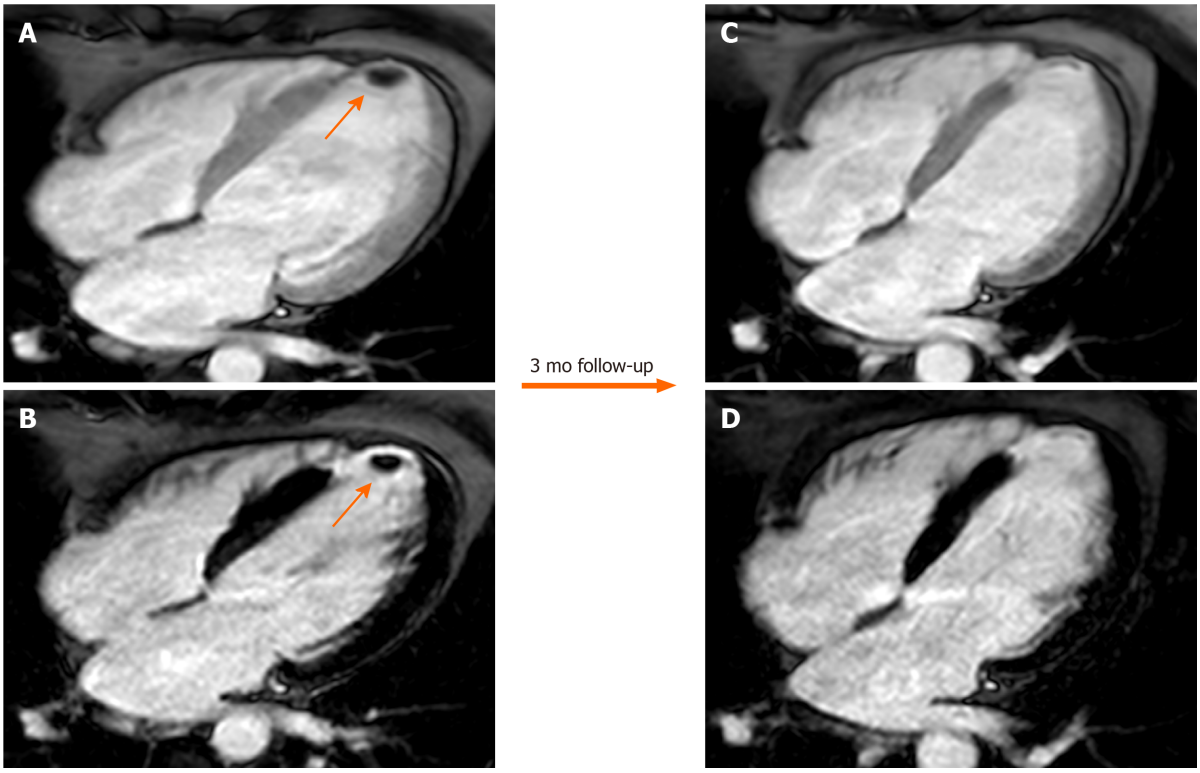


Figure 4 Sixty-six-year-old male patient with a history of myocardial infarction and suspected thrombotic formation at echocardiographic transthoracic examination. Cardiovascular magnetic resonance shows a hypointense intraventricular "mass" at the left ventricular apex (orange arrow) in the early gadolinium enhancement (A) and late gadolinium enhancement (LGE) (B) sequences near the infarcted wall (*i.e.* with transmural LGE involvement). The patient underwent 3 mo of anticoagulant therapy with disappearance of the thrombus in the follow-up examination.

acids, and amorphous eosinophilic infiltrate, with a surrounding rim that encloses macrophages, lymphocytes and multiple necrotic areas with calcifications[29].

In contrast to the previous entity, the proteinaceous and fatty components of the central part of the lesion may manifest with high signal on T1- and T2-weighted sequences. Moreover, core enhancement is typically observed, either in the early or late phases after gadolinium injection[29]. Both these entities are considered benign and they are usually asymptomatic and discovered as incidental findings. Symptoms are usually caused by related complications such as mitral stenosis or regurgitation, infective endocarditis and embolization.

Vegetations

CMR can be of help in visualization of valve or mural vegetations, either to clarify echocardiographic findings or to establish the diagnosis. They may not be visible on dark-blood imaging, while they are better depicted on cine-CMR, manifesting as low-signal areas that follow the motion of the cusp to which they are connected[52]. The differentiation from thrombus may be difficult, because both masses usually do not show contrast enhancement. However, a peripheral rim enhancement on LGE imaging has been observed in vegetations and might facilitate the differentiation from other cardiac masses. The presence of adjacent myocardial enhancement or endothelial lining may indicate irreversible myocardial damage or fibrosis, and they may represent indirect signs of infective endocarditis or perivalvular abscess[53].

Cardiac vegetations can also be found secondary to inflammation, in association with sterile endocarditis, as Libman-Sacks endocarditis. This is characteristic of patients suffering from systemic lupus erythematosus and can manifest with small verrucous vegetations, more frequently involving the mitral and aortic valves[54].

NEOPLASTIC-BENIGN

Myxoma

Cardiac myxomas, the most common primary benign cardiac tumor, are well-defined

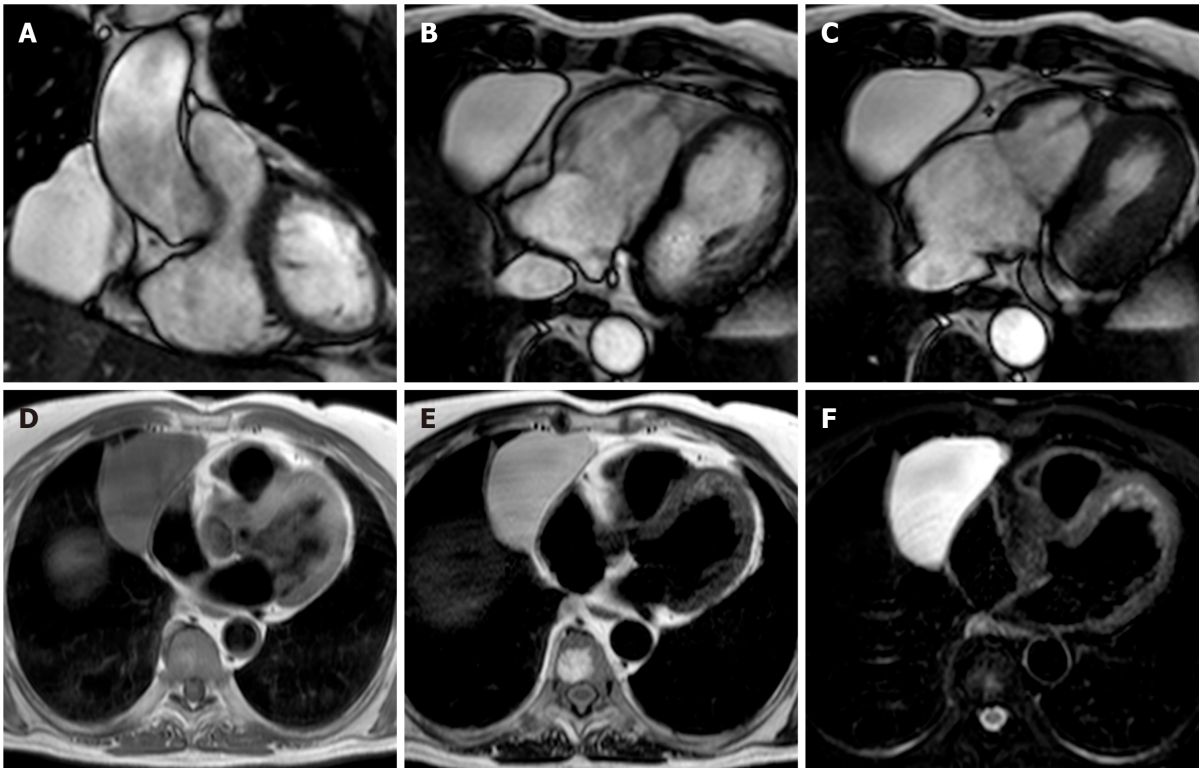


Figure 5 Fifty-seven-year-old female patient with parenchymal mass in the right cardiophrenic angle on chest X-ray. This finding was first investigated by chest computed tomography and then by cardiovascular magnetic resonance (CMR) (A-C). The CMR confirm the presence of the mass on cine-steady state free precession images (A and B, two orthogonal diastolic frames of plane through the mass respectively), without sign of infiltration confirmed by the preserved movement of the heart chambers in relation to the mass itself. The mass shows low signal on T1-weighted sequences (D) and high signal on T2-weighted images (E and F, without and with fat suppression, respectively). These findings are in keeping with pericardial cyst.

spherical or ovoidal mobile lobulated masses frequently in the LA (80%), arising from the IAS (80%)[55,56]. Less common locations are the posterior and lateral LA wall, the LAA, the mitral and tricuspid valve, the posterior RA wall and, rarely, the ventricles and the pulmonary artery[57]. The endocardial attachment point may be broad, sessile or narrow or pedunculated (typically mobile). Myxomas prolapse through the mitral valve has been reported in 30% of cases. Cardiac myxoma may be part of the Carney complex[58].

There are three patterns on CMR: Most frequently it is isointense in T1-weighted and hyperintense in T2-weighted images. Conversely, it might appear hypointense in both T1 and T2 due to calcifications or extremely hyperintense in T2 with "pseudo-cystic" appearance[56,57]. At first pass perfusion, it presents weaker enhancement than myocardium (16%-66%)[55]. About half of cardiac myxomas present heterogeneous LGE[23,57] (Figure 7). On parametric imaging, they show elevated native T1 and T2 relaxation times and extracellular volume values[27].

Papillary fibroelastoma

Papillary fibroelastoma (PF) is the most common cardiac valve tumor. It can arise from any endocardial surface but the most common locations are the atrial side of the mitral valve and the aortic surface of the aortic valve leaflets[23]. PFs are usually small lesions (< 1.5 cm) composed of collagen and elastic fibers lined by endothelium with a short pedicle[59]. PF presents signal isointense to normal myocardium in both T1- and T2-weighted images. On SSFP sequences, it appears as a well circumscribed mobile valve nodule with possible perilesional artefact[60]. PFs may have homogeneous LGE [61] (Figure 8). PFs have elevated native T1 and T2 relaxation times[23].

Lipoma

Lipoma is the second most common benign cardiac tumor; most frequently it grows within the atrial septum and epicardium, but it may occur anywhere in the heart.

At CMR lipoma generally shows a homogeneous nodular elevated signal intensity on T1-weighted sequences, slightly hyperintense on T2-weighted images and hypointense on fat-saturated images. Lipomas do not present contrast enhancement or

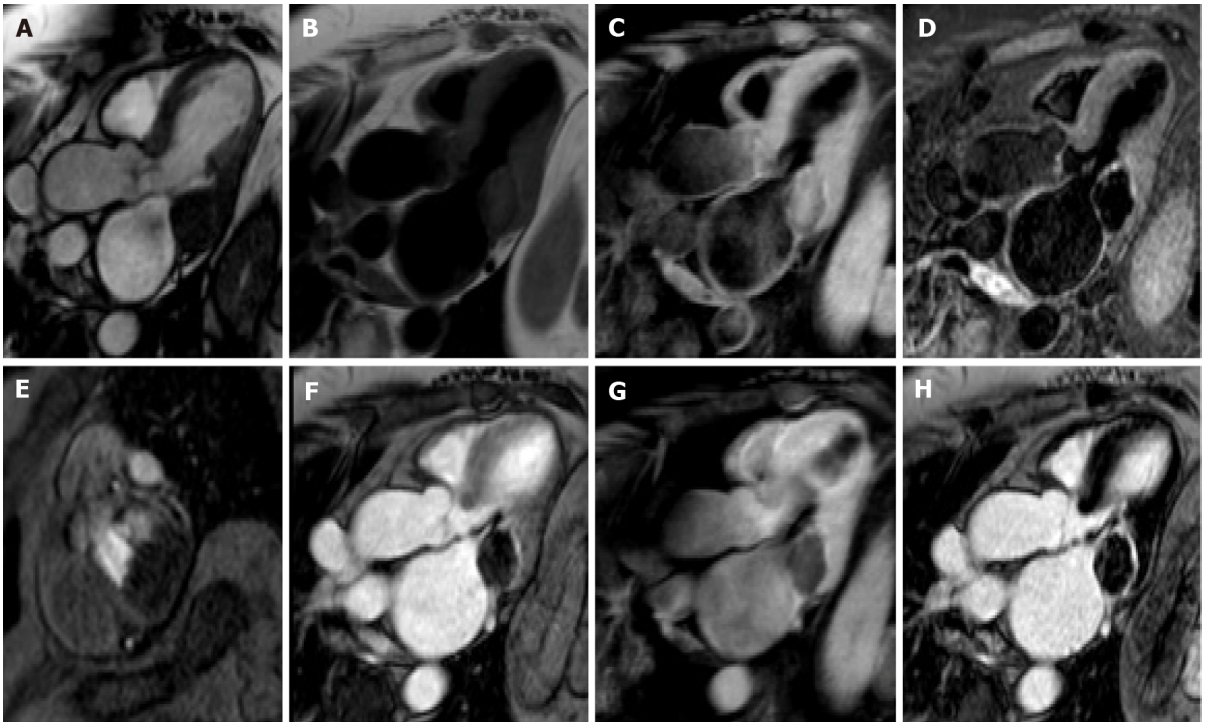


Figure 6 Eighty-year-old female with hyperechoic mass of uncertain significance in the left atrio-ventricular groove discovered at transthoracic echocardiography. Cardiovascular magnetic resonance confirms the presence of the mass with the cine- steady state free precession images (A). The mass shows slight hyperintense signal on T1-weighted images without and with fat suppression (B and C, respectively), due to the presence of proteinaceous material, and hypointense signal on short tau inversion recovery images (D). The mass shows no contrast uptake during perfusion sequences (E) and no contrast enhancement both on early gadolinium enhancement images (F), T1- weighted images (G) repeated after the contrast medium injection, and late gadolinium enhancement images (H) with a peripheral rim of enhancement. These findings are in keeping with caseous calcification of the mitral valve.

LGE (Figure 9). They have elevated T1 relaxation times with intermediate values on T2 mapping[23,62].

Hemangioma

Hemangioma accounts for approximately 5%-10% of benign cardiac masses. They are slow flow vascular malformations that can arise in every cardiac chamber and also from pericardial space. Most patients are asymptomatic, and cardiac hemangioma is discovered serendipitously; symptomatic patients may present with dyspnea on exertion, chest pain, arrhythmias, pericarditis, pericardial effusion, syncope and sudden death. Cardiac hemangiomas can occur in Kasabach-Merritt syndrome, characterized by multiple systemic hemangiomas, recurrent thrombocytopenia and consumptive coagulopathy[63].

At CMR hemangiomas have isointense signal to myocardium on T1-weighted images because of slow blood flow and high signal intensity on T2-weighted images [23,63,64]. On first pass and LGE sequences they have intense and prolonged enhancement and may appear heterogeneous depending on the presence of fibrotic tissue and calcifications[23,64].

Fibroma

Fibromas are benign neoplasms of the connective tissue that originate from fibroblasts, predominantly seen infants and children (the second most common congenital tumor after rhabdomyoma). Almost one-third of patients with cardiac fibroma are asymptomatic and they are mostly diagnosed incidentally. Symptomatic patients may present with arrhythmias, heart failure, or sudden death. Fibromas are usually solitary tumors (unlike rhabdomyomas) usually with intramural growth that involve the ventricles, either in interventricular septum or ventricular free walls[41,65]. They do not regress, unlike rhabdomyomas, therefore surgery is required[66]. Macroscopically, they are solid tumors with dimensions varying from few millimeters to a size that can obliterate cardiac chambers. Microscopically, they are composed of fibroblasts, and calcification is a common finding[67]. At echocardiography, they appear as a large, noncontractile, heterogeneous solid mass[65]. On CMR fibroma are well-defined masses, generally isointense or hypointense on T1-weighted images, and homogen-

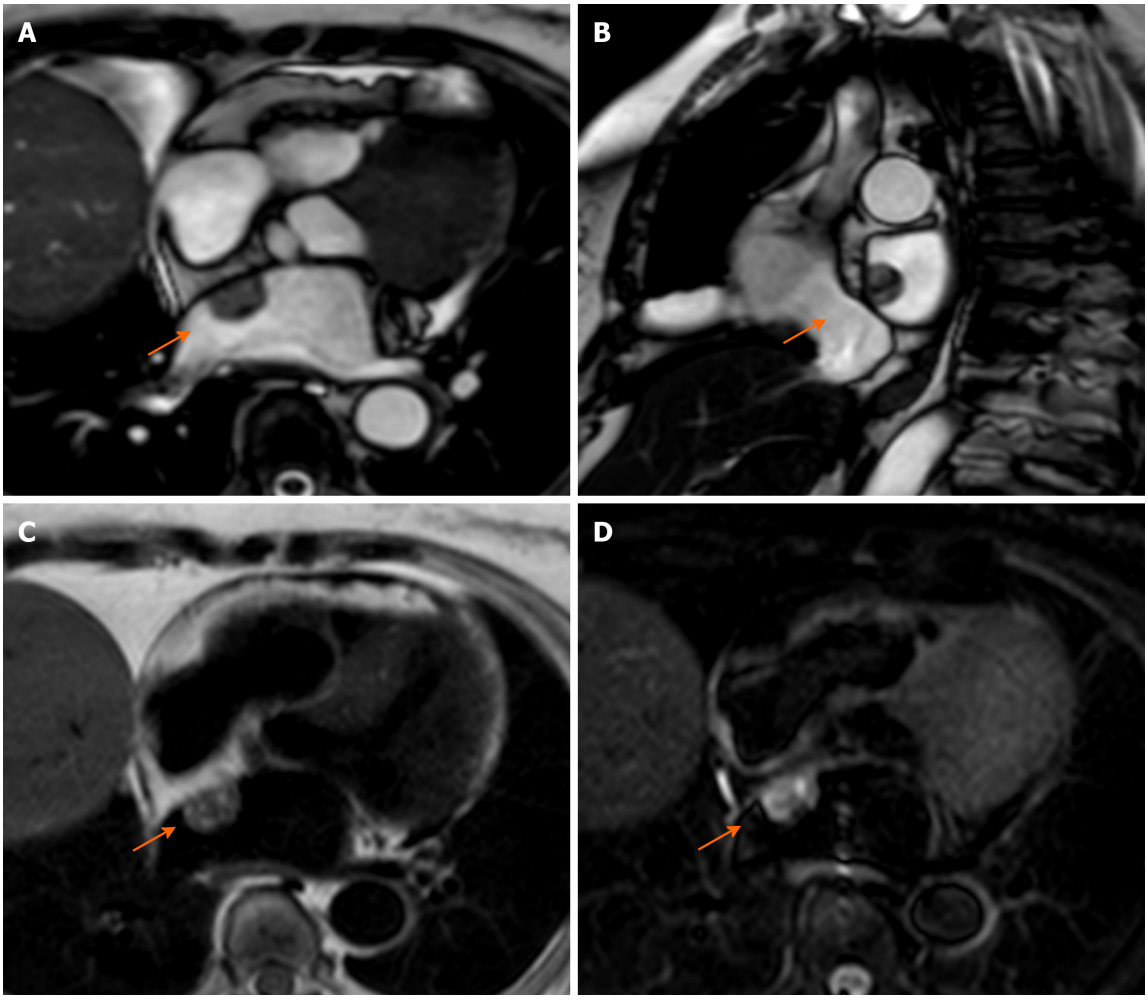


Figure 7 Seventy-nine-year-old female patient with left atrial mass adherent to the interatrial septum discovered on cardiac computed tomography angiography. The cardiovascular magnetic resonance confirms the presence of the mass using the cine- steady state free precession images (A and B, two orthogonal planes along the mass respectively). The site of lesion and its heterogeneous appearance on T2-weighet sequence (C and D) short tau inversion recovery, are in keeping with cardiac myxoma.

eously hypointense on T2-weighted images[41,65].

Fibromas can show different enhancement patterns after gadolinium administration. In fact, they may not show any LGE, or manifest homogeneous or heterogeneous enhancement with isointense rim and hypointense core, which is due to decreased blood supply from the surrounding myocardium[64] (Figure 10).

Rhabdomyoma

Rhabdomyomas are very rare in adults, while they are the most common cardiac tumors during fetal life and childhood. From a histopathological point of view, rhabdomyomas are hamartomas, and they are often associated with tuberous sclerosis. In particular, the incidence of tuberous sclerosis in patients with cardiac rhabdomyomas is 60%–80%, and more than 50% of patients with tuberous sclerosis have rhabdomyomas[65].

Rhabdomyomas are multiple in more than 60% of cases, and this multiplicity has an even higher association with tuberous sclerosis; nevertheless, findings of multiple cardiac masses at prenatal echocardiogram can be the first suggestion of tuberous sclerosis[65]. Rhabdomyomas are usually intramyocardial or intracavitary, with intraventricular growth that may cause outflow obstruction; less commonly, they may be located in the atrioventricular groove ,possibly causing arrhythmias related to an accessory pathway[65]. The majority of rhabdomyomas spontaneously regress in early childhood, therefore surgery is needed only in case of heart failure due to outflow obstruction or arrhythmias[68]. Rhabdomyomas appear as hyperechoic solid masses on echocardiogram[65]. On CMR, they are isointense (or slightly hyperintense) on T1-weighted images, and hyperintense on T2-weighted images with mild LGE[29].

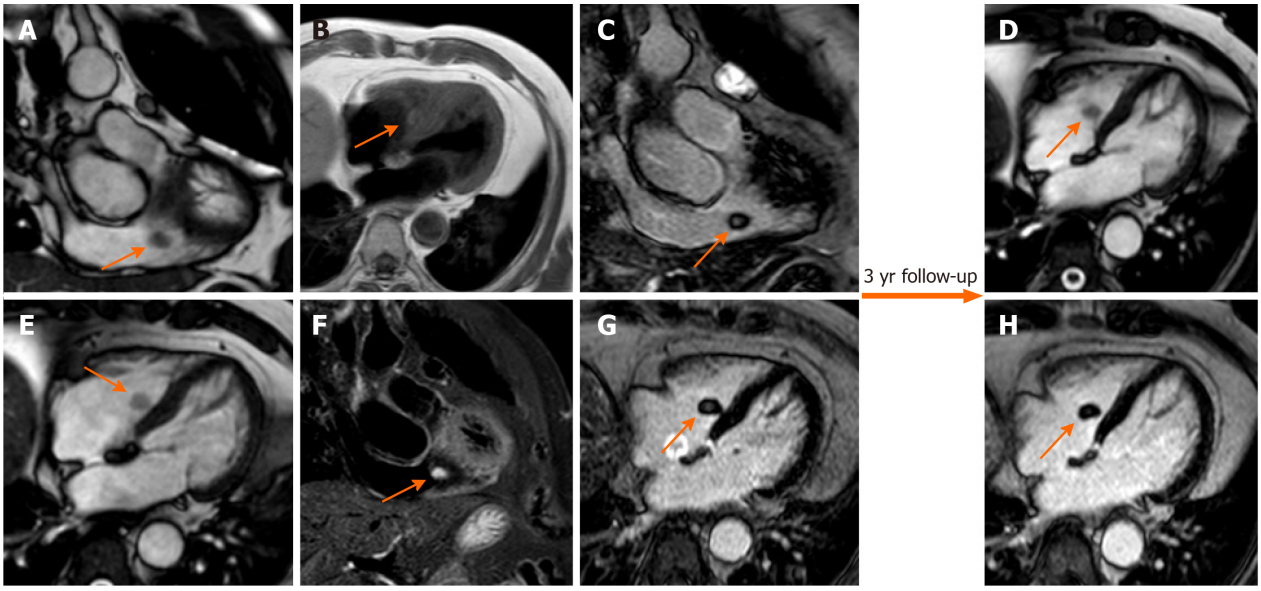


Figure 8 Seventy-one-year-old female with incidental finding of cardiac mass adherent to the septal leaflet of the tricuspid valve on cardiovascular magnetic resonance. The examination was performed for suspected noncompact myocardium on a previous ultrasound examination in a patient with known metastatic thyroid cancer. Orange arrow shows a mobile "valvular" mass at cine-steady state free precession (SSFP) imaging (A and B), with intermediate signal on T1-weighted images (C), high signal on T2 short tau inversion recovery images (D) and with poor enhancement at late gadolinium enhancement (LGE) images (E and F). This location of the mass and its cardiovascular magnetic resonance (CMR) features are in keeping with fibroelastoma. The patient underwent a periodic CMR follow-up for 3 years (G: cine-SSFP and H: LGE sequences), and the mass shows no change.

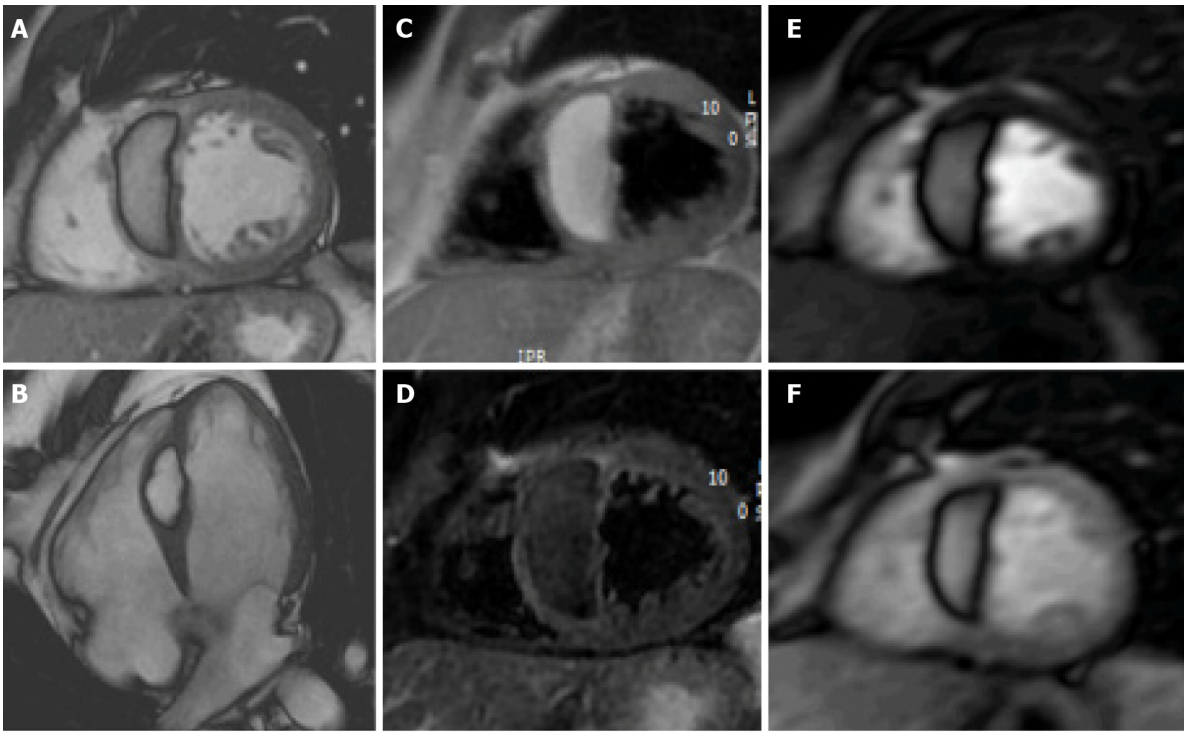


Figure 9 Fifty-one-year-old male patient, with incidental finding of a suspicious intraseptal hyperechoic mass at transesophageal echocardiography. Cine-steady state free precession magnetic resonance (A and B) confirms the presence of an intraseptal mass with a chemical shift artefact at the border. The mass shows high signal intensity on proton density-weighted images (C) and low signal intensity on short tau inversion recovery images (D). The mass shows no enhancement on perfusion images (E and F, two different frame). These findings are in keeping with cardiac lipoma.

Cardiac teratomas

Cardiac teratomas are rare and usually occur in children, representing the second most common primary cardiac tumor in newborns and fetal life. Cardiac teratomas derive from germ cells localized in pericardium. Usually, it is intrapericardial and attached to

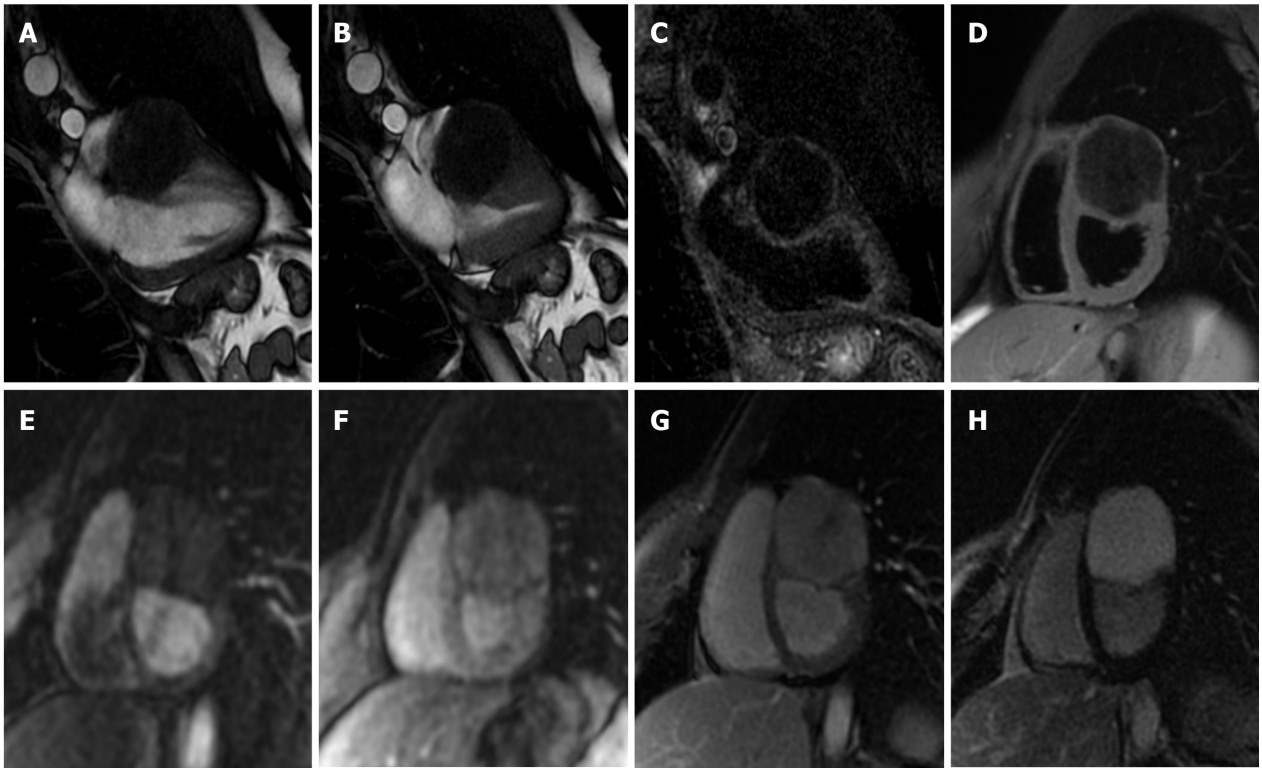


Figure 10 Twenty-five-year-old male patient with a ventricular mass of uncertain significance on computed tomography scan performed after an episode of dyspnea and chest pain. The cardiovascular magnetic resonance demonstrates a well-defined, solitary solid mass with intramural growth in the anterior wall of the left ventricle (A and B, cine steady state free precession diastolic and systolic frame, respectively). The mass shows homogeneous hypointense signal on short tau inversion recovery (C) and T1-weighted images (D). Homogeneous contrast uptake during perfusion sequences (E and F, two different frame of the perfusion sequence) and homogeneous hyperintensity in the early (G) and late gadolinium enhancement images (H). These findings are in keeping with cardiac fibroma. The patient finally underwent cardiac surgery, and the final histopathological diagnosis confirmed the radiological suspicion.

pulmonary artery and aorta and can compress SVC and RA. Intramyocardial teratoma is extremely rare and often manifests with congestive heart failure. Surgery is the treatment of choice. Recurrence or malignant degeneration is rare[68].

Typically, imaging modalities show an intrapericardial multilocular mass with cystic and solid components near aorta and pulmonary artery. On CMR, teratomas may appear iso- or hypointense on T1-weighted images, hyperintense on T2-weighted images and hypointense on first-pass myocardial perfusion imaging, with this latter allowing to differentiate them from hemangiomas. After contrast injection teratomas appear hypointense on first pass perfusion, with heterogeneous LGE[69].

Paragangliomas

Paragangliomas are extremely rare, with an incidence varying between 1.5-9 cases per million people, and it is higher in the fourth decade of life. Up to a third of them may be familial, which makes important a proper family screening. Cardiac paragangliomas represent up to 2% of all paragangliomas[70,71].

They are chromaffin-cell tumors that arise from parasympathetic or sympathetic ganglia of neural crest cells localized outside adrenal glands. They may present as a cardiac mass associated with hypertension and/or palpitation. Echocardiography, computed tomography and CMR can provide valuable anatomical and tissue characterizations, however laboratory investigations such as urine and blood tests for analysis of catecholamines and catecholamines metabolites are required to assess the diagnosis[72] .

CMR shows hypointense signal on T1 weighted images and hyperintense signal on T2 with "salt and pepper" appearance on both T1 and T2 weighted sequences; salt represents hemoglobin degradation products from intralesional hemorrhage and pepper depends on flow voids due to high vascularity. Paragangliomas show strong and early contrast enhancement after gadolinium injection, which follows the arterial vessels enhancement[72]. These tumors are characterized by peripheral LGE, due to tumor necrosis.

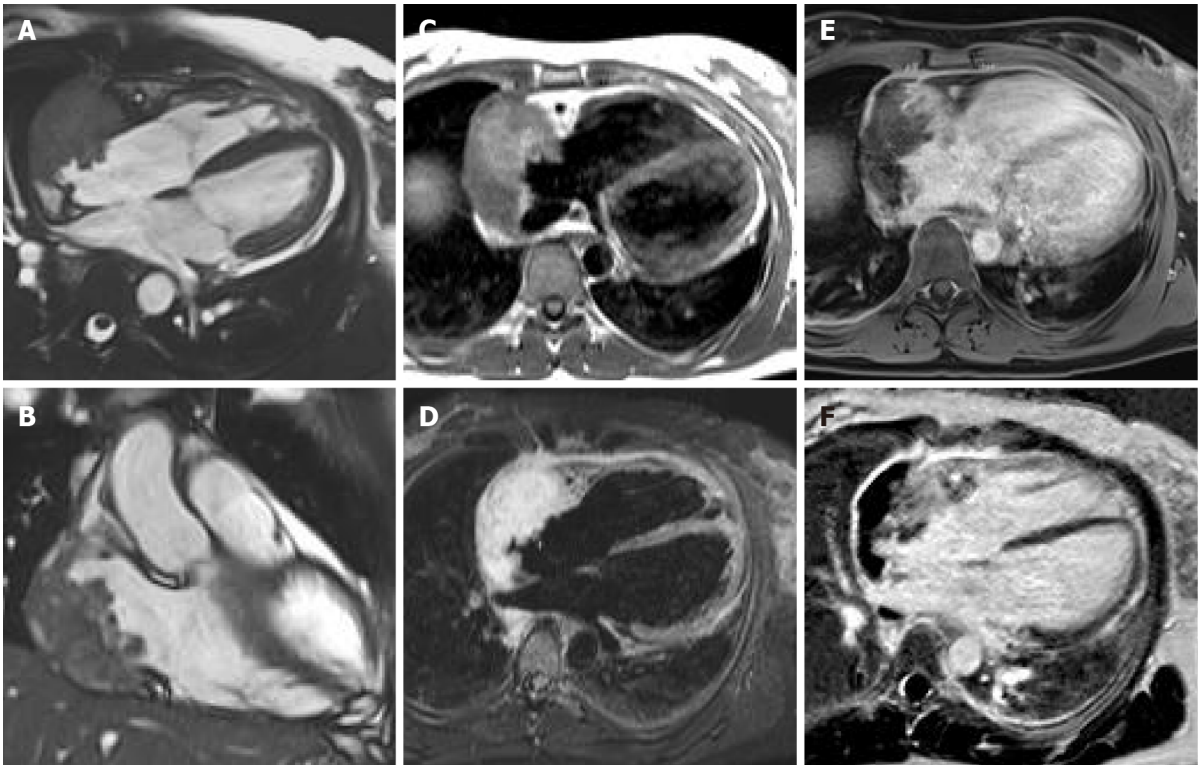


Figure 11 Sixty-five-year-old female patient with transthoracic echocardiogram finding of irregular mass originates from the right atrium wall with intracavitary expansion. Cardiovascular magnetic resonance with cine-steady state free precession images (A and B) confirms the presence of an infiltrative atrial mass in the proximity of atrio-ventricular sulcus. T1-weighted and short tau inversion recovery images (C and D, respectively) show an heterogenous hyperintense signal intensity due to complex composition of the mass. The mass shows inhomogeneous enhancement at early gadolinium enhancement and late gadolinium enhancement sequences (E and F, respectively). These findings are in keeping with a malignant primary cardiac tumor. The patient underwent myocardial biopsy with diagnosis of angiosarcoma.

Biopsy is contraindicated in these hyper-vascularized tumors due to the high risk of life-threatening bleeding.

NEOPLASTIC–MALIGNANT: PRIMARY CARDIAC TUMOR

Table 2 shows the CMR characteristics of cardiac masses that facilitates the differential diagnosis between benign and malignant masses.

Sarcomas

Angiosarcoma is the most common cardiac mass and accounts approximately for 30% of malignant primary cardiac tumors[73]. It occurs mainly in the middle-aged adults and males are more often affected than females at a ratio of 2:1. Angiosarcoma is highly aggressive neoplasm characterized by rapid local spread and distant metastases. In approximately 75% of cases, angiosarcomas are located in RA close to atrio-ventricular sulcus[19]. However, as mentioned above, the loco-regional infiltration with involvement of pericardium, tricuspid valve, SVC, right ventricle and right coronary artery is also common[19]. It can cause symptoms such as chest pain and arrhythmias. The most common site of metastasis of angiosarcoma is lung followed by liver and brain[74].

The CMR characteristic of angiosarcoma reflects the heterogenous composition of angiosarcoma characterized by high vascularization, necrosis, hemorrhage and calcification[19]. T1 and T2 weighted images show heterogenous hyperintense signal intensity due to complex composition of mass with marked enhancement after contrast medium injection due to hyper vascularized nature of the mass[19] (Figure 11).

Leiomyosarcoma usually represent the 8%-9% of cardiac sarcomas and is associated with a worst prognosis in 6-14 mo[19,75]. In 60% of cases, leiomyosarcoma involve the LA followed by the involvement of right ventricle, RA and left ventricle[19]. Similar to other cardiac masses the main problems caused by tumors are mainly due to loco-regional invasion. The presence of leiomyosarcoma in the LA can cause pulmonary

Table 2 Malignant tumor characteristic

Size	More than 5 cm
Number	More than one
Location	Right heart involvement or more than one cardiac chamber
Implantation	Broad base of implantation
Infiltration	Direct infiltration of structures such as myocardium, valves, epicardial fat and pericardial leaflets
Effusion	Pericardial or pleural hemorrhagic effusion
Signal intensity	Heterogeneous signal intensity in T1-weighted and T2-weighted images
Perfusion	Heterogeneous enhancement
EGE and LGE	Heterogeneous enhancement

EGE: Early gadolinium enhancement; LGE: Late gadolinium enhancement.

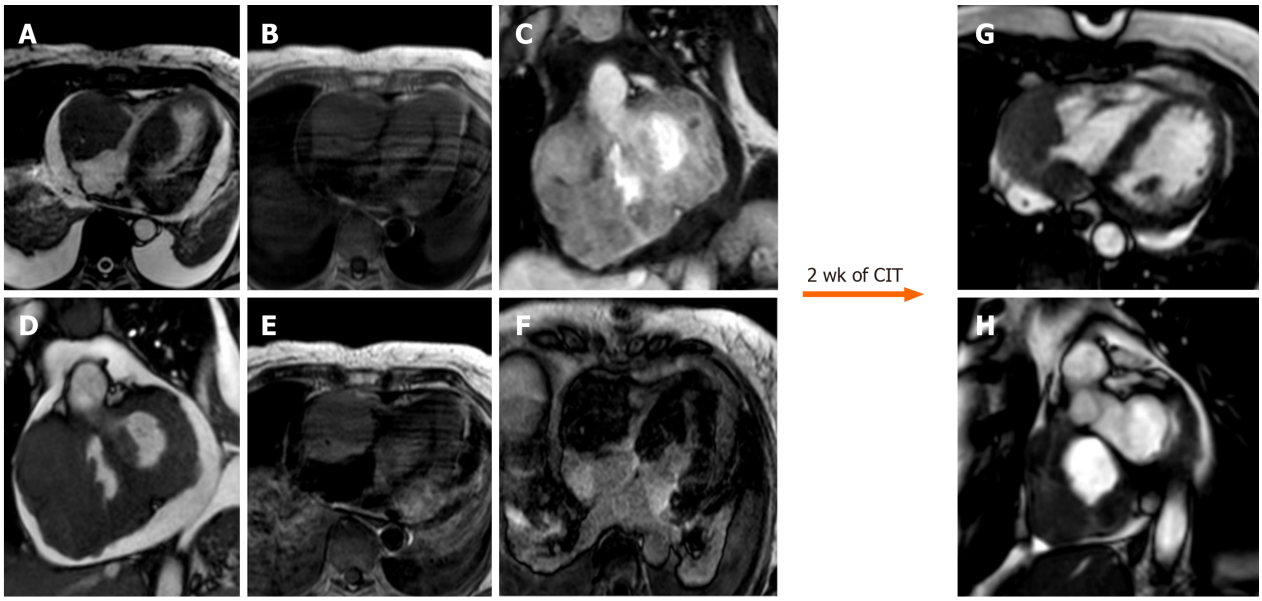


Figure 12 Sixty-five-year-old female with transthoracic echocardiogram finding of two masses in the left ventricle and right cavities following an episode of lipothymia. Cardiovascular magnetic resonance (CMR) with cine-steady state free precession images (A and B) demonstrates the presence of four distinct masses, the most voluminous mass with infiltrative features and irregular margins, extending from the right atrio-ventricular groove to both atrial and the ventricular walls. These lesions are characterized by a substantially isointense signal to cardiac muscle in T1-weighted images (C), slightly hyperintense in T2-weighted images (D) with heterogeneous enhancement at early gadolinium enhancement and relatively homogeneous hypointensity at late gadolinium enhancement images (E, F). These findings are in keeping with cardiac lymphoma. The patient underwent biopsy with a diagnosis of cardiac large B-cell lymphoma and started a chemoimmunotherapy with an excellent response as shown on CMR (G and H, cine steady state free precession) after 2 wk. CIT: Chemo-immunotherapy.

vein obstruction, pericardial effusion, chest pain, atrial arrhythmias and congestive heart failure. Furthermore, leiomyosarcoma is often characterized by rapid growth with distant metastasis and local recurrence after removal[75]. The CMR characteristics show hypo-isointense mass in T1 weighted sequences and hyperintense signal intensity in T2 weighted images[19]. LGE images show heterogenous signal intensity on post-contrast images due to hypervascular areas and necrosis[19].

Rhabdomyosarcoma represent the most common malignant cardiac mass in childhood[23]. Patients with rhabdomyosarcoma often show multiple masses, and there is not any predilection in terms of cardiac structures involved[23]. Rhabdomyosarcoma has the tendency to infiltrate the surrounding structures and in particular pericardium and valves[76]. Common symptoms include arrhythmia and heart failure sometimes associated with eosinophilia[19]. CMR shows isointense signal intensity on T1 and T2 images with hyperintense signal intensity on STIR images in presence of necrosis[23]. After the administration of contrast medium, rhabdomyosarcoma shows enhancement due to increased vascularization[19].

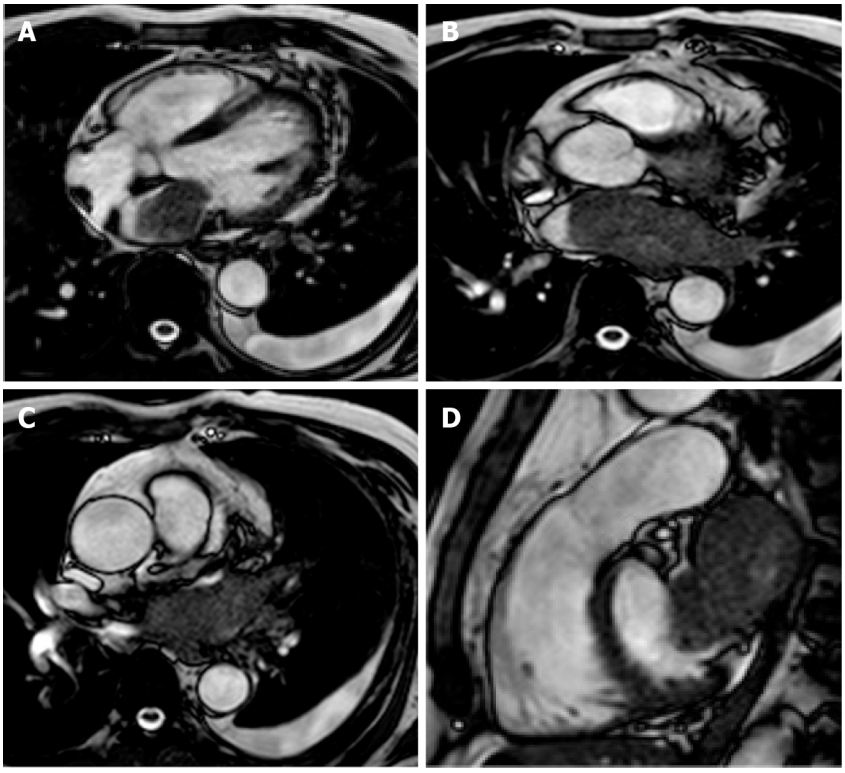


Figure 13 Sixty-five-year-old male with lung cancer. Cardiovascular magnetic resonance examination with cine-steady state free precession sequences in planes of various orientations (A-D) clearly shows infiltration of the atrium through the pulmonary veins.

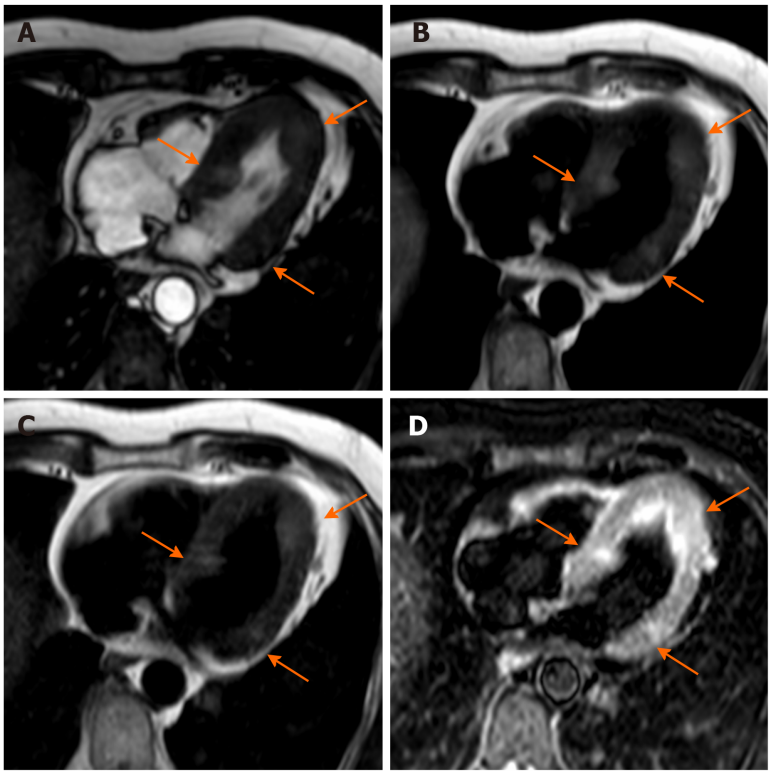


Figure 14 Sixty-four-year-old male with ocular melanoma with multiple metastases underwent cardiovascular magnetic resonance for characterization of a myocardial mass discovered at echocardiography. Nine oval nodules (three are indicated by orange arrows) with diameters ranging from 5 mm to 19 mm, slightly hyperintense in cine-steady state free precession images, T1-weighted (due to the presence of melanin) and T2-weighted sequences. The findings are in keeping with cardiac melanoma localization.

Lymphoma

Primary cardiac lymphoma usually occurs in 1.3% of primary cardiac tumors; typically arising from large B-cells in immunocompromised patients with an average age of 60-years-old[19]. Usually, masses are allocated in right chambers, often right ventricle, and are associated with pericardial effusion[63]. Despite the aggressive nature of this tumor, it shows a good response to monoclonal anti-CD20 antibody[23]. CMR images can be identified usually with the following two patterns: The first pattern shows multiple isointense masses in T1 and mildly hyperintense in T2 weighted images often located in right ventricle[77], while the second pattern is characterized by diffuse pericardial invasion of soft tissue associated with hemorrhagic effusion[23]. After administration of contrast agent, LGE usually shows no or progressive mild enhancement (Figure 12).

Mesothelioma

Pericardial mesothelioma is usually associated with asbestos exposure, and it is characterized by masses arising from pericardium, with pericardial thickening and hemorrhagic pericardial effusion[19]. Involvement of myocardium by mesothelioma is extremely rare, however protrusion of nodular mass from myocardium is suggestive for tumor invasion[19,78]. Symptoms related to pericardial mesothelioma often include breathlessness, chest pain and sometimes pericardial constriction or cardiac tamponade[23]. T1-weighted images show isointense mass, while T2-weighted images present heterogeneous hyperintense signal intensity[23]. Post-contrast images show high intense signal intensity on LGE images[23].

NEOPLASTIC–MALIGNANT: METASTATIC DISEASE

Secondary malignant cardiac tumors, also known as cardiac metastases, are cancerous tumors with spread to cardiac structures. Cardiac metastasis are very common in patients with primary tumors (usually arise from lung, breast and melanoma[12]), often clinically silent and mainly involve myocardium and pericardium[73].

Tumors can spread to the heart through four alternative pathways: Coronary arteries, lymphatic system, direct extension from nearby tissue and intracavitary diffusion through either the IVC or the pulmonary veins[23] (Figure 13).

CMR finding on tissue characterization are not specific and can change based on the metastasis component, however the most common pattern show low signal intensity on T1 and high signal intensity on T2 weighted images with high signal intensity on LGE[23]. Metastasis due to melanoma are characterized by high signal intensity on T1 weighted images[79] (Figure 14).

CONCLUSION

CMR is a fundamental radiological method in patients with suspected cardiac mass. It allows an optimal non-invasive localization of the lesion, providing multiplanar information on its relation to the surrounding structures. Moreover, with the additional feature of tissue characterization, CMR can be highly effective to distinguish pseudomasses from masses, as well as benign from malignant masses, that can also be used for differential diagnosis in the latter. Although histopathological assessment sometimes has an important role to make a definitive diagnosis, CMR is a key modality in the diagnosis of suspected cardiac masses with a great impact on patient management.

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EDITORIAL

Improving the heart team: An interdisciplinary team and integrated practice unit

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Abstract

Heart Team emerged as an important tool in the cardiovascular care, improving the efficiency of decision-making process. In addition to the benefits in patient care, it symbolizes a new culture and mindset. However, beyond the clinical condition, in low/middle-income countries other concerns arise regarding patient's background and these demands are, usually, as challenging as the medical treatment. New models have been proposed face these demands and to assure a holistic care by Integrated Practice Units. Optimization and reorganization of already existing resources and promotion of interdisciplinary and holistic care may be an effective manner to improve outcomes despite socioeconomic barriers.

Key Words: Heart team; Interdisciplinary; Integrated practice units; Cardiovascular; Perioperative; Surgery

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Core Tip: Despite emerging technologies and advanced devices, the real-world situation of low- to middle-income countries presents several socioeconomic concerns that jeopardize patients and, consequently, resources and outcomes. Our pioneer project "interdisciplinary heart team and integrated practice unit" emerged as a means by which to address these demands by prioritizing the management of existing resources.

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INTRODUCTION

Heart Team (Table 1) emerged as an important tool in the cardiovascular care, improving the efficiency of decision-making process[1,2]. This multidisciplinary team-based approach has been used for decades in fields as oncology[3] and organ transplantation[4,5] to deliver the best patient care. Although is not a new concept, the term *Heart Team* was incorporated in the cardiovascular care since the publication of SINTAX Trial[6] and, more recently, the PARTNER Trial[7]. Both trials used a collaborative team-based approach to decide the better strategy to the myocardial revascularization (surgical or percutaneous) or valvular replacement (surgical or transcatheter), respectively.

Using the theory of Venn diagrams[8], this expertise's overlap among different specialties may improve the challenging decision-making process. In addition to the benefits in patient care, the *Heart Team* also promotes continue education[1,9] through the share-of-knowledge and the built of respect, trust and lasting professional relationship between its members. Besides, the interdisciplinary rounds[10,11] and the incorporation of new devices[12] has been currently used in intensive care medicine [13], reducing miscommunication and improving the comprehension of goals by all team members and patient/family satisfaction[14].

More than a medical multi-specialty interaction, it symbolizes a new culture and mindset, and it has been adopted in many cardiology fields as cardio-obstetrics[15-17], heart failure[18], valvular disease[19-21] and coronary artery revascularization[3]. Furthermore, recently published professional societies guidelines for valvular[22-24] and coronary diseases[25] includes the *Heart Team* as pivotal to both clinical and interventional therapeutic strategies, especially in complex or high-risk patients.

Beyond the clinical condition, in low/middle-income countries other concerns arise regarding patient's background and these demands are, usually, as challenging as the medical treatment[26]. Notedly on valvular disease, the socioeconomic circumstances are crucial. Low scholarity, malnutrition, limited access to the primary care, a high prevalence of rheumatic fever, management of anticoagulation and delayed time referral to cardiac surgery are some of these concerns[27]. To face these demands, new models have been proposed[28] to assure a holistic care by *Integrated Practice Units*[29].

Our institution is the public biggest cardiovascular center in Latin America, and, beyond the traditional *Heart Team*, a pioneer interdisciplinary perioperative project coordinated and supported by the Management Executive Direction has been implemented in our Valvular Diseases Unit to optimize resources and improve outcomes. Since 2018, are part of this *Interdisciplinary Heart Team* the cardiovascular surgeon, clinical cardiologist, anesthetist, nursing, psychologist, nutritionist, physiotherapist, welfare service and pharmacists. Beyond these professional, we count on a management team responsible for the logistics to optimize further necessary exams, team re-evaluation and surgical scheduling. Before referral to surgery, all-team come together to expose and solve each patients' demands. If no concerns are pending, patient is referred to waiting surgery list.

On the procedure eve the entire preoperative routine is checked by clinician, surgeon and nursing. The intraoperative and intensive care unit, patient is under care according to the clinical, safety and handover protocols. In the ward, besides daily assessment, every patient is reviewed by the entire *Interdisciplinary Heart Team*. Forecast of hospital discharge, referral to backup hospitals and other demands are discussed. At the hospital discharge, nursing and medical team provide guidance to patients and schedule the postoperative return visit consultation.

CONCLUSION

Even with an unfavorable profile (high proportion of rheumatic disease, redo procedures, multivalvular disease and advanced heart failure status) preliminary results demonstrated reduction of waiting for surgery time and lowering mortality rates. As part of an upper-middle income country, optimization and reorganization of already existing resources and promotion of interdisciplinary and holistic care may be an effective manner to improve outcomes despite socioeconomic barriers. There is always a manner to the improvement.

Table 1 Members of the interdisciplinary heart team responsible to solve patient's demands before they are referred to waiting surgery list

Interdisciplinary heart team members	
Clinical cardiologist	Cardiovascular surgeon
Anesthetic	Nursing
Management team	Welfare service
Psychologist	Physioterapist
Nutritionist	Pharmacist

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REVIEW

Chagas heart disease: An overview of diagnosis, manifestations, treatment, and care

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Abstract

Chagas heart disease (CHD) affects approximately 30% of patients chronically infected with the protozoa *Trypanosoma cruzi*. CHD is classified into four stages of increasing severity according to electrocardiographic, echocardiographic, and clinical criteria. CHD presents with a myriad of clinical manifestations, but its main complications are sudden cardiac death, heart failure, and stroke. Importantly, CHD has a higher incidence of sudden cardiac death and stroke than most other cardiopathies, and patients with CHD complicated by heart failure have a higher mortality than patients with heart failure caused by other etiologies. Among patients with CHD, approximately 90% of deaths can be attributed to complications of Chagas disease. Sudden cardiac death is the most common cause of death (55%–60%), followed by heart failure (25%–30%) and stroke (10%–15%). The high morbimortality and the unique characteristics of CHD demand an individualized approach according to the stage of the disease and associated complications the patient presents with. Therefore, the management of CHD is challenging, and in this review, we present the most updated available data to help clinicians and cardiologists in the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

Key Words: Chagas disease; Diagnosis; Treatment; Heart failure; Arrhythmia; Stroke

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quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Core Tip: Chagas heart disease (CHD) is associated with high mortality and a myriad of clinical manifestations, including bradyarrhythmias, tachyarrhythmias, stroke, heart failure, and sudden death. Therefore, adequate care of these patients requires careful follow-up, clinical stratification, and knowledge of possible CHD complications and their treatment. In this review, we present the most up-to-date available data to optimize the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

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INTRODUCTION

Chagas disease (CD) is responsible for the highest economic and health burden among parasitic diseases in the Western hemisphere[1]. It is caused by the protozoa *Trypanosoma cruzi* (*T. cruzi*), which infects 6 to 7 million people worldwide[2]. Although it has usually been confined to endemic rural areas in Latin America, migration movements have caused the urbanization of the disease, followed by its spread to other continents. Currently, CD is not only a major cause of death in endemic countries[2], but is also an important cause of morbidity and mortality among immigrant populations in non-endemic countries, such as Spain and the United States [3]. At least 300000 up to 1000000 people living in the United States have chronic CD [4]. Most of them are unaware of their condition but are at risk of developing Chagas heart disease (CHD). For instance, among relatives of patients with CD in California, 7.4% had CD diagnosed after a screening test[5]. The same situation may be reproduced in other countries where significant migration movement from Latin American countries occurred. In Europe, there is an estimated 120000 people living with CD, around 43% of which are in Spain[6], with a prevalence of *T. cruzi* infection among Latin American migrants of 6.08%[7].

The main route of transmission in people born in endemic areas is vector-borne transmission. However, food-borne transmission has recently become a concern in the Amazon region, with an increasing number of acute CD cases[8]. Other routes of transmission may occur in endemic and non-endemic countries, including blood transfusion, congenital, and organ transplantation. Adequate control measures can decrease the risk of transmission by all of these routes; however, patients who are already infected require proper care to prolong their lives, prevent complications, and improve quality of life.

CHD pathophysiology is influenced by parasite persistence, together with an inflammatory response that leads to chronic fibrosing myocarditis, ventricular remodeling, and damage to the electrical conduction system[1,9]. There is evidence that an imbalance favoring an inflammatory response against persistent parasites within the myocardium is one of the main mechanisms for CD progression[10,11]. Other possible mechanisms involved in CD progression include coronary microvascular disease and cardiac autonomic dysfunction[12]. Ultimately, patients will present with a myriad of clinical manifestations, including bradyarrhythmia, tachyarrhythmia, cardioembolic events, heart failure (HF), and sudden death[1,9,12,13]. They present with a high 10-year mortality rate, ranging from 10% in the low-risk group to 84% in the high-risk group[14]. Sudden cardiac death is the main mode of death, followed by HF and stroke[1,9,12]. Importantly, CHD has a higher incidence of sudden cardiac death and stroke than most other cardiopathies, and patients with CHD complicated by HF have a higher mortality than patients with HF caused by other etiologies[15,16].

Specific CD treatment with trypanocidal drugs is indicated during the acute phase of the disease or in cases of reactivation that may occur due to immunosuppression[9]. In patients with chronic indeterminate CD, trypanocide treatment should also be offered because it decreases the rate of CD progression[17,18], the occurrence of a composite outcome of clinical events (HF, stroke, or device implantation with a pacemaker or implantable cardioverter defibrillator)[17], and the risk of congenital transmission. However, in patients with CHD, trypanocide treatment was not associated with improved outcomes[19]. Therefore, the care of patients with CHD relies on measures to prevent or treat CHD complications to improve their survival and quality of life. In this review, we present the most up-to-date available data to help clinicians and cardiologists in the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

DEFINITION AND DIAGNOSIS CRITERIA

CD presents with two distinct temporal phases: acute and chronic. The acute phase begins soon after infection, presenting with fever and systemic symptoms, inflammatory physiopathogenesis, and intense parasitemia. Meanwhile, the chronic phase begins after regression of the acute phase and remains throughout life. It is characterized by fibrosis as the main physiopathogenic mechanism and progresses with no or extremely low parasitemia[1,9]. The chronic phase is comprised of three well-defined clinical forms: The first, affecting approximately 60% of patients, is the indeterminate form, which is classically characterized by the absence of symptoms and signs, with no changes identified on electrocardiography (ECG), chest radiography, and gastrointestinal tract examinations; the second is the cardiac form, which presents with rhythm and/or conduction disorders, segmental (most frequent) or global left ventricular (LV) systolic dysfunction with or without HF, and/or thromboembolic events; and the third is the digestive form, which presents with esophageal and intestinal peristaltic dysfunction, with symptoms related to megaesophagus and megacolon[9].

The first study that described CHD was published by Carlos Chagas and Eurico Villela in 1922[20]. This study presented a new cardiopathy observed in 63 patients with CD. It was associated with rhythm and conduction disorders. In the 1940s, Dias *et al*[21] and Laranja *et al*[22] defined the first clinical criteria for CHD and presented it as a well-defined clinical entity that could be distinguished from other chronic heart diseases, in addition to particular ECG changes that were not found in the analysis of similar groups with other heart diseases. In 1956, Dias *et al*[23] presented a pioneering study on an extensive series of patients with CHD from endemic areas, in which they consolidated the histopathological, clinical, and ECG criteria that define this heart disease.

CHD is one of the most frequent and severe clinical presentations of the chronic phase of CD. It is responsible for significant morbidity and mortality[14]. Classically, CHD is diagnosed when the patient presents with a positive serological or parasitological test for *T. cruzi* and ECG shows typical CHD changes in the absence of other heart diseases that may cause these changes[9]. However, patients with the indeterminate form based on ECG criteria may present with wall motion abnormalities in 13% of echocardiograms[24]. Therefore, others use ECG, clinical and echocardiographic criteria to categorize patients into those with definite, probable, and possible CHD diagnoses[25]. The possible presence of wall motion abnormalities in patients with normal or nonspecific changes on ECG indicates that at least one echocardiogram should be obtained for all patients with CD[1]. However, at the primary care level in places with limited access to health resources, the echocardiogram may be postponed until typical CD changes appear on ECG[9].

The ECG changes considered typical (definitive CHD) were systematized by Biolo *et al*[26] and included second- and third-degree right bundle branch blocks, whether or not associated with a left anterior fascicular block; frequent polymorphous or repetitive ventricular premature beats (VPBs) > 1 on ECG; nonsustained ventricular tachycardia (VT); second- and third-degree atrioventricular blocks; sinus bradycardia with a heart rate < 40 beats/min; sinus node dysfunction; second- and third-degree left bundle branch blocks; atrial fibrillation; and electrical inactive segment and primary ST-T wave changes. Nonspecific (non-definitive CHD) changes on ECG include sinus bradycardia with heart rate ≥ 40 beats/min; low voltage QRS; nonspecific ST-T wave

changes; first-degree right bundle branch block; left anterior fascicular block; isolated VPBs; and first-degree atrioventricular block.

CHD CLASSIFICATION

There are several different classification systems for chronic CD that share some similarities, such as the use of ECG and echocardiographic findings as classification criteria, but also disparities that make comparisons between clinical studies and management guidelines complicated. Moreover, current classifications share similar codes for strata classification but with different meanings, which can lead to difficulties when comparing clinical studies and discussing cases. Furthermore, several studies classify patients as symptomatic or asymptomatic. This specific classification is troublesome, as the "asymptomatic patient" class includes patients with both indeterminate and cardiac forms at earlier stages, with isolated changes on ECG or wall motion changes on echocardiography but no HF symptoms.

Here, we will discuss five CD classifications: the Kuschnir classification[27], the Brazilian Consensus on Chagas Disease[9], the modified Los Andes classification[28], the Latin American Guidelines[12] and the American Heart Association (AHA) Statement[1]. They take into account the ECG, chest radiography, echocardiogram, and clinical symptoms of HF, including the New York Heart Association (NYHA) functional class, which have implications on patient prognosis. All of them have some limitations in identifying the risk of events other than HF, such as cardioembolism or sudden cardiac death. In fact, HF is the focus of the question in all these scales. However, sudden cardiac death is a relevant mode of death in CD and manifests frequently without previous symptoms or even without severe LV systolic dysfunction [29].

The Tables 1-5 show the description of these five classifications. Figure 1 presents these different classification systems to facilitate their understanding and shows a comparison of the results from different clinical studies. We assumed that patients with an enlarged heart on radiography would have an abnormal LV ejection fraction to be able to include the Kuschnir classification in Figure 1. However, the Los Andes IB group cannot be compared to other classifications, as it is comprised of patients with normal ECG and abnormal echocardiogram.

It would be interesting to evaluate the discriminatory capacity of each classification system in relation to prognosis. The Kuschnir classification[27] considers only the findings on ECG, radiography, and clinical symptoms, without echocardiogram findings. Therefore, patients with echocardiographic findings, such as mild LV systolic dysfunction, aneurysms, and LV wall motion changes, who have a worse prognosis than patients with isolated ECG changes are not discriminated by this classification. Furthermore, this classification loses the ability to stratify the severity of heart disease.

The Brazilian Consensus Classification[9] was designed to classify patients with CHD into stages with prognostic value. It includes patients with abnormal ECG, since patients with normal ECG findings might have a similar prognosis and risk of death as the population without CD. The classification was derived from a cohort study that observed that global LV systolic dysfunction and HF were the most important markers of prognosis. The mortality rates in 5 years were as follows: stage A, 13%; B (1 and 2), 45%; C, 91%; and D, 98%. Since the difference between stages B and C was significant, stage B was divided into B1 and B2, with a cut-off point at an LV ejection fraction of 45%[9].

The Los Andes classification is divided into four categories. However, two of them include a normal ECG and may have a similar prognostic value. In addition, patients with an abnormal ECG and/or changes in echocardiogram were grouped together in the same stage (stage II), although patients with isolated changes on ECG have a better prognosis[9].

The Latin American Guidelines Classification includes patients with normal ECG (indeterminate chronic form) in stage A. Stage B1 includes those with abnormal ECG and mild echocardiographic alterations in the same group, which decreases the potential for stratification of the classification. The other stages consider the presence of systolic ventricular dysfunction and HF symptoms to discriminate the different prognostic stages (stages B2, C, and D)[12].

The AHA statement classification describes stage A as an indeterminate chronic form without cardiac or digestive abnormalities. Stage B1 includes patients with segmental contractility abnormalities and normal or altered ECG, which mixes different prognoses in the same group. In addition, stage B2 includes patients with

Table 1 Kuschnir classification (1985)[27]

Classification	ECG	X-ray / cardiac symptoms
0	Normal ECG findings	Normal heart size (on chest X-ray)
I	Abnormal ECG findings	Normal heart size (on chest X-ray)
II		Left ventricular enlargement
III		Congestive heart failure

ECG: Electrocardiogram.

Table 2 Brazilian consensus classification[9]

Classification	ECG	Echocardiogram	HF
A	Abnormal	No LV wall motion abnormalities	No
B1	Abnormal	LV wall motion abnormalities with LV ejection fraction (LVEF) ≥ 45%	No
B2	Abnormal	LV wall motion abnormalities with LVEF <45%	No
C	Abnormal	LV wall motion abnormalities	Compensated HF
D	Abnormal	LV wall motion abnormalities	Refractory HF

ECG: Electrocardiogram; HF: Heart failure; LV: Left ventricular.

Table 3 Modified Los Andes classification[28]

Classification	ECG	Echocardiogram	HF
IA	Normal	Normal	No
IB	Normal	Abnormal	No
II	Abnormal	Abnormal	No
III	Abnormal	Abnormal	Yes

ECG: Electrocardiogram; HF: Heart failure.

Table 4 I Latin American guidelines[12]

Classification	ECG /X-ray	Echocardiogram	HF
A	No structural heart disease (normal ECG and chest X-ray)	_	No
B1	ECG changes (arrhythmias or conduction disorders)	Mild contractile abnormalities with normal LVEF	No
B2		Decreased LVEF	No
C		Decreased LVEF	Prior or current symptoms of HF
D			Symptoms of HF at rest, refractory to maximized medical therapy (NYHA functional class IV).

ECG: Electrocardiogram; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association.

mild and severe systolic dysfunction, which also results in a heterogeneous group with different therapeutic approaches and prognoses[1].

We adopted the Brazilian Consensus Classification throughout this review, as we understand that CHD is better stratified into stages of increasing severity and worsening prognosis by this classification system.

Table 5 American Heart Association Statement[1]

Classification	ECG/ Echocardiogram	HF	Digestive changes
A (Indeterminate form - patients at risk for developing HF)	Normal ECG	Neither structural cardiomyopathy or HF symptoms	No
B1	Structural cardiomyopathy evidenced by ECG or echocardiographic changes with normal LVEF	Neither current or previous signs and symptoms of HF	
B2	Structural cardiomyopathy characterized by decreased LVEF	Neither current or previous signs and symptoms of HF	
C	LV systolic dysfunction	Current or previous symptoms of HF (NYHA functional class I, II, III, or IV)	
D		Refractory symptoms of HF at rest despite optimized clinical treatment requiring specialized interventions.	

ECG: Electrocardiogram; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association.

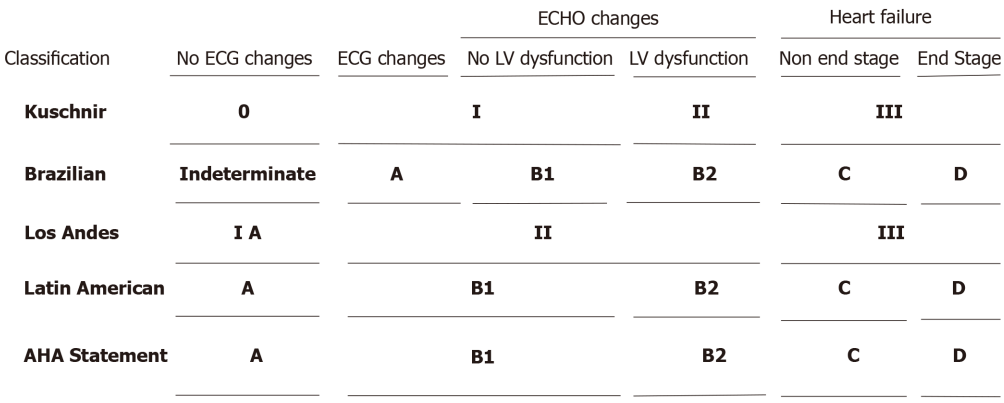


Figure 1 Schematic representation of the different classification systems of Chagas disease. We assumed that patients with an enlarged heart on chest radiography would have left ventricular systolic dysfunction on echocardiography in order to be able to compare all classifications.

ROUTINE ASSESSMENT AND FOLLOW UP

The clinical management of patients with chronic CD should consider the various forms of the disease. Clinical procedures, guidelines, directives, and protocols have been presented in the last decade to improve the comprehensive approach to CD in terms of patient care at the primary, secondary, and tertiary levels[9,12,30,31].

Patients with CD should be clinically evaluated and should undergo an ECG to diagnose CHD. In cases of CHD, it is necessary to identify the degree of myocardial involvement, determine clinical prognosis with emphasis on stratification of the risk of death, and initiate pharmacological management. Patient education should be part of the patients' integrative care.

The initial diagnostic evaluation of patients with CHD includes clinical, epidemiological, and social evaluation[9,32], which is comprised by their medical history, physical examination, and collection of epidemiological and social data. General laboratory evaluations include complete blood count, biochemistry, electrolytes, liver function, and lipid count tests. This initial evaluation is important to identify possible comorbidities, such as essential arterial hypertension, diabetes mellitus, dyslipidemia, obesity, kidney failure, and thyroid disorders. Specifically, B-type natriuretic peptide (BNP and NT-ProBNP) analyses may be useful for diagnosing HF in clinically suspected patients, as well as to define the prognosis[33]. Imaging tests include posteroanterior and lateral chest radiography with the contrasted esophagus, ECG, echocardiography, 24-h Holter monitoring, and cardiac stress test. In the context of primary care and the presence of a normal ECG, echocardiography is not mandatory [9]. In case of ECG changes, an echocardiogram and Holter monitoring are mandatory. If the initial diagnostic evaluation suggests CD with digestive involvement, the patient can be referred for a radiologic contrast study of the esophagus and/or colon, upper

digestive endoscopy, and/or colonoscopy. Patients with a previous history or symptoms suggestive of coronary disease and/or ECG changes compatible with ischemic heart disease should be investigated with diagnostic tests as recommended in specific guidelines. It is important to emphasize that the accuracy of functional tests (cardiac stress test and myocardial scintigraphy) for diagnosing coronary disease is reduced in patients with CHD, and preference is given to invasive (coronary cineangiography) or noninvasive (coronary computed tomography angiography) anatomical tests, which are the best choice according to the estimated pre-test probability of coronary disease.

During routine follow-up, it is essential to characterize and monitor the NYHA functional class. In CHD staging, the algorithm used to evaluate patients with CD is based on ECG and echocardiogram[9]. Asymptomatic patients with ECG changes and normal echocardiograms are included in stage A CHD. Follow-up should be maintained at the primary care level, and patients should undergo ECG annually and echocardiography every 2 years. Asymptomatic patients with ECG changes presenting with LV wall motion changes and LV ejection fraction > 45% are included in stage B1 CHD. Follow-up should be maintained at the primary care level, and patients should undergo ECG annually and echocardiography every 2 years or whenever clinical progression is suspected. Asymptomatic patients with ECG changes and LV ejection fraction < 45% are included in stage B2 CHD. Patients should be referred to the secondary care level, with consults every 3-4 mo, and ECG and echocardiograms performed annually or whenever there are clinical changes. Patients with HF symptoms responsive to treatment are included in stage C CHD and should also be referred to the secondary care level, with consultations every 3 mo, and ECG and echocardiograms performed annually or whenever there are clinical changes. Patients with HF symptoms refractory to conventional treatment are in stage D CHD and should be referred to the tertiary care level. The need for other procedures, such as cardiac resynchronization[34], cardiopulmonary rehabilitation program[35], use of new pharmacological drugs[36], and heart transplantation[37] should be evaluated.

Risk stratification in CHD aims to identify patients with increased mortality risk in order to define therapeutic interventions and closer surveillance. The most powerful predictor of CHD is LV systolic function. The Rassi score is the most commonly used risk score, which includes six independent prognostic factors: NYHA class III or IV (5 points), increased cardiothoracic ratio on chest radiography (5 points), LV systolic dysfunction on echocardiography (3 points), nonsustained VT on 24-h Holter monitoring (3 points), low QRS voltage on ECG (2 points), and male sex (2 points)[14]. Patients were classified into three risk groups: low risk (0–6 points), intermediate risk (7–11 points), and high risk (12–20 points). The 10-year mortality rates for these three groups were 10%, 44%, and 84%, respectively[14]. Other risk score has recently been proposed, including age (10 points per decade), NYHA functional class higher than I (15 points), heart rate ≥ 80 beats/min (20 points), QRS duration ≥ 150 ms (15 points), and abnormal NT-proBNP adjusted by age (55 points). The patients were classified into three risk categories at baseline (low, < 2%; intermediate, ≥ 2% to 10%; high, ≥ 10%). The observed mortality rates in the low-, intermediate-, and high-risk groups were 0%, 3.6%, and 32.7%, respectively[38]. Both scores[14,38] underwent external validation and used all-cause mortality as the endpoint. However, the mechanisms underlying the three main modes of death in CHD may influence the risk scores. Therefore, other scores have been proposed to assess the risk of specific modes of death in CHD. Our group published a score to predict sudden cardiac death based on clinical, echocardiographic, and ECG data, which classifies patients into low, intermediate, and high risk of sudden death[29]. Similarly, our group also proposed a score to identify CHD patients at higher risk of stroke, which includes four variables: LV systolic dysfunction, apical aneurysm, primary ST changes on ECG, and age > 48 years[39].

Many other predictors of poor outcomes in CHD have been published, including right ventricular (RV) systolic dysfunction[40], left atrial (LA) volume and function [41], LV diastolic function[41,42], and biomarkers such as BNP, transforming growth factor β1, and metalloproteinase[33,43-45].

ECHOCARDIOGRAPHY AND NEW IMAGING EXAMS

Echocardiography is a key method for the evaluation and follow-up of patients with CHD due to its wide availability, machine portability, and the information it provides. Echocardiography allows the classification of CHD patients into stages, identification

of complications, and follow-up and risk assessment of patients with CD. Echocardiography can identify chamber size, global and regional LV contractility, LV aneurysms, LV diastolic dysfunction, LA size and function, and RV systolic dysfunction[9,12,41]. Echocardiography is also important to identify the presence of other non-CHD diseases that may be responsible for clinical and/or ECG changes.

In the early stages of chronic CHD, echocardiography may demonstrate segmental LV wall motion abnormalities and diastolic dysfunction[46]. Segmental wall motion disturbances may range from hypokinesis to small or large aneurysms. The LV segments that most commonly present wall motion abnormalities are the inferior and inferolateral walls, and the apex[24] (Figure 2). These wall motion abnormalities can be detected in one or more LV segments in the same patient, and have prognostic implications[47]. LV aneurysm prevalence in patients with CD ranges from only 2% in patients with the indeterminate form to approximately 45% of CD patients with LV systolic dysfunction and HF[48]. Most aneurysms are found in the classic narrow-neck apical location, but they can also be found in other sites, such as the inferolateral and basal inferior walls, the interventricular septum, and even the RV apex[49]. Chagas heart aneurysms have crucial importance because of their relationship with embolic [39,50-52] and arrhythmic[49,53,54] events. Apical aneurysms are more associated with intraventricular thrombi (Figure 3) and stroke risk, while inferolateral aneurysms are more associated with arrhythmia risk. However, apical aneurysms can be missed in conventional 2D apical views due to apical foreshortening, dropout, or near-field artifacts. Therefore, echocardiographic examinations require standard views and modified four- and two-chamber views to detect small apical aneurysms with or without thrombus. Contrast echocardiography, better harmonic imaging, and three-dimensional (3D) applications may allow for more accurate detection of LV aneurysms and thrombi in CD, especially in those with inadequate acoustic windows.

Because of the extensive wall motion abnormalities in CHD, LV volumes and ejection fraction are preferably estimated according to the modified Simpson's rule instead of the Teicholz method.

Even early in the disease, chronic CHD may already affect diastolic function[41]. Usually, the first abnormality is impaired LV relaxation, and as CHD progresses to the late stages, LV pseudo-filling and restrictive patterns increase in prevalence[41]. The prevalence of diastolic function abnormality varies according to study methodologies, but has been described to range from 10% of patients with the indeterminate form to almost 100% of patients with HF[41]. Studies using tissue Doppler imaging have shown that progressive worsening of the e' velocity appears to be a good parameter to identify the progressive nature of LV diastolic dysfunction[41].

As CHD progresses to its late stages, more LV walls are affected and LV dilatation and global LV systolic dysfunction ensue with diffuse hypokinesia. However, even at this stage, LV aneurysms and more pronounced LV wall motion abnormalities in the inferior and inferolateral walls are still present. LV dysfunction has prognostic implications in chronic CHD and is the strongest predictor of death in patients with CD[13].

RV systolic dysfunction has been reported in all CHD stages[40,55]. RV systolic dysfunction can be an isolated finding, but it is most commonly associated with LV dysfunction. Several echocardiographic parameters have been used to assess RV function in CD, including qualitative evaluation, tissue Doppler imaging, myocardial performance index, tricuspid annular plane systolic excursion, speckle tracking strain, and 3D-imaging[13].

Echocardiography of patients with CHD may also reveal mitral and tricuspid regurgitation. Mitral regurgitation is secondary to the distortion of the mitral annulus and the subvalvular apparatus due to LV remodeling and fibrosis of the inferolateral wall. Moderate to severe mitral regurgitation may worsen the symptoms and prognosis of HF[56]. Tricuspid regurgitation is secondary to dilation of the tricuspid annulus, pulmonary hypertension, and/or the presence of a pacemaker lead through the tricuspid valve. Tricuspid regurgitation may worsen right-sided HF symptoms.

Newer imaging methods have potential utility in the diagnosis of cardiac complications and prediction models for CD. However, cost-effectiveness studies are necessary before they are implemented in clinical practice. Reviews of new imaging tools for CD can be found elsewhere[13]. Briefly, newer echocardiographic methods such as speckle tracking echocardiography can be used in early CHD stages to identify early changes in myocardial contractility or strain[57-59]. Analysis of the LV strain may also yield a new prognostic index for CHD. In a short-term follow-up of a population comprised of patients with HF due to CD and idiopathic dilated cardiomyopathy, LV longitudinal strain was an independent predictor of cardiovascular events [60]. Another new echocardiographic method is 3D echocardiography (3DE), which can be potentially useful in CHD because of the more accurate evaluation of the LV

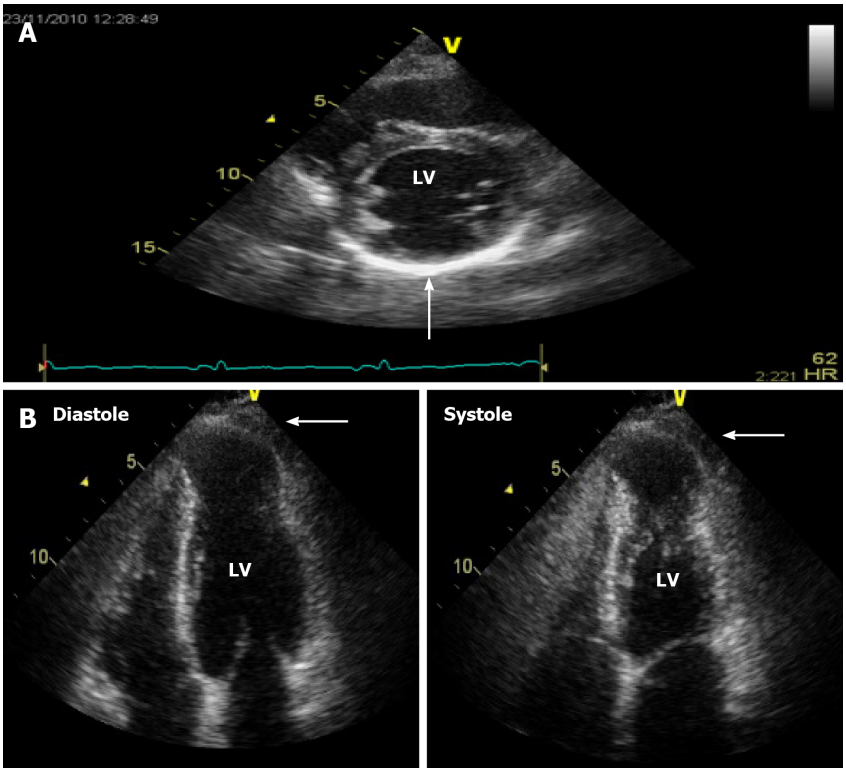


Figure 2 Note the hyperrefringent akinetic area in the basal inferolateral left ventricular wall (A) and the left ventricular apical aneurysm in the diastolic and systolic left ventricular images (B).

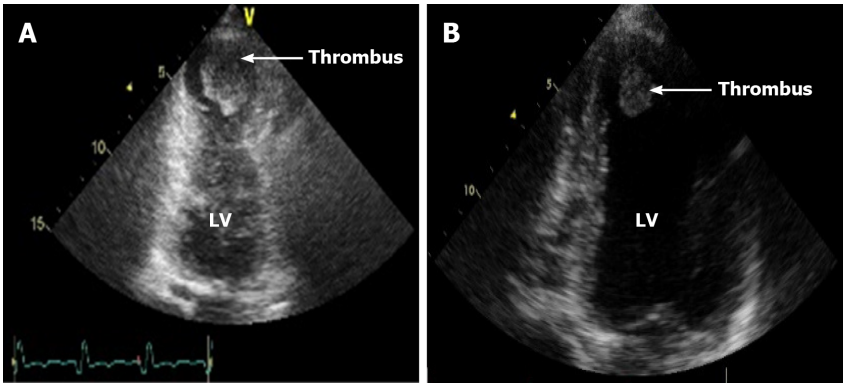


Figure 3 Note the thrombi in the apical location in a patient with a large apical aneurysm (A) and a patient with severe left ventricular dilation and dysfunction (B).

apex, avoiding LV foreshortening. In addition, 3DE is more accurate than 2D Simpson's biplane rule for assessing LV volumes and ejection fraction in patients with significant wall motion abnormalities. LA volume and function assessed by 3DE and strain may be able to predict atrial fibrillation in CD[61].

Cardiac magnetic resonance imaging (MRI) can improve the evaluation of chamber volume and segmental and global function over bidimensional echocardiography, identify aneurysms and intracardiac thrombi[13], and evaluate the extension of myocardial fibrosis (Figure 4), which correlates with increased risk of VT[62] even in the absence of global LV systolic dysfunction[13], and is an independent predictor of the combined endpoint of cardiovascular death and sustained VT[63], and all-cause mortality[64]. Cardiac MRI can identify areas of fibrosis in 20% of patients with the indeterminate form of CD and in 43.7% of patients with CHD stage A. Cardiac fibrosis is detected in 89% to 100% of patients in the late stages of CHD[13].

Another imaging method with potential utility in risk stratification of CD is myocardial scintigraphy using iodine-123 metaiodobenzylguanidine testing. This can identify areas of myocardial sympathetic denervation, which are associated with the

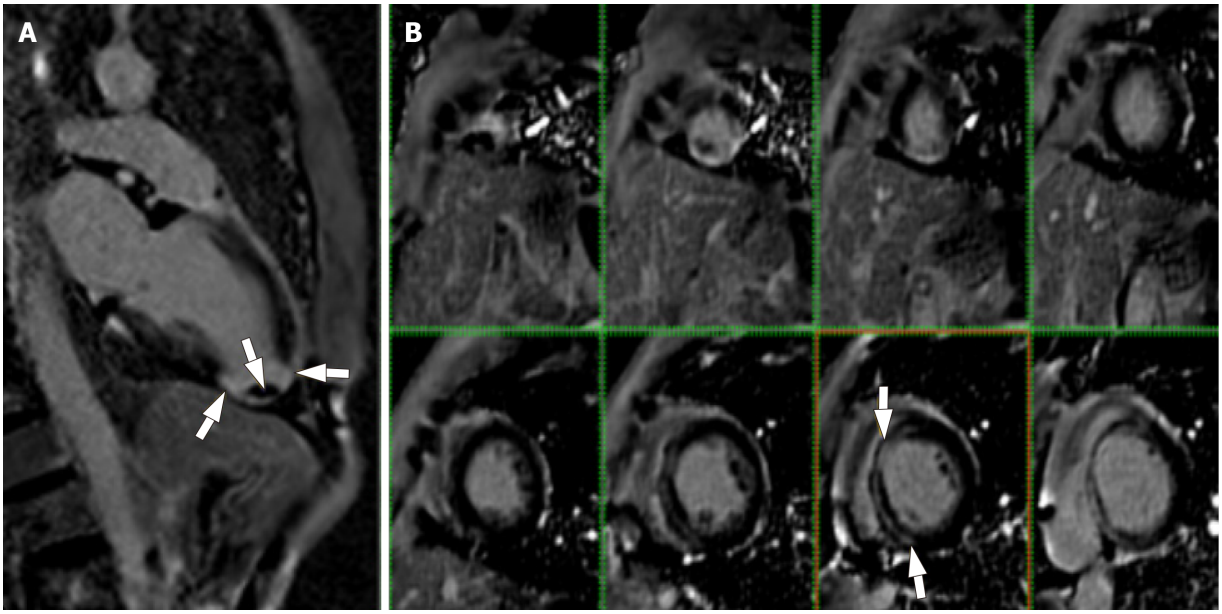


Figure 4 Cardiac magnetic resonance imaging of a patient with stage B1 Chagas heart disease. A: Myocardial delayed enhancement on 2-chamber apical slice depicts areas of cardiac fibrosis in the apical segments and an apical thrombus; B: Myocardial delayed enhancement protocol on left ventricular short-axis slices depicts areas of cardiac fibrosis in the apical and basal left ventricular walls of a patient at stage B1 of Chagas heart disease.

risk of VT in CHD[13]. The detection of areas of cardiac fibrosis by single-photon emission computed tomography and areas of myocardial sympathetic denervation identify patients at risk of developing malignant ventricular arrhythmia[65].

ARRHYTHMIA

Arrhythmias in CHD can either be bradyarrhythmias or tachyarrhythmias.

In the case of bradyarrhythmias, patients may present with presyncope, syncope, fatigue, atypical chest pain, or exertional dyspnea, even with preserved LV systolic function. ECG, 24-h Holter monitoring, and electrophysiological studies are usually enough to clarify the diagnosis. Advanced atrioventricular block and symptomatic sick sinus syndrome are the main reasons for pacemaker implantation. However, all medications capable of worsening heart conduction should be withheld prior to pacemaker implantation. Recommendations for pacemaker implantation in CHD follow the same guidelines for other conditions. However, some aspects need to be highlighted. The RV electrode position should be midseptal due to possible excessive fibrosis at the apex[66] and the LV systolic function may worsen after pacemaker implantation due to LV systolic dyssynchrony related to LV pacing. Another aspect to bear in mind is that whenever it is anticipated that a pacemaker-derived rhythm will predominate or patients already have a left bundle branch block, a resynchronization device should be chosen.

With regard to ventricular arrhythmias, isolated VPBs are the most common, and they do not need treatment unless symptomatic. Asymptomatic nonsustained VT also does not require treatment in patients with preserved LV systolic function, and pharmacological treatment of patients with symptomatic nonsustained VT or asymptomatic nonsustained VT with LV systolic dysfunction is controversial[67]. On the other hand, malignant ventricular tachyarrhythmias are the main cause of sudden death in CHD and require treatment. Amiodarone is the drug of choice in patients with CHD as it improves symptoms and decreases the density of ventricular arrhythmia[68]. However, amiodarone has side effects, and there is no convincing evidence that amiodarone decreases mortality in patients with CHD[68,69]. Nevertheless, amiodarone should be used in high-risk patients with LV systolic dysfunction and nonsustained VT with symptoms. In addition, amiodarone should be considered in patients with a high percentage of ventricular ectopic beats and nonsustained VT on 24-h Holter monitoring because these can result in tachycardiomyopathy.

Another approach to secondary prophylaxis against malignant ventricular arrhythmias in patients with CHD is an implantable cardioverter defibrillator (ICD).

ICDs are indicated in patients with HF and LV ejection fraction < 35% with or without a previous history of VT[70]. However, the studies that supported this recommendation included only a few patients with CHD. Currently, ICDs are recommended in CHD for secondary prevention after documented VT, ventricular fibrillation, or aborted sudden death; in patients with LV ejection fraction < 35% and documented syncope secondary to VT; in patients with LV ejection fraction > 35% who have experienced syncope secondary to VT; and in patients with syncope and inducible sustained VT during electrophysiological study[12]. In a single study, patients with CHD and LV ejection fraction < 40% with documented prior life-threatening arrhythmia had better survival with ICDs than patients given amiodarone[71]. Amiodarone should be considered even after ICD placement to decrease the number of shocks, because CHD patients have intense ventricular arrhythmic activity[72] and a high number of shocks may cause myocardial necrosis and worse LV systolic function [73].

It is important to identify patients with an increased risk of VT, as sudden death can be the first manifestation of a malignant arrhythmia. In the previous sections of this review, we have discussed the prognostic value of cardiac MRI and the detection of areas of myocardial sympathetic denervation by myocardial scintigraphy with iodine-123 metaiodobenzylguanidine to identify patients at increased risk of sustained VT. We also discussed a score based on clinical, echocardiographic, and ECG data (QT dispersion, syncope, premature ventricular contractions, and LV function) to predict sudden cardiac death. This score classifies patients into low (0–2 points), intermediate (3–4 points), and high (> 5 points) risk of sudden death[14]. Nevertheless, ICD implantation for primary VT prophylaxis based on such findings in complementary examinations is still not indicated in clinical practice.

Ablation therapy (catheter-based) is an option to treat recurrent VT in patients with CHD, as VT in CHD is typically reentrant[74]. Most reentrant circuits are located in the same LV walls that are frequently affected in CHD[75]. However, the fibrosis pattern in CHD is not necessarily subendocardial or transmural, as in ischemic cardiomyopathy, but can also be midwall and subepicardial[59]. Therefore, careful electrophysiological mapping is necessary to achieve successful ablation[76]. The recommendation for VT ablation in CHD follows the indication for other clinical conditions[77]: Symptomatic sustained monomorphic VT, including VT terminated by ICD, that recurs despite drug therapy or when antiarrhythmic drugs are not tolerated or not desired, and when there is a suspected trigger that can be targeted for ablation; control of incessant sustained monomorphic VT or VT storm that is not the result of a transient reversible cause; and bundle branch reentrant or interfascicular VT.

STROKE

CD is responsible for up to 20% of stroke cases in endemic areas[78]. The main mechanism of stroke in CD is cardioembolism from thrombi arising mainly in apical ventricular aneurysms. However, as patients with CD have a high prevalence of atrial fibrillation[79,80], thrombi originating from the LA and the LA appendage also contribute to stroke in CHD[81]. The risk factors already identified for stroke in CHD are apical aneurysm, LV thrombus, severe atrial dilation, LV systolic dysfunction, older age, and atrial fibrillation[39,52]. Recently, risk factors for atrial fibrillation were identified, including LA function[61] which could possibly become a new risk factor for stroke in CHD. Importantly, CHD patients are aging, and other possible mechanisms for stroke related to comorbidities (hypertension, dyslipidemia, smoking), such as small vessel disease and large vessel atherosclerosis, may also play an important role in CHD[50]. Moreover, proinflammatory and prothrombotic disease states[50,82,83] and endothelial dysfunction may also contribute to a higher incidence of stroke in CHD.

The most frequent signs and symptoms presented by CHD patients with stroke are related to ischemia in the distribution of the anterior or middle cerebral arteries in the brain, and include unilateral weakness and/or numbness, facial droop, and speech deficits ranging from mild dysarthria and mild aphasia to global aphasia[50]. Stroke may also contribute to cognitive impairment and dementia in endemic areas[84,85]. Stroke can be the first clinical manifestation of a patient with CHD[51,86] and examinations for CD must be part of the diagnostic work-up when investigating stroke in patients with epidemiological history positive for CD.

Transthoracic echocardiography is indicated in all patients with CD and thromboembolic events in order to rule out LV mural thrombi, especially in LV apical

aneurysms. Transesophageal echocardiography must also be performed in cases of documented or suspected atrial fibrillation in order to investigate thrombi within the LA and the LA appendage. Holter monitoring is also indicated to investigate occult paroxysmal atrial fibrillation, whenever the source of cardioembolism is still unclear [79]. Cardiac MRI may detect intracardiac thrombi, but its routine use in patients with CHD and stroke is not warranted[87].

Secondary prophylaxis with anticoagulation is indicated in all patients with a previous history of stroke. The timing of initiating anticoagulation in case of a stroke or transient ischemic attack (TIA) due to atrial fibrillation is within 14 d after the onset of neurological symptoms[88] but can be delayed beyond 14 d in cases that are at high risk for hemorrhagic conversion (*i.e.*, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhagic tendency)[88]. Consultation with a specialist is advisable, as most neurologists recommend starting anticoagulation within 96 h of the event in patients with small strokes without hemorrhagic transformation or TIA, and halting anticoagulation for more than 14 d in case of symptomatic hemorrhagic transformation; however, there is little consensus on the exact timing to initiate anticoagulation in other cases[89]. Given that most stroke cases in CHD patients are related to LV thrombi, most neurologists recommend an earlier start of anticoagulation therapy in such cases. In cases of acute stroke in CHD, the experience with thrombolysis is limited, but short-term treatment with thrombolytics seems to have similar success compared to non-Chagas stroke[90,91].

Antiplatelet agents for secondary prophylaxis in patients with CD and stroke considered to be non-cardioembolic are recommended based on studies with non-CD patients, and must follow the published guidelines[88].

Regarding primary prophylaxis, few studies have addressed stroke prediction models for CHD. Our group identified four variables associated with stroke occurrence in patients with sinus rhythm: LV systolic dysfunction, apical aneurysm, primary ST changes, and age > 48 years[39]. A score was created with two points attributed to LV systolic dysfunction and one point for each of the other variables. The annual risk of stroke was 4.4% among patients with a score of 4 or 5, and anticoagulation is indicated in such patients. For patients with a score of 2 to 3, the risk of stroke is lower and may be similar to the risk of bleeding; hence, either anticoagulation or aspirin can be prescribed. Patients with a score of 1 had a low incidence of ischemic events, and we recommend treatment with aspirin or no treatment at all is recommended[39]. Anticoagulation for primary prophylaxis is also indicated whenever intracardiac thrombi are diagnosed by cardiac imaging. In cases of paroxysmal or permanent atrial fibrillation, primary stroke prophylaxis follows the same recommendations for non-CD patients[9].

The drug of choice for anticoagulation in CHD is warfarin, which is the drug that cardiologists have the largest experience with in clinical practice in CHD. At present, no study has compared warfarin with direct oral anticoagulants in CD. However, patients with contraindications or those who cannot tolerate warfarin may be treated with direct oral anticoagulants, especially patients with atrial fibrillation. Regarding LV thrombi, the experience with direct oral anticoagulants is still limited, but a meta-analysis of five retrospective observational studies suggested that both warfarin and direct oral anticoagulants have a similar rate of thrombus resolution, major bleeding, and stroke or systemic embolization. However, none of these studies included patients with CD[92].

HEART FAILURE

CHD has an important burden on the public health system due to frequent cardiovascular complications[93]. One of the most important CHD complications is HF with reduced ejection fraction (HFrEF).

Patients with CD and HFrEF usually present a dilated cardiomyopathy with a large amount of fibrosis, ventricular remodeling, and damage to the electrical conduction system. These changes ultimately lead to bradyarrhythmias, tachyarrhythmias, and progressive LV global systolic dysfunction[12] with hemodynamic and neurohormonal responses similar to those observed in other cardiomyopathies. This common pathophysiology suggests that the treatment usually recommended for HFrEF could also be prescribed to CHD patients with HF[1]. However, most previous studies that tested such medications in HF included a small proportion of CHD patients.

Right-sided HF are more prominent than left-sided HF symptoms and signs in CHD patients with HF[1]. Typical physical examination reveals deviated and sustained ictus of the LV, usually with prominent RV, third heart sound, and varying degrees of mitral and tricuspid regurgitation. Splitting of the second heart sound may be associated with right bundle branch block. Edema, jugular venous distention, dyspnea, and fatigue are common symptoms, but orthopnea is less common than in other cardiomyopathies[15]. In addition to ECG, echocardiography is essential in patients with HF, as outlined in the "Imaging Exams" section of this review.

In a meta-analysis of 143 studies, CD was responsible for 13% of all HF cases in Latin America[94]. Patients with HF due to CD have a more dismal prognosis than patients with HF due to other etiologies, which includes a higher proportion of hospital admissions due to HF and arrhythmia, pacemaker implantation, and stroke [15]. Moreover, the importance of HF as a mode of death in CHD has increased in recent years[95]. Patients with asymptomatic LV systolic dysfunction should be started on angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers, as recommended by the HF guidelines[36].

Non-pharmacological treatment strategies for HF are described in a specific section of this review.

The pharmacological treatment in patients with HF due to CD follows the recommendations of HF guidelines[36] and CD consensus[1,9,12] and includes a neurohumoral block (beta-blockers, ACEI or angiotensin receptor blockers, and mineralocorticoid receptor antagonists). However, the recommended full doses of these drugs are often not reached, as patients with CHD have a high prevalence of atrioventricular block and autonomic nervous system disorders. Carvedilol is the most frequently used beta-blocker in CHD, although the quality of evidence is low and based on a meta-analysis that included 69 participants and found a lower all-cause mortality in the carvedilol group than in the placebo group[96].

Patients with HF due to CD receive amiodarone more often because of a higher risk of ventricular malignant arrhythmias. The same occurs with anticoagulants due to a higher frequency of cardioembolic events[1].

Diuretics should also be added to the patients' prescription whenever there is clinical evidence of congestion, and the doses should be tapered to the lowest possible dosage in order to avoid electrolyte and metabolic disorders[1].

In case the patient persists with symptoms compatible of NYHA functional class III or above despite neurohumoral block and diuretics, digitalis may be added to the prescription. Another indication for digitalis is the presence of atrial fibrillation with a rapid ventricular response. However, it is necessary to monitor digitalis serum levels and the occurrence of atrioventricular block[1].

The experience with new drugs recently added to the HF treatment portfolio is very limited. Regarding ivabradine, a *post hoc* sub-analysis of the SHIFT trial suggested that ivabradine was associated with improvement in NYHA functional class and a trend toward reduction in mortality[97]. However, the indication for ivabradine in CD patients is limited due to electrical conduction system disturbances characteristic of CHD[12]. Regarding sacubitril/valsartan, only 7.6% of Latin American patients with HFrEF randomized to angiotensin receptor-neprilysin inhibitors in the PARADIGM-HF and ATMOSPHERE trials had CHD. An underpowered analysis suggested that patients with CHD treated with sacubitril/valsartan had a lower risk of cardiovascular death or HF hospitalization[98]. Therefore, a specific multicenter, prospective, randomized, controlled phase 4 study including only patients with HFrEF due to CD, named PARACHUTE-HF study, is currently in progress in order to testing the superiority of sacubitril/valsartan over enalapril in improving the composite endpoint of cardiovascular death or first HF hospitalization (NCT04023227).

When overt and refractory HF occurs, alternative therapies are still possible for CHD. Orthotopic heart transplantation (OHT) and cardiac resynchronization therapy are such therapies. Although there is a risk of CD reactivation after OHT, advances in immunosuppression protocols and careful reactivation monitoring after surgery allowed successful OHT in CHD. In fact, CD is the third most common indication for OHT in South America[12]. The selection criteria are the same as those in the general OHT evaluation, but an active pre-transplantation search for chronic digestive complications (megaesophagus and megacolon) is necessary to avoid postoperative complications. The mortality rate is high for CHD patients on the waiting list, suggesting the need for earlier intervention. On the other hand, post-OHT survival is higher, despite the risk of reactivation, perhaps because the patients included in the previous series were younger, with fewer comorbidities and less risk of pulmonary hypertension. Monitoring of reactivation throughout life is mandatory, especially during increases in immunosuppression therapy for transplant organ rejection.

Universal trypanocidal prophylactic therapy before OHT is not recommended, but benznidazole is the drug of choice in cases of reactivation[1,9].

Different devices for cardiac assistance could be used in patients with end-stage HFrEF due to CD. These could be applied as a bridge to transplantation, a bridge to recovery, or even as a destination therapy. Unfortunately, the limited access to health services in endemic countries makes this option uncommon, but some successful experiences have been described[99].

NON-PHARMACOLOGICAL STRATEGIES

Several non-pharmacological strategies based on lifestyle modifications have demonstrated beneficial effects in the clinical management of patients with CHD, including nutritional counseling, pharmaceutical care, and exercise-based cardiac rehabilitation (CR). The first approach involves dietary guidelines, encouragement to self-care, adherence to treatment, regular physical activities, and prohibition of alcohol and tobacco use. These strategies are usually easy to implement and have a low maintenance cost; therefore, they should be included in clinical practice.

Nutritional counseling

CHD promotes physiological changes that can directly influence nutritional status. In this setting, nutritional counseling aims to provide adequate calories and nutrients to maintain an ideal body composition[9], especially considering patients who progress with cardiac cachexia. Nutritional counseling should consider the eating behaviors and cultural habits of each patient, as well as access to food and the presence of other clinical conditions, such as dysphagia, intestinal constipation, dyslipidemia, diabetes mellitus, and hypertension[9].

For patients with HF, nutritional intervention also includes the control of salt consumption, limiting it to 3 to 4 g/d for those with mild to moderate disease, and less than 2 g/d for more severe cases (decompensated HF)[9]. The restriction of sodium consumption can cause low adherence to dietary recommendations[100,101], due to low food palatability, resulting in insufficient food intake with energy and nutrient supply below the recommendation. Culinary preparations using spices, herbs, condiments, and different techniques have been recommended to improve palatability and encourage healthy food consumption[102]. In severe HF, restriction of fluid intake is necessary, and patients should be encouraged to closely control their body weight [9].

Pharmaceutical care

Considering that as high as 30% to 40% of patients with CD will develop cardiac or digestive symptoms that chronically require medical assistance and pharmacological treatment[9], pharmaceutical care emerges as an important auxiliary strategy to improve medication compliance, minimize adverse drug events, and improve quality of life[103]. Therefore, pharmaceutical care is an important strategy that should be implemented in the follow-up of patients with CHD and HF, as it could help to identify adverse drug events and suggest alternatives to minimize these side effects [104].

Exercise-based cardiac rehabilitation

Exercise-based CR has emerged as an important strategy to improve functional capacity and quality of life in patients with CHD complicated by HF[35]. Before participating in an exercise program, patients must undergo a clinical evaluation including anamnesis, physical examination, and complementary tests to minimize the risk of adverse events during exercise practice. The anamnesis should include information regarding the stage of CHD, history of arrhythmias, organ damage, comorbidities, devices (pacemaker or ICD), previous hospital admissions, allergies, and history of physical activity. On physical examination, cardiac and pulmonary auscultation are important, together with evaluation of musculoskeletal limitations, surgical scars, and any other signs of diseases that may limit exercise practice. A basic laboratory investigation with a complete blood count, lipid profile, and coagulation factors is also important.

A resting ECG should be performed to assess rhythm disturbances, and a maximal exercise test (with or without gas exchange analysis) should be performed to evaluate clinical, hemodynamic, and electrocardiographic responses during exercise. If not available, a submaximal test (*e.g.*, the 6-min walk test) can provide parameters for

monitoring functional capacity. Exercise tests must be performed under the usual medications, especially for patients with chronotropic negative drugs, such as beta-blockers, digitalis, or antiarrhythmics, to mimic the condition that they will be in during physical training sessions. An echocardiographic evaluation is also useful, as it provides additional information for risk stratification[105].

During exercise sessions, electrocardiographic monitoring should be performed to detect malignant exercise-induced arrhythmias. Heart rate monitors can also be used, but the CR team must pay attention to possible errors due to electrical interference and check with manual verification, if necessary. Blood pressure and oxygen saturation should also be assessed before, during, and after exercise. Blood glucose measurements can be performed before and after exercise sessions for diabetic patients.

Ideally, the CR training program should be comprised of 150 to 300 min per week (divided into 3 to 5 wkly sessions) of moderate-intensity activities, including aerobic, strength, stretch, and balance exercises. The intensity of aerobic exercise usually ranges from 70% to 85% of the peak heart rate obtained in the exercise test or 90% to 110% of the ventilatory threshold obtained in the maximal exercise test with gas exchange analysis. The perception of effort scale (*i.e.*, Borg scale) is also a valuable instrument that can be used to control exercise intensity. Resistance exercises should be performed at least twice a week at moderate intensity, with greater emphasis on large muscle groups (upper limbs, lower limbs, and trunk), which can be performed using free weights, elastic bands, and resistance equipment. Stretching and balance exercises improve performance of functional activities, reduce cardiovascular overload in some daily situations, decrease the risk of falls, and improve autonomy[106].

In addition to low aerobic capacity and peripheral muscle weakness, inspiratory muscle weakness is estimated in 30% to 50% of patients with CHD[107]. Inspiratory muscle training (IMT) alone and associated with aerobic training[108,109] may improve exercise capacity in HF patients by reducing diaphragmatic metaboreflex activity and respiratory muscle fatigue[110]. IMT should be considered in CR, in combination with aerobic endurance or peripheral resistance training[111]. IMT should start at 30% of maximal inspiratory pressure (MIP), followed by a gradual increase to 60% MIP, for 20 to 30 min per session, with a frequency of 3 to 5 exercise sessions per week[112]. Despite the growing recommendation of IMT to become a part of CR, little is known about this strategy for CHD. Recently, two IMT protocols (30% and 60% of MIP) have been safely tested in patients with CHD[107].

CONCLUSION

CHD is still a major cause of hospital admissions, cardiac device implantations, stroke, and death in endemic Latin American countries. CHD must also be investigated as a cause of cardiac complications in migrant populations in non-endemic countries. The routine performance of diagnostic examinations and therapies described here can help identify CHD complications and minimize their consequences in order to improve quality of life and, possibly, survival.

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REVIEW

Cardiovascular benefits from SGLT2 inhibition in type 2 diabetes mellitus patients is not impaired with phosphate flux related to pharmacotherapy

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Abstract

The beneficial cardiorenal outcomes of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM) have been substantiated by multiple clinical trials, resulting in increased interest in the multifarious pathways by which their mechanisms act. The principal effect of SGLT2i (-flozin drugs) can be appreciated in their ability to block the SGLT2 protein within the kidneys, inhibiting glucose reabsorption, and causing an associated osmotic diuresis. This ameliorates plasma glucose elevations and the negative cardiorenal sequelae associated with the latter. These include aberrant mitochondrial metabolism and oxidative stress burden, endothelial cell dysfunction, pernicious neurohormonal activation, and the development of inimical hemodynamics. Positive outcomes within these domains have been validated with SGLT2i administration. However, by modulating the sodium-glucose cotransporter in the proximal tubule (PT), SGLT2i consequently promotes sodium-phosphate cotransporter activity with phosphate retention. Phosphatemia, even at physiologic levels, poses a risk in cardiovascular disease burden, more so in patients with type 2 diabetes mellitus (T2DM). There also exists an association between phosphatemia and renal impairment, the latter hampering cardiovascular function through an array of physiologic roles, such as fluid regulation, hormonal tone, and neuromodulation. Moreover, increased phosphate flux is associated with an

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associated increase in fibroblast growth factor 23 levels, also detrimental to homeostatic cardiometabolic function. A contemporary commentary concerning this notion unifying cardiovascular outcome trial data with the translational biology of phosphate is scant within the literature. Given the apparent beneficial outcomes associated with SGLT2i administration notwithstanding negative effects of phosphatemia, we discuss in this review the effects of phosphate on the cardiometabolic status in patients with T2DM and cardiorenal disease, as well as the mechanisms by which SGLT2i counteract or overcome them to achieve their net effects. Content drawn to develop this conversation begins with proceedings in the basic sciences and works towards clinical trial data.

Key Words: Sodium-glucose cotransporter 2; Phosphate; Hyperphosphatemia; Cardiovascular; Canagliflozin; Dapagliflozin; Empagliflozin; Endothelial

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Core Tip: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have received increased attention regarding their pleiotropic effects given their markedly impressive performance in cardiovascular outcome trials (CVOT). Preliminary evidence shows that their role as antidiabetic agents is not their sole mechanism in achieving these cardiorenal protective properties. Therefore, investigation in the auxiliary properties that they hold concomitant with glucose control, vindicated by not only CVOTs, but meta-analyses, retrospective studies, and case reports has led to increased interest in delineating their global pharmacodynamic effects across the spectrum of gene expression and molecular modulation to end-organ translational biology. Such a full profile of their effects is not yet understood given the refractory period between clinical evidence supporting their utilization and a proclivity for their implementation in practical clinical environments. In this review, we answer inquiries regarding how *via* a multifarious avenues, SGLT2 inhibitors, while carrying a negative effect of induced phosphatemia (which is deleterious to the heart), compensate for this phenomenon, retaining their propensity for net cardiac benefit upon pharmacotherapeutic administration under appropriate clinical circumstances.

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INTRODUCTION

In addition to serving a role as antidiabetic agents by mediating glycemic control, the cardiovascular benefits associated with sodium-glucose cotransporter 2 inhibitors (SGLT2i) administration is a boon for patients with type 2 diabetes mellitus (T2DM) given that such patients suffer immensely from increased risk of microvascular and macrovascular complications attributable to T2DM, such as diabetic nephropathy and major adverse cardiovascular events (MACE), respectively[1]. It is noteworthy to state these sequelae are not mutually exclusive when one discusses the cardiovascular health of patients with T2DM and the renal considerations of phosphate dynamics with SGLT2i administration on MACE. An example highlighting these interdigitated cardiorenal pathways can be appreciated when considering that cardiovascular demise in patients with T2DM may predispose to acute kidney injury (AKI) through hypoperfusion and consequently, a diminished capacity to efficiently maintain glomerular filtration rate (GFR). Conversely, pathologic nephropathy from T2DM unveils baneful circumstance within the nephron conducive to MACE *via* mismanagement of fluid and ion flux as well as pathologic neurohormonal activation *via* the renin-angiotensin-aldosterone system (RAAS)[2-4].

Estimates suggest that T2DM is prevalent in roughly 40% of chronic kidney disease (CKD) patients in the United States[5]. Epidemiological studies further contextualize this association, with one United States Renal Data System (USRDS) report implicating diabetes in 44% of end-stage renal disease (ESRD) cases[6]. Moreover, examinations of 10-year cumulative mortality profiles of participants in the Third National Health and Nutrition Examination Survey (NHANES III) linked with the National Death Index has shown that among individuals with diabetes and kidney disease, standardized mortality was 31.1% (95%CI: 24.7%-37.5%) relative to 7.7% within the reference group, a patient populous defined as that without diabetes or kidney disease (95%CI: 7.0%-8.3%)[7]. This represents a statistically significant absolute risk difference of 23.4% (95%CI: 17.0%-29.9%, $P < 0.01$). Such emphasis on the baleful aspects of T2DM is important as cardiovascular disease (CVD) burden and T2DM presents with a similarly grim association, as seen in an incidence-based study by Straka *et al*[8], which followed 29863 patients (5501 with T2DM and 24362 without T2DM). In this study, it was observed that patients with T2DM exhibited a statistically significant relative risk of 1.53 for myocardial infarction (MI), 1.1 for coronary artery disease (CAD), 2.12 for heart failure, and 1.58 for stroke.

With an expanded understanding of the pathophysiologic pathways that stem from T2DM and branch towards its sequelae comes a paradigm shift in which T2DM is no longer focused solely as a disorder of hyperglycemia and aberrant insulin regulation warranting the reduction of hemoglobin A1C (HbA1C) for adequate clinical management[9-12]. Rather, an appraisal of diabetic complications is giving rise to a change in therapeutic approaches that target T2DM sequelae in tandem with glucose and insulin dynamics for expanded, and flexible T2DM treatment strategies. This can be appreciated by the advent of pharmacotherapeutic options with various mechanisms of action and pleiotropic effects, in addition to the Food and Drug Administration's shift towards expectations that antidiabetic agents being considered for approval undergo scrutiny that is validated by trial data that takes into account the systemic effects of T2DM (with an emphasis on microvascular and macrovascular pathophysiology)[13]. Evidence for this change in doctrine can be seen in the elevation of SGLT2i to more preferential recommended therapeutic options for complicated T2DM by authoritative bodies and medical societies such as the American College of Cardiology (ACC), the American Diabetes Association (ADA), and Kidney Disease Improving Global Outcomes (KDIGO)[14-17].

Affirmation for the beneficial clinical outcomes with SGLT2i pharmacotherapy is validated by favorable results in landmark clinical outcome trials. These aforementioned trials scrutinized the effects of multiple SGLT2i agents (namely, empagliflozin, dapagliflozin, and canagliflozin) in their ability to reduce endpoints defined by cardiovascular mortality, hospitalizations for heart failure, and renal considerations of associated cardiovascular demise such as death from renal failure and end-stage renal disease exacerbation, to name a few[18-21]. These drugs work (as illustrated in Figure 1) by blocking the reabsorption of glucose *via* the SGLT2 protein, which is responsible for the reuptake of the vast proportion of glucose in the proximal renal tubule. The latter causes glucosuria and decreased serum glucose levels, which inhibits the salient pathophysiologic pathways in T2DM triggered by hyperglycemia. The degree of glucosuria varies depending on drug metabolism, SGLT2 protein expression as well as distribution, and diabetic status. However, narrative reviews backed by quantitative estimates of the nephron's functional capacity and a general window of SGLT2i efficacy suggest that the glucosuria induced can lead to the excretion of up to 150 g of glucose daily with pharmacotherapy[22].

Associated with such glucosuria is also the liberation of fluid with SGLT2i therapy among patients with T2DM. In normal, healthy adults, the kidneys have the propensity to filter roughly 180 g of glucose per daily, the vast majority of which is usually reabsorbed at the proximal convoluted tubule (PCT) *via* sodium-glucose cotransport[23]. Due to insulin resistance exhibited in patients with T2DM, peripheral GLUT4 expression is decreased in T2DM, leading to increased serum glucose, and increased filtered glucose load through the glomerulus once perfusion reaches the nephron. The low affinity-high capacity properties of the SGLT2 protein within the PCT, allows for substantial glucose reabsorption, with reabsorption dynamics reaching up to 90% in certain physiologic scenarios[24,25]. By inhibiting where the majority of glucose reabsorption at the PCT, there remains feeble opportunities for glucose reabsorption to take place along downstream sites within the nephron, resulting in an increase in osmotic pressure to the flow en route to eventual urinary output[26]. Subsequently, an increased osmotic pressure from a rise in SGLT2i mediated increase in luminal glucose prevents the egress of glucose across tubule cells (and by proxy, the interstitial compartments) resulting in increased urinary volume[27-29] and liberation

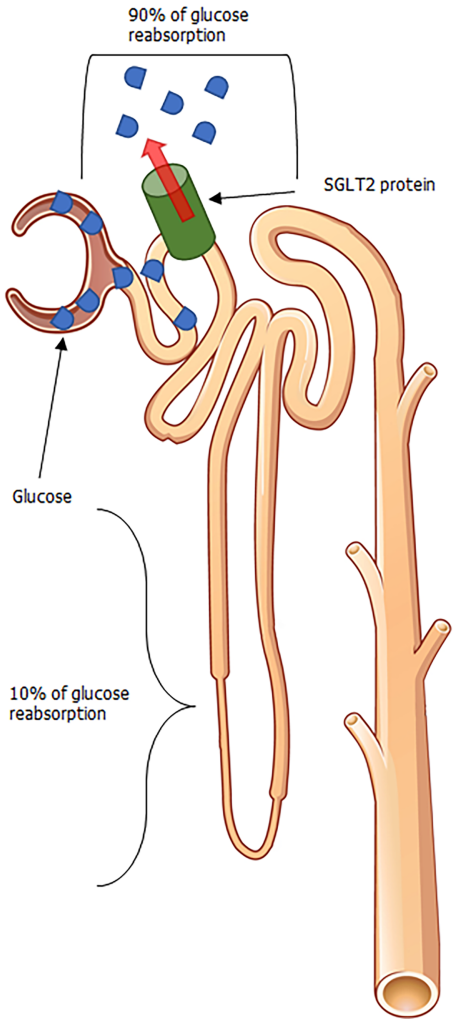


Figure 1 Glycosuria mediated from sodium-glucose cotransporter 2 inhibition. Adapted from OpenStax College, which is licensed under a Creative Commons Attribution 3.0 Unported License. SGLT2: Sodium-glucose cotransporter 2.

of systemic fluid.

The natriuresis involved in SGLT2i pharmacotherapy has recently been scrutinized and there are mixed views as to the degree of natriuresis involved in SGLT2i therapy, as while there is an osmolarity of sodium that would have been tethered for sodium-glucose cotransport, inhibition does not preclude this sodium from undergoing reabsorption at other sites, with some sites even performing compensatory roles in sodium reabsorption after transient natriuresis has been completed[30]. For example, in the thick ascending loop of Henle the Na-K-Cl cotransporter shunts luminal sodium that would have been excreted in urine. Then sodium is discharged into the blood *via* ATP-dependent sodium-potassium pump, resulting in retention of sodium. While playing a minor role, sodium reabsorption also takes place in the distal convoluted tubule through a sodium-chloride symporter that harvests urinary sodium that is also discharged *via* ATP-dependent sodium-potassium pumps. Nevertheless, studies with SGLT2i administration over a 4-week course of empagliflozin resulted in a 30%-60% increase in urinary sodium (which pulls water along for excretion) in patients with T2DM ($P \leq 0.001$), and was positively correlated to the degree of glucosuria ($P \leq 0.001$) [31]. The cumulative effects of this fluid loss can be appreciated from a cardiovascular perspective as a reduction in blood pressure as vindicated by the landmark trials, implying a reduced afterload. Moreover, studies show that the fluid loss in SGLT2i therapy occur *via* losses in intravascular compartments, implying a reduction in preload. This dual reprieve in those with heart disease promotes a physiologic status that leads to improved ventricular loading without maladaptive compensatory changes such as remodeling, and may be partially responsible for positive CVOT results, although it shown be mentioned there are many pleiotropic effects of these drugs under investigation[32-34].

SLGT2i also promote cardiovascular benefits in patients with T2DM through auxiliary avenues deeply rooted in diabetic sequelae such as through the blunting of harmful reactive oxygen species (ROS), modulating detrimental neurohormonal activation, improving oxygen flux, and preserving a positive vascular biology profile [35-38]. However, since the capacity for SGLT2i agents hinder the cotransport and reabsorption of sodium and glucose, the sodium gradient is therefore retained for sodium-dependent phosphate cotransporters (SLC34A1 and SLC34A3) as referenced in Figure 2[39-41]. The consequence of this shift in renal cotransporter dynamics is a resultant increase in phosphate reabsorption at the site of the proximal tubule, resulting in hyperphosphatemia. Albeit a recognized a process, ramifications of phosphate flux with SGLT2i administration within the literature have largely been centered upon a controversial dialogue on whether or not these agents contribute to deficits in bone mineral density of significance to subsequently provoke bone fractures [42-44]. Scant in the literature however, is a commentary highlighting the role of serum phosphate changes mediated by SGLT2i on CVD, considering CVOT have vindicated SGLT2i in mitigating CVD burden. Nevertheless, the pharmacology of SGLT2i theoretically induces increased serum phosphate, which is associated with vascular calcification and stiffness, cardiac remodeling, and other pathologic changes conductive to MACE (observed in settings independent of SGLT2i administration), especially in populations with aberrant metabolic derangements such as T2DM and diabetic CKD[45-49]. A discussion of the relative degrees of phosphate induction with SGLT2i therapy in relation to the attenuation of T2DM and its sequelae conferred with therapy (as is supported by multiple clinical trials) is prudent for giving full context on the pharmacology of SGLT2i while affirming that these drugs are still associated with remarkably beneficial cardiovascular benefit.

The effects of phosphate on cardiovascular function and also renal physiology which thereby impacts cardiovascular function is well documented. While discussed primarily within the scope of the nephron, hyperphosphatemia as a side effect associated with SGLT2i administration has been vindicated in human studies. In one study by Blau *et al*[50], among 25 research participants receiving Canagliflozin 300 mg over placebo, a marked increase in sodium excretion with an increase in associated serum phosphate levels were noted, giving validation for the sodium-phosphate cotransporter mechanism of SGLT2i mediated phosphatemia. Moreover, Canagliflozin administration was associated with a 16% increase in serum phosphate levels over placebo ($P < 0.001$).

In another *post-hoc* analysis of a double-blind, randomized, crossover trial in 31 patients with T2DM and early-stage diabetic kidney disease (defined as an albumin-to-creatinine ratio between 100 and 3500 m/g, eGFR ≥ 45 mL/min per 1.73 m^2, and 11.4% > HbA1c ≥ 7.2%, patients were randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin administration increased serum phosphate by 9% (95%CI: 4%-15%, $P = 0.002$)[51]. Interestingly, this increase in phosphate was not correlated with changes in eGFR or 24-h albumin excretion, a known marker of renal and by proxy, cardiovascular impairment[52-54]. Such an increase in phosphate with dapagliflozin administration is noteworthy when considering that a 2016 analysis incorporating over an ethnically diverse cohort of 94989 patients stratified for population-based phosphorus quartiles by ethnicity demonstrated that 0.5 mg/dL serum phosphorus increases were associated with adjusted hazard ratios of increased renal mortality[55]. Examinations of NHANES III with incident ESRD and elevated phosphate (> 4 mg/dL) proved elevated ESRD incidence compared to those with lower phosphate levels (RR = 1.90; 95%CI: 1.03–3.53; $P = 0.04$)[56]. The latter two studies show a disparity between the dogma of phosphatemia and empiric findings of studies using dapagliflozin.

Associated with hyperphosphatemia is the elevation of fibroblast growth factor 23 (FGF23)[57,58]. This protein has received interest in its clinical applications due to its potential in mediating aberrant metabolic pathways associated with cardiovascular health, as marked by its associated with MACE providing a link between hyperphosphatemia and the heart[59-61]. There is a growing body of evidence that FGF23 is a key player in signaling pathways related or as a biomarker related to distinct pathologic avenues of diminished cardiovascular function- these include left ventricular hypertrophy (LVH), endothelial cell dysfunction, arterial fitness, and atherosclerosis[60,62]. Nevertheless, we can appreciate that SGLT2i, despite promoting hyperphosphatemia (and subsequently FGF23 as marked by the Canagliflozin and Dapagliflozin phosphate studies) mitigate cardiovascular disease buden[50,51]. We speculate that despite being central to pathways that hamper cardiovascular disease outcome, the mechanisms by which phosphatemia and FGF23 expression induce these impairments are also attenuated by SGLT2i in their pleiotropic effects, with even more

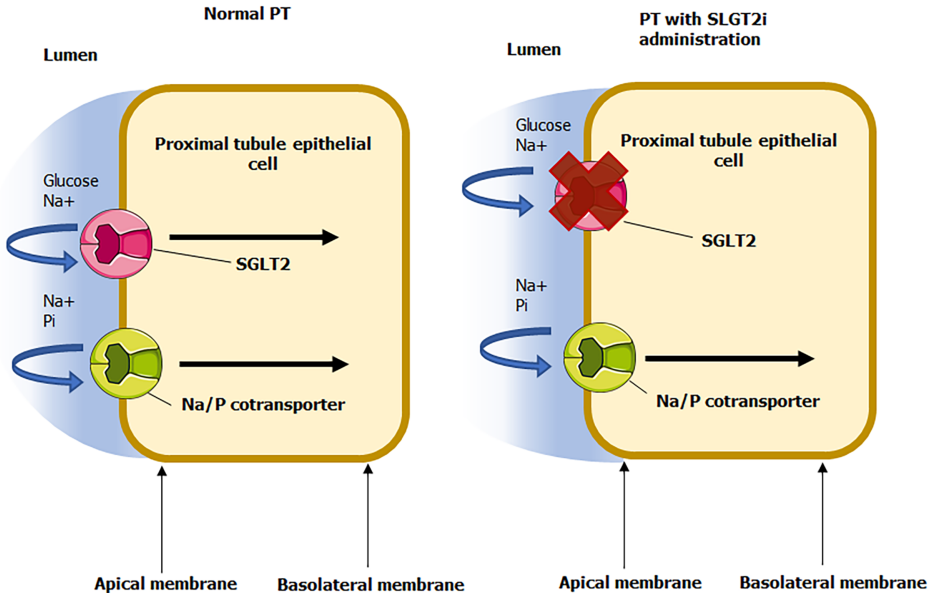


Figure 2 Glycosuria mediated from sodium-glucose cotransporter 2 inhibition. Adapted from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 Unported License. PT: Proximal tubule; SGLT2i: Sodium-glucose cotransporter 2 inhibitors.

mechanisms of cardiovascular benefit and thus, leading to a "net" positive outcome. The course of this review will outline these pathways from a phosphate metabolism perspective, and subsequently *via* commentaries on how SGLT2i overlap with these pathways and go beyond these collective pathways to further support cardiovascular health.

Moreover, the associated osmotic diuresis promotes the loss of sodium and water, which decreases blood pressure and improves oxygen flux and hemodynamic status. For example, in EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes), 7020 patients with established coronary artery disease and T2DM were slated to receive 10 mg empagliflozin (n = 2345), 25 mg empagliflozin (n = 2342) or placebo (n = 2333)[63]. The results were reductions in the risk of cardiovascular (CV) death by 38% relative to placebo (3.7% *vs* 5.9%, HR = 0.62; 95%CI: 0.49-0.77; P < 0.001). An exploratory mediation analysis of EMPA-REG attempted to identify elements influencing CVD death risk reduction with empagliflozin by analyzing *post hoc* mediators through Cox regression[64]. A significant finding of this audit of trial covariates and their influence in survival identified that hematocrit and hemoglobin mediated roughly 50% of the propensity of empagliflozin to improve CV survival relative to placebo. One possible reason for this rise in red blood cell (RBC) magnitude may be due to more efficient erythropoiesis *via* the renoprotective properties of SLGTI2[65,66]. Support for this theory can be found in a small-scale study of 66 patients administered empagliflozin over four weeks, with a 31% increase in erythropoietin (P = 0.0078) seen in 64 patients[31]. Similar improvements in erythropoiesis have been observed in other classes of SGLT2i, dapagliflozin and canagliflozin[67,68]. The role for this phenomenon in CV survival is not well studied however and can be attributed from improvements in oxygen flux and global metabolic resource allocation. Alternatively, parsimony would suggest that osmotic diuresis and improved handling of fluid would result in an increase in RBC constituents *via* dilution-concentration dynamics, and the CV survival observed would be attributable to the mitigation of edema and ventricular stress. Nevertheless, lessons from SGLT2i therapy show us that the improved prospects for patients with T2DM are pleiotropic in nature and extend beyond correction of hyperglycemia. This concept is congruent with the focus in this work that multiple axes promote improved outcomes notwithstanding phosphate metabolism. Such principles will be reinforced throughout this commentary.

PHOSPHATE METABOLISM, DIABETES, HEART DISEASE- LOADING SGLT2 IN THE PICTURE

Within the context of the pleiotropic effects of SLGT2i administration and phosphate metabolism, it is noteworthy to mention that the ramifications of phosphate metabolism occur peripherally and not directly within the heart itself. The SGLT2 protein is not expressed within cardiac tissue, as demonstrated by sequencing studies [69]. Therefore, to make remarks about SGLT2 inhibition within the context of phosphate metabolism, a query of phosphate metabolism beginning within the nephron is warranted.

In normal settings of serum hyperphosphatemia, the parathyroid glands address this homeostatic imbalance through the secretion of parathyroid hormone (PTH). PTH acts on the PT to inhibit sodium/phosphate cotransport, resulting in the excretion of phosphate through urine. There is also a secondary implication of increased sodium flux on the cotransporters hosted on distal portions of the nephron and their relative dynamics Moreover, PTH also has an auxiliary role of promoting phosphate absorption from the small intestine as well as bone, shuttling phosphorus into serum. It also has a role in the activation of vitamin D *via* secondary hydroxylation, which has cardiorenal implications which will later be discussed. For brevity and completeness, this activation of vitamin D is implicated in the absorption of calcium and phosphate within the intestine, with less reliance on phosphate flux on Vitamin D, resulting in a net decrease of phosphate[70].

However, the metabolism of phosphorus and its associated compounds in the context of contemporary lifestyle and diet with an emphasis on heart disease and T2DM has caused a paradigm shift in how this homeostatic mechanism plays out for such patients. Current diets, especially in the western world, are dense in phosphate and have ramifications in a populous that has a significant burden of T2DM and heart disease[71,72]. Animal studies conducted have shown that both genetically impairing sodium-phosphate cotransporter function as well as hyperphosphatemia-induced *via* diet in wild-type mammals results in a phenotype akin to metabolic syndrome, which includes loss of lean skeletal muscle mass, increased reactive oxygen species formation, and renal impairment and cardiopulmonary deficits[73]. This dual-approach of the elicitation of increased serum phosphate with similar end-point results confirmed by histologically analyses was cited as giving credence towards the notion that absolute hyperphosphatemia was the end insult responsible for these findings [73]. These findings mirror the components of derangements seen in patients with T2DM and cardiovascular disease.

For example, earlier animal studies show support for hyperinsulinemia promoting reductions in the fractional excretion of phosphate in dogs, caused mainly by abatement in the ratio of tubular fluid to plasma phosphate domineered primarily by proximal tubular phosphate reabsorption ($P < 0.02$), lending an association between dysfunctional glucose metabolism and phosphate flux with consequences in disease states such as cardiovascular disease[74]. Further evidence for an association between derangements in glucose and phosphate are furthered by one human study, ^{31}P magnetic resonance spectroscopy (MRS) assessing the effects of a hyperglycemic-hyperinsulinemic clamp experiment augmented on study subjects noted an increase in inorganic phosphate and reductions in phosphocreatinine (PCr)[75]. The reductions in PCr have direct implications in heart disease, as one study by Bhella *et al*[76] recruited healthy patients and those with heart failure with preserved ejection fraction (HFpEF) to perform lower limb exercises with MRI scanning evaluation to assess myocyte function. HFpEF patients were noted to have reduced rates of oxidative phosphorylation rates, with an increase in refractory period to normalization of phosphocreatine when compared to healthy sedentary age-matched controls. Blunted PCr replenishment can cause concern as it functions as a phosphate derivative that skeletal muscle may opt to metabolically activate when ATP reserves are not high enough to sustain a respective workload. Reductions in PCr as seen in hyperphosphatemic states show an increased in the proclivity for cardiomyocytes to undergo apoptosis or irregular phenotypes[77].

Irregularities in phosphate in hyperinsulinemic states as mentioned above have also been directly studied in patients with T2DM, setting the foundation for investigation in diabetic heart disease and phosphate metabolism, with SGLT2i. ^{31}P MRS scanning the vastus lateralis of patients with T2DM compared to healthy, aged-controlled matches showed an absolute decrease in PCr, (PCr 28.6 ± 3.2 *vs* 24.6 ± 2.4, $P < 0.002$), which is supported by a negative correlation between PCr and HgbA1C ($r = -0.63$, $P < 0.01$)[78]. These findings support that the diabetic state as well as the cardiovascular

state are impacted by sequelae related to hyperphosphatemia, especially in patients with conditions related to insulin resistance where SGLT2i utilization would be warranted given appropriate consideration considering their increased use in patients with diabetes and cardiovascular disease.

Another derangement observed in the Ohnishi study was renal impairment seen in the form of renal arteriole calcification with apoptotic cells upon histology directly associated with heavy phosphate burden, indicative of maladaptive renal calcification. Such observations have been observed in humans, with ramifications of CKD and ESRD[79]. Prevailing theories include phosphate aggravating vascular smooth cells or the buildup of calcium byproducts in the form of nephrocalcinosis[80]. Similar derangements, albeit by different constituents, occur in T2DM. Such processes both however heavily similarly impact the cardiovascular benefits in patients with T2DM. Patients with T2DM experience insulin resistance and as result experience blunted responses to glucose attenuation, precluding euglycemia. The excess of glucose tends to undergo nonenzymatic glycosylation with amine groups of the glomerular basement membrane of the kidney, causing protein leakage which occludes the arterial lumen. This process propensity to impact the efferent arteriole sooner and with more impact than the afferent arteriole, causing an increase in intraluminal pressure and GFR[81].

One consequence of this relative mismatch in luminal caliber is an initial hyperfiltration cascade that ultimately damages the renal mesangium. Subsequent hyalinization of the afferent arteriole decreases GFR, ultimately manifesting as diabetic kidney disease and subsequently, CKD. The decrease in afferent lumen caliber is noted by afferent baroreceptors and elicits renin secretion by the juxtaglomerular cells. Subsequently this promotes the renin-angiotensin-aldosterone system (RAAS) cascade [82]. Ramifications of the RAAS system include an increase in blood pressure as marked by the activity of angiotensin II on the systemic vasculature, causing an increase in afterload as well as sodium retention. Chronically, this can lead to left ventricular hypertrophy and subsequently MACE. We will see that phosphate ultimately impacts the heart in a critical manner similarly, however, the net benefit of SGLT2i through their pleiotropic effects negate the deleterious effects of increased phosphate levels and lead to beneficial cardiorenal outcomes.

Compromised kidneys, such as in the case of phosphate and T2DM flux promotes a physiologic equilibrium that is acclimated to the retention of metabolic toxins which directly serve as insults to the heart and kidney in cardiorenal syndrome as defined by KDIGO[3]. In normal physiologic circumstances, increased congestion caused by edema results in stretch of native mechanosensory nerve fibers scattered throughout the abdominal and pelvic wall[83]. This leads to a phenomenon known as the renorenal reflex, by which activation of this system attenuates efferent renal sympathetic nervous system activity (ERSNA)[84,85]. Decreased ERSNA is associated with a higher threshold for α1-adrenoceptor activation. These receptors play a vital role in the activation of transporters in the proximal tubule that lead to a state of net sodium reabsorption. By decreasing their function, the renorenal reflex induces natriuresis and relief of central congestion. However, chronic kidney disease and ESRD is associated with dysregulation of the renorenal reflex[86,87]. SGLT2i therapy approaches this consequence of renal impairment and promotes homeostatic renal function by offering liberating sodium. Patients with T2DM experience an increase in filtered glucose, which is reabsorbed along with sodium in the proximal tubule with a higher affinity[88]. SGLT2i, mitigates the reabsorption of glucose of up to 90%, with concomitant sodium loss, disinhibiting the juxtaglomerular apparatus from promoting the hyperfiltration loop. Sodium is subsequently diuresed, sparing the kidney from edema and congestion.

In spite of phosphate mediated renal decline, SGLT2i have been shown to improve cardiovascular as well as renal health in patients with T2DM and CKD. CANVAS-Renal (Canagliflozin and cardiovascular and renal events in type 2 diabetes) was one trial that elucidated the effects of canagliflozin on cardiorenal outcomes[89]. Primary outcomes of interest were drawn from composites of cardiovascular death (CVD), nonfatal myocardial infarction (MI), and nonfatal stroke. Death from any cause, CVD related death, albuminuria exacerbation, and heart failure hospitalization. The primary outcome showed improvements in patients receiving canagliflozin compared to placebo (HR = 0.86; 95%CI: 0.75-0.97, P = 0.02)[20]. Cardiovascular secondary outcomes did not demonstrate superiority, (death from any cause, P = 0.24), and thus hypothesis testing was discontinued[20]. However, we will see that other SGLT2i have differential profiles conducive to cardioprotection in spite of phosphate mediated damage, and this example of CANVAS-Renal was included to illustrate that phosphate mediated nephrotoxicity with SGLT2i is not a significant factor as

demonstrated by clinical trial data as will be discussed. Interestingly, it is noted that magnesium modifies the cardiovascular mortality profile of patients undergoing hemodialysis in a positive respect[90]. In one meta-analysis, it was shown that SGLT2i improved serum magnesium levels with the potential to attenuate PTH, and was implicated as a potential underlying factor in cardiorenal mortality benefits in one SGLT2i trial[91]. This is just one of the multiple pleiotropic effects of SGLT2i.

As we see the continuous deleterious effects of hyperphosphatemia, a query in its mechanisms naturally arises. Investigations into the mitochondrial physiology has shown that oxidative stress, as seen in patients with T2DM, can exacerbate phosphate mediated toxicity and cause insulin and glucose dysregulation[92]. Mitochondrial deficits are the central theme in reactive oxygen species (ROS) formation belief in which by hyperglycemia mediates ROS formation, which impacts nodes of cardiorenal significance[35].

HYPERPHOSPHATEMIA, SGLT2, AND CARDIORENAL IMPLICATIONS

One prevailing study directly linking increased intracellular phosphate with cardiovascular incidents a la ROS is through endothelial dysfunction, which act by various mechanisms such as nitric oxide mitigation leading to decreased vascular compliance, vascular apoptosis, and the promotion of atherosclerotic plaques[91-93]. It has also been shown to promote arterial stiffness in healthy individuals[94]. The aggregate effect of these processes limits vascular compliance and the ability for the heart to adapt to hemodynamic instability. T2DM overlays this effect by inducing the formation of one member of the ROS family, NF-κB, which increases cardiomyocyte tension through activating processes related to pressure-induced remodeling and fibrosis as well as upregulates pro-coagulant factors such as tissue factor VIII and by proxy, downregulates anticoagulant factors such as plasminogen and urokinase[95, 96]. The net effect of both processes would have ramifications in oxygen flux and the propensity for the cardiovascular system to abate vascular injury caused by shear stress, with potential consequences being thrombosis and embolization, and subsequently MACE. An overview of these processes can be seen in Figure 3.

Maladaptive ramifications of MACE are vast, and may include arrhythmia from hypertrophy and disequilibrium of the electromechanical conduction system of the heart in relation to cardiac geometry, to coronary events or heart failure. Both T2DM and aberrant phosphate toxicity have been implicated in modulating the redox state of mitochondria, causing disruptions in important cardiomyocyte channel regulators such as MAPK and calcium flux *via* SERCA with the propensity to cause abnormal heart rhythm[97-99].

Yet, evidence with SGLT2i continue to redeem their propensity to bolster the cardiovascular profile of patients with T2DM. The EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) was one of the initial SLGT2i trials that gave insight into the utilization of SGLT2i for patients with a high cardiovascular risk profile[89]. In the study, three randomized groups were given empagliflozin 10 mg (n = 2345), empagliflozin 25 mg (n = 2342), or placebo (n = 2333). EMPA-REG defined its primary outcomes to note a composite of CVD death, nonfatal MI(s) (not including silent MI), or nonfatality associated with primary endpoint considerations. Unstable angina culminating in hospitalizations were designated as the secondary outcome[90]. Reports from this trial noted relative risk reduction (RRR) of around 13% in the primary outcome group taking both empagliflozin dosages when compared to placebo (HR = 0.86; 95%CI: 0.74-0.99; superiority P = 0.04)[18]. Secondary outcome was not statistically significant (12.8% *vs* 14.3%, HR = 0.89; 95%CI: 0.78-1.01; superiority P = 0.08).

Moreover, Sato *et al*[100] examined 46 patients with T2DM given SGLT2i and observed their QTc_d (the absolute range of QT-intervals in a 12-lead electrocardiogram, and a surrogate for ventricular depolarization. It was shown that SGLTi pharmacotherapy resulted in a reduction of QTc_d by roughly 9%. It is believed that this reduction in QTc_d is not related to glycemic control, but blood pressure reduction. These findings are interesting as the show the propensity to regulate ventricular depolarization, and shedding a potential perspective to one pleiotropic effect of mortality reduction in EMPA-REG as a substantial portion of the cohort in of hypertensive EMPA-REG cohort participants were designated as having left ventricular hypertrophy per ECG findings[101,102]. Cardiovascular benefits that deviate from the antidiabetic effects of SGLT2i such as a decrease in blood pressure show that these agents may hold promise

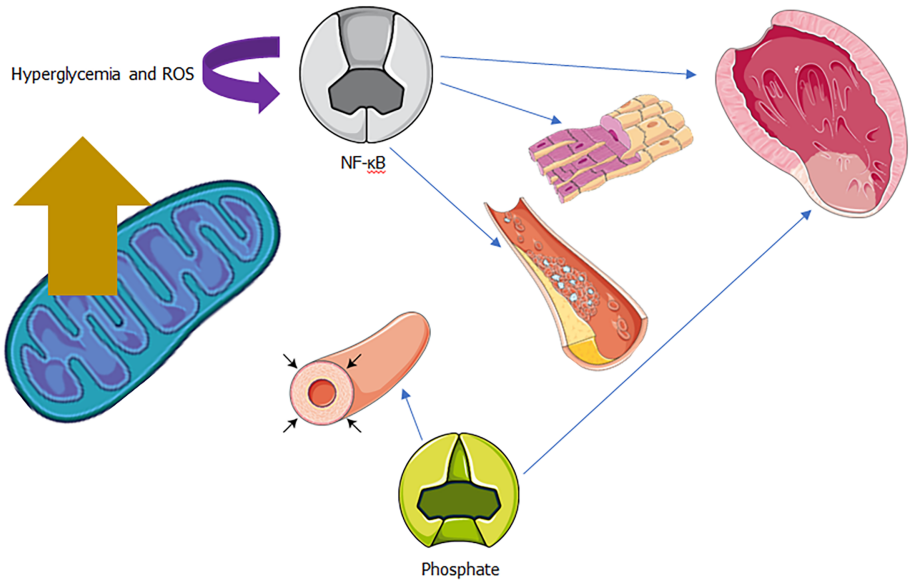


Figure 3 Examples of deleterious cardiovascular pathways associated with hyperphosphatemia and reactive oxygen species. Adapted from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 Unported License. ROS: Reactive oxygen species; NF-κB: Nuclear factor kappa-B.

in counterbalancing the deleterious effects of ROS and phosphate on multiple fronts.

Another class of SGLT2i, Dapagliflozin, has also been vindicated and shows propensity to leverage the negative vasoconstrictive effects of phosphate and hyperglycemia mediated ROS as demonstrated by Li *et al*[103]. The ability for SGLT2i to reduce blood pressure was examined *via* application of dapagliflozin on the aortic rings of male New Zealand white rabbits. Subsequently, vasodilatory events were noted due to the activation of voltage-dependent potassium channels. Moreover, it was shown that SGLT2i had the ability to affect cellular signaling pathways *via* protein kinase G, which has been speculated to play a role in the opening of calcium-activated potassium channels, with a concomitant influx of positive ions into the vasculature, resulting in cellular hyperpolarization, relaxation, and vasodilation. SGLT2i still had the propensity to induce vasodilation after the aortic rings were removed of their endothelium with nifedipine, a calcium channel blocker, or with administration of nitric oxide inhibitors. Voltage-dependent potassium channels and protein kinase G inhibitors however resulted in amelioration of vasodilation, suggesting that SGLT2i may work *via* signaling pathways to attenuate extraneous negative players in cardiovascular health.

DECLARE TIMI-58 (Dapagliflozin Effect on CardiovascuLAR Events) is yet another clinical trial redeeming the cardioprotective profile of SGLT2i in spite of phosphate mediated increases with pharmacotherapy. This trial recruited 17160 patients with T2DM[104]. DECLARE TIMI-58 defined their co-primary endpoints as MACE (defined by CVD, MI, or ischemic stroke), with positive results (HR = 0.93; 95%CI: 0.84-1.03). Second co-primary endpoints included HF hospitalization or CVD death composites with results yielding a 18% relative risk reduction (4.9% *vs* 5.8%; HR = 0.83; 95%CI: 0.73-0.95). Second co-primary endpoints in this study were attributed to a relative risk reduction of 27% regarding heart failure hospitalizations (HR = 0.73; 95%CI: 0.61-0.88).

While the clinical data supports that an increase in phosphate and potential roles it has on vascular calcification, ROS modulation, and exacerbation in the patient with T2DM has no effect and in fact, is shown to improve cardiovascular mortality with SGLT2i, multiple questions arise to how. Glucosuria induced by SGLT2i in patients with T2DM has been shown to reduce the maximal renal glucose transport in addition to the threshold for glucosuria, resulting in a loss of glucose that would otherwise be used to help procure deleterious ROS in the inflamed mitochondria. As demonstrated previously, however, the effects of SGLT2i to taper phosphate effects go beyond antidiabetic properties, and include rhythm control, cellular signaling pathways, hemodynamics, and mineral turnover. More work needs to be done to elucidate the mechanisms of mineral turnover in the nephron given the total variants of SGLT2 proteins in the kidney as well as the pharmacotherapeutic agents, and this work will help understand contextually the full scope of cardiovascular mortality benefits seen with this drug and as validated by clinical trial data.

SGLT2i and other electrolytes: An annotation towards inclusive insight in pharmacodynamics

While this review focused on the effect of phosphate in relation to its changes with SGLT2i therapy correlated with cardiovascular mortality, a brief commentary on the other electrolytes affected by SGLT2i pharmacotherapeutics offers a proclivity to understand the global influence of these drugs. Moreover, these electrolytes have their own cardiorenal effects, and a succinct commentary is warranted given that scope. Therefore, we will include a remark on the current literature using the same standards regarding a focus on evidence-based medicine indexed to translational biology and clinical explanations to share the effects that SGLT2i have on such electrolytes.

A meta-analysis that included a query which successfully harvested random clinical trial (RCT) data of 15309 patients with T2DM taking four SGLTi (canagfliflozin, dapagliflozin, empagliflozin, and iprafliglozin) offers significant insight on the administration of SGLT2i and magnesium levels[89]. Meta-regression analyses for each agent was implemented by the authors of the aforementioned meta-analysis to evaluate the dose-dependent effects for each SGLT2i given the different classes involved. Scrutinization of this study showed that SGLT2i therapy have the propensity to elevate serum magnesium levels 0.08–0.2 mEq/L in T2DM patients compliant with pharmacotherapy. One limitation of this meta-analysis was that patients with CKD are not mentioned in this study. Both magnesium metabolism is impacted in this population group, and there is significant evidence to show a considerable proportion of SGLT2i-eligible patients with CKD are not prescribed in this population despite guideline recommendations for their utilization in this population[19]. Nevertheless, there is some evidence that shows canagliflozin as an agent is beneficial in magnesium retention in patients who have T2DM and CKD (defined as $30 \leq \text{eGFR} \leq 50$ mL/min/1.73 m^2) giving reassurance that these agents may be indicated for the regulation of cardiorenal pertinent electrolytes[104,105].

It should be noted in the scope of cardiovascular disease; magnesium levels hold value as supported by another meta-analysis able to aggregate 313,041 patients. Of these patients, 11995 cardiovascular disease risk stratification[106]. It was determined that each increase in 0.2 mmol/L of serum magnesium conferred a 30% decreased risk of CVD acquisition (RR = 0.70; 95%CI: 0.56-0.88 per 0.2 mmol/L step-size in the physiologic range).

There are many interesting insights to gain from the role of other electrolyte influences in cardiovascular mortality, especially when compared to phosphate metabolism and its seemingly deleterious effects that were offset by SGLT2i. Cohort studies using CKD patients as a model for hyperphosphatemia show those with lower magnesium levels exhibited increased cardiovascular mortality[107]. Cardiovascular mortality risk in the setting of hyperphosphatemia has been shown to be blunted in those who have normal to high serum magnesium levels. These same cohort studies show evidence that that magnesium, in-vitro, offsets hyperphosphatemia mediated sequelae conducive to a MACE phenotype, such as the induction of vascular smooth muscle cell calcification that may affect endothelial cell function. Moreover, higher serum magnesium levels hampered the progression of CKD in patients with hyperphosphatemia, highlighting a shared cardiorenal protective nature with SGLT2i.

There are multiple mechanisms by which magnesium may achieve this affect. With respect to the heart, magnesium has been shown to stimulate ATPase, critical for the maintenance of the sodium-potassium pump within the ventricular myocardium[108]. Further investigations have shown that deficiencies in magnesium lead to aberrant potassium and sodium balances, leading to an increased risk of arrhythmia. Moreover, magnesium serves a role as mitochondrial enzyme cofactors, and its dearth leads to a deficient mitochondrial metabolic status, leading to increased reactive oxygen species, a propensity for thrombus formation, and endothelial dysfunction[109]. These antiarrhythmic affects may explain have played a role in the reduction of arrhythmias as marked by stability of QT_c observed in one study that attempted to elucidate the affects SGLT2i therapy had on the positive clinical end-outcomes in the EMPA-REG outcome trial, showing that Empagliflozin helped mitigate abnormal heart rhythms, and was attributed to be a major cause of mortality and morbidity reduction[110,111]. Magnesium is also noted to be a $Gaba_A$ potentiator in the central nervous system, and its binding has been hypothesized to promote a decrease in blood pressure, decreased sympathetic tone, and the mitigation of tachyarrhythmias *via* parasympathetic and anxiolytic properties[100].

Magnesium wasting is common in patients with T2DM and it is believed that SGLT2i help normalize magnesium levels through an array of mechanisms. For example, T2DM is associated with an increase in transporters that promote

magnesium transport across to the luminal side of the nephron lead in diuresis of magnesium, and reduction of hyperglycemia is believed to give a reprieve from this wasting of magnesium[112]. The proposed mechanism are that in-vivo studies have noted increased magnesium increased magnesium reabsorption at the distal convoluted tubule within the nephron through an insulin dependent mechanism that activates increased expression of TRMP6, an ion channel that allows for entry of luminal magnesium ions into the distal convoluted tubule. Within the tubule, a sodium-magnesium that is believed to be putative in nature, represents the proclivity for basolateral transit of magnesium[113]. This process functionally represents the most terminal opportunity for magnesium reabsorption in the nephron beyond the loop of Henle[114]. It should be noted that this mechanism is partially sodium dependent and may involve increased absorption due to the increased tubular retention of sodium that would have otherwise been excreted in the proximal convoluted tubule by the sodium-glucose cotransporter without SGLT2i therapy[114, 115]. In insulin resistance, there is a decrease in TRMP6 expression, leading to decreased tubular magnesium ion flow, and loss of magnesium in urine. This is consistent with the association of low magnesium levels in patients with T2DM. Moreover, intra-pancreatic magnesium has been shown to improve insulin sensitivity by serving as a potentiator of depolarization of pancreatic β-cells responsible for insulin release[116]. However, deficits in insulin utilization and magnesium availability may lead to a cycle in which the diabetic status is exacerbated. This represents an opportunity for SGLT2i therapeutics to normalize insulin-magnesium dynamics and could be used to explain some components of positive clinical endpoint response. It should be noted that markedly decreased magnesium levels in lieu of activating parathyroid hormone when mildly depressed, prevent parathyroid hormone secretion. The purported mechanism for this phenomenon is that some basal level of magnesium ions is required for the function of the calcium-sensing receptor (CaSR) expressed in the parathyroid gland and renal tubules, and is responsible for regulating calcium by regulating the release of parathyroid hormone (PTH)[117].

This leads to our second ion of consideration in SGLT2i therapy- calcium. Calcium serves multiple roles as a protein activator or inhibitor, can form pathologic deposits, or mediate neurologic signaling- all important in cardiovascular health. Within electrophysiologic considerations, calcium ions are important during the phase 0 upstroke stage in pacemaker action potentials when voltage-gated calcium channels open, and due to their relatively lower negative resting potential, fast-voltage gated sodium channels expressed remain permanently inactivated. This results in a "lag" effect that the AV node utilizes to prolong potential transmission from the atria to the ventricles for a unified beat. In the myocardium, calcium plays an important role in the maintenance of depolarization. As depolarization begins, intracellular potassium channels open and are released to bring the membrane potential to equilibrium, which would terminate the depolarization sequence. However, voltage-gated calcium channels promote the inward flux of calcium ion that activates further calcium release from the sarcoplasmic reticulum, maintaining a plateau that prolongs myocyte contraction and adequate myocardial tension to initiate the stroke volumes needed to maintain perfusion. It is postulated the calcium channel itself in myocardiocytes is dependent upon calcium for its closing[118]. A hypocalcemic state leads to slower calcium leakage within the myocardial membrane, meaning a longer time to reach a concentration to close the L-Type calcium channels, extending the action potential, and by proxy, initiating QT prolongation[119]. In the previously mentioned study by Blau *et al*[50], the 25 research participants who received 300 mg Canagliflozin over placebo for 5 d revealed no change in the serum concentration and ionized-calcium concentration among the participants over this period. However, calcium excretion defined as (mmol/d)/(grams of creatinine) as a function of the day on which urine was collected revealed a statistically significant differential decrease in urinary calcium excretion on day 4 (1.50 *vs* 1.78; $P = 0.04$)[50]. The subsequent day showed a trend, albeit not statistically significant, towards the same trajectory of urine calcium dynamics (day 5, 1.40 *vs* 1.66; $P = 0.09$).

Within the biomarkers assessed in the Canagliflozin study, fibroblast growth factor 23 (FGF23) was tracked. FGF23 is known to be provoked by increased phosphate, and the latter also provokes PTH excretion. Therefore, by proxy, SGLT2i by increasing phosphate, increase both FGF23 and PTH[120,121]. Within this small study, FGF23 levels peaked roughly 12 h after phosphate reached its maximus, consistent with physiologic studies of FGF23 expression[122]. FGF23 acts on the proximal tubule, inhibiting NPT2, a cotransporter of sodium and phosphate (which may further explain why natriuresis is not the predominant mechanism of urinary loss within SGLT2i administration after phosphate levels subsequently reach clinically relevant concen-

trations)[123]. Interestingly, FGF23 suppresses 1-α-hydroxylation of Vitamin D to activate it , while PTH promotes 1-α-hydroxylation resulting in a mismatch of calcium reabsorption[121]. The dynamics of this small-scale Canagliflozin study that measured FGF23, PTH, and 1,25-dihydroxyvitamin D levels on a daily basis implied that early FGF23 expression resulted in a transient hypocalcemia. The decrease in 1,25-dihydroxyvitamin D theoretically decreased the gastrointestinal harvest calcium ion, further stimulating PTH, which has already been induced by SGLT2i mediated phosphatemia. PTH in this cohort may have resulted in net renal tubular reabsorption of calcium ion by the relative influence of SGLT2i. The effect of hypercalciuria may have been a temporary transient effect of osmotic diuresis, as it resolved by day 5. A study involving higher power may be needed to elucidate the effects of SGLT2i on calcium metabolism, as FGF23 expression has been noted to promote paracrine regulation resulting in left ventricular hypertrophy, contraindicative to net positive CVOT outcomes, while also promoting degenerative vascular changes in the kidney [124].

It seems however based on data related electrolyte flux, calcium may not be as significant player in SGLT2i therapy. The only CVOT trial in which bone fractures (a surrogate for phosphate and calcium metabolism) seemed to exhibit a differential risk for bone fractures was CANVAS, a Canagliflozin based trial. Total fracture incidence for bone fracture was more prominent in the canagliflozin group relative to placebo (15.4 *vs* 11.9 fractures among participant per 1000 patient-years; HR = 1.26, 95%CI: 1.04–1.52)[20]. However, this trial when compared to the plethora of dapagliflozin and empagliflozin CVOT trials employed a larger proportion of T2DM diagnosis, female gender, and degree of obesity- all factors associated with bone fractures and by proxy, calcium and phosphate flux relative to other SGLT2i. CREDENCE, another canagliflozin trial, did not report a differential fracture risk among patients. Nevertheless, scrutinizing the role of calcium in SGLT2i therapy has important ramifications when discussing the role they pose in cardiac electrophysiology, wasting in those with CKD, their ability to act as signal transduction messengers, and other downstream factors to explain their role in SGLT2i mediated health benefits.

CONCLUSION

Through the use of translational biology, a known side-effect of SGLT2i, phosphatemia, was able to be shown as diminutive relative to the pleiotropic effects of these new class of antidiabetic agents. Commentaries such as these show that despite theoretical contraindications to pharmacotherapy, the full spectrum of drug effects may outweigh what seems to be harmful, resulting in a net positive clinical profile. Yet, more work needs to be done on elucidating the pathways by which SGLT2i act peripherally beyond the nephron. There is a slew of research implicating cytokine modulation, gene expression, and inflammasome activation in avenues not previously discovered that may give new insight into how these agents have propelled their way to shifting from antidiabetic agents to pharmacotherapeutic options with cardiovascular benefits.

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REVIEW

Current role and future perspectives of cardiac rehabilitation in coronary heart disease

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Abstract

Ischaemic heart disease (IHD) is a major cause of morbidity and mortality worldwide. While there have been major advances in this field, these patients are still a higher risk subgroup. As such, strategies to mitigate risk and tailor secondary prevention measures are of the utmost relevance. Cardiac rehabilitation (CR), encompassing several domains including exercise training, cardiovascular risk factor optimization, nutritional and psychological assessments, as well as other ancillary interventions has shown to be one of the pillars in the contemporary management of patients with IHD. Indeed, CR is associated with several benefits in this population, ranging from functional capacity to improvements in outcomes. Whilst this, there are still several issues concerning the optimal application of CR which are still not fully ascertained, such as lack of referral and completion, as well as questions related to programme design (particularly among patients with multiple comorbidities). In this review, we aim at presenting a pragmatic overview on the current role of CR in the management of individuals with IHD, while also discussing some of the caveats in the current data, as well as future concepts which could help improve the uptake and personalization of this pivotal time-tested intervention.

Key Words: Cardiac rehabilitation; Secondary prevention; Myocardial infarction;

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Grade A (Excellent): 0
Grade B (Very good): 0
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Grade D (Fair): 0
Grade E (Poor): 0

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Core Tip: Ischaemic heart disease (IHD) is a leading cause of morbidity and mortality. Cardiac rehabilitation (CR) programmes have evolved over the years, as to provide comprehensive frameworks encompassing several domains of secondary prevention and forming an integral part of the contemporary management of individuals with IHD. Whilst this, the optimal application of these programmes, in diverse subsets of patients, remains an evolving and challenging field. In this review, we present a pragmatic overview on the current data concerning CR in IHD, while also discussing some of the caveats and future perspectives in this topic.

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INTRODUCTION

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality worldwide[1-3]. Ischaemic heart disease (IHD) is one of its most common presentations, and though significant advances have been made in terms of both its diagnosis and management, patients with IHD still represent a higher risk subgroup[4-6]. Given this background, strategies focused on optimizing overall secondary preventive measures have been the focus of increased interest[4,7,8].

Cardiac rehabilitation (CR) programmes are one of the pillars of the contemporary management of individuals with IHD, being associated with improvements in both morbidity and mortality[6,7,9,10]. Over the years, these programmes have evolved into comprehensive and multidimensional secondary prevention frameworks encompassing several domains ranging from exercise training (ET) to lifestyle counselling, cardiovascular risk factor (CVRF) optimization, psychological interventions, as well as nutritional support and other ancillary interventions[11,12]. While the central role of CR programmes in the management of IHD is currently consensual, there are still several hinderances concerning its optimal application, as manifest by the diversity in programme designs, availability, and patient enrolment [11,13-15]. Moreover, tailoring of these programmes for traditionally less referred subgroups of patients such as women and the elderly, as well as the role of novel strategies to improve referral and completion are also areas of intense interest[8,16-18].

In this review, we aim at presenting a focused and pragmatic overview of the role of CR programmes in the management of individuals with IHD, as well as reviewing some of the challenges and future perspectives concerning this intervention.

CR IN ISCHAEMIC HEART DISEASE

General concepts

Over the last decades, the important role of exercise in the management of individuals with IHD has come under the spotlight[19,20]. Though its potential role in the modulation of anginous symptoms is often ascribed to the classical work of Heberden in the 18th century, the first descriptions of exercise-based rehabilitation in individuals after a myocardial infarction were only reported several years later, well into the 20th century[19,21,22]. Importantly, these early pioneers had a crucial role in changing the then-current *status quo* of prolonged immobilization, by reporting on the benefits of exercise (adapted to the individual patient) in this specific setting[19]. Since these pivotal landmarks, several studies have extensively reported on the myriad benefits of ET in individuals with IHD[8,9,23,24].

Exercise can have a profound impact on the cardiovascular (CV) system, both in the heart as well as in the peripheral vasculature[10,20,25-27]. Interestingly, though its effect on left ventricular systolic function *per se* can vary (depending on factors such as the population under study, timing of introduction and type of protocol), data concurs as to the improvements in functional capacity [as assessed by surrogates such as the peak oxygen consumption (pVO2)][20,28-30]. In addition, its impact on other sites such as the pulmonary and musculoskeletal systems should also be kept in mind, particularly when analysing data related to overall functional capacity as well as its impact in the face of the complex multimorbidity patient[20,31-33]. Moreover, and given recent reports illustrating the putative role of inflammation in IHD, the potential modulation of inflammatory pathways by physical activity has also been postulated as being one of the mechanisms underlying the benefits of exercise-based CR[25,34]. Of note, however, that while some mechanistic as well as clinical data have supported this hypothesis, further research is still needed to fully ascertain the potential relative contribution of inflammatory modulation and metabolic substrate utilization to the overall improvements in individuals undergoing CR[25,34-36].

The role of exercise in preventing CVD has been extensively explored, as depicted by the data showing its relevance in reducing the incidence of several pathologies such as heart failure (HF) and mortality[4,37,38]. Interestingly, though some reports have explored the notion that intense ET could potentially lead to detrimental CV effects, as manifest by phenomena ranging from elevations in cardiac biomarkers (such as cardiac troponin and natriuretic peptides) to coronary artery calcification and myocardial fibrosis, data has consistently shown the beneficial effects of moderate regular exercise[27,38-41]. As such, though these factors should be taken into consideration, particularly in terms of exercise prescription and personalization, the plethora of benefits associated with ET should be further highlighted, namely in the setting of IHD[9,10,42] (Figure 1).

CURRENT EVIDENCE CONCERNING CR

As discussed above, there are several potentially beneficial biological effects of ET[25,38,43] (Figure 1). In accordance with these data, it has become one of the central components in the management of IHD[4,6-8]. While the contribution of ET is undisputable, CR programmes have progressively incorporated increasingly different facets, as to provide a comprehensive approach to the individual patient[8,11,12,44]. This progression mirrors the growing complexity of both patients (including multiple comorbidities, the inclusion of older individuals as well as differences in terms of socio-cultural backgrounds) as well as of therapeutic modalities, and as such the need to provide an ever more patient-centred intervention, as to improve outcomes[11,44-46]. Interestingly, as the concept of global CV risk (comprising different CVRF, as well as modulators which could have varying levels of influence) becomes paramount in the CV assessment, the utility of CR in tackling different components of CVD gains additional relevance[4,8,11]. Indeed, reports have shown the benefits of comprehensive programmes, when compared to isolated interventions[44,47]. These concepts are reflected in the current recommendations by different societies, which reinforce the need for CR programmes to include multiple components, as to provide optimal risk management strategies[11,48-50]. In this regard, the European Association of Preventive Cardiology (EAPC) has recently provided guidance on the core components of CR programmes in individuals with IHD (as well as in other CVD), while also presenting a position statement concerning standardization of this intervention[8,11].

Different studies have assessed the impact of CR programmes in the setting of IHD [9,23,51,52]. A meta-analysis performed by Anderson *et al*[23] reported on significant benefits in terms of CV mortality, hospitalizations, and quality of life. Subsequently, and as to address the relevance of this intervention in a contemporary setting, the CROS-II meta-analysis (including only individuals enrolled by 1995 or later) provided further evidence on CR, as attested by reductions in mortality[9]. The benefits for patients undergoing CR in this setting have also been reported in observational real-word studies[53-55]. Importantly, the CROS-II study also reinforced the need for standardization across different programmes, as to allow further assessments[9,51]. This point should be particularly taken into consideration when analysing data from studies which do not report on benefits in terms of outcomes[51,56-58], as differences in programme design, ET compliance and intensity could (at least partially) explain some of these discrepancies[59-63]. This latter point should be further considered, and

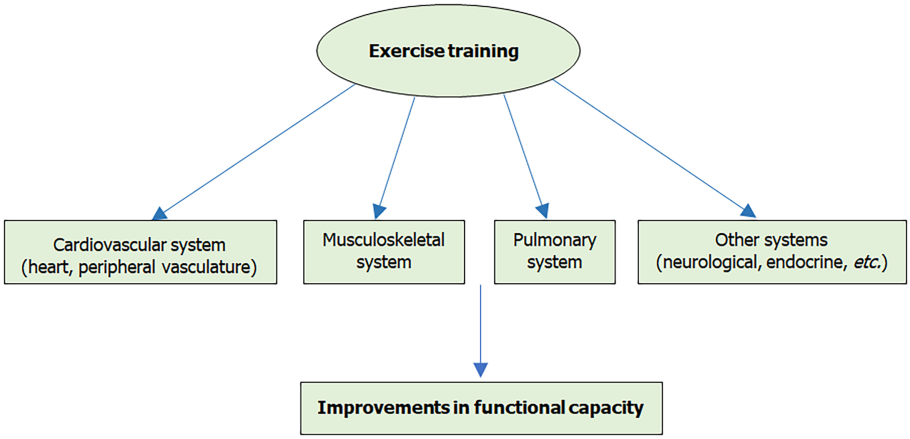


Figure 1 Overview of some of the sites related to the overall effects of exercise training.

it has also been explored when addressing different training methodologies[62,63]. In this regard, albeit high-intensity interval training (HIIT) showed interesting results when compared to moderate continuous training, three large randomized controlled trials in coronary artery disease (CAD), HF with reduced and preserved ejection fractions (respectively) failed to show an advantage of HIIT in terms of the pVO2[62-64]. Importantly, exercise prescription played a pivotal role, as acknowledged by the authors, reinforcing the need for a personalized and highly integrated approach[62,63]. It should also be recalled that the number of CR sessions performed can influence results, as illustrated by data showing that performing a smaller number can lead to worse outcomes[65,66]. These concepts had previously been elegantly raised by Sandercock *et al*[56] by comparing the case of ET to the prescription of pharmacological therapies, where in both cases dosing issues could affect the overall results of the intervention.

Differential responses should also be further explored, as studies have shown that the functional response to CR (namely as expressed by the pVO2) can be associated with outcomes[67,68]. In this regard De Schutter *et al*[67], assessing data from 1171 individuals with coronary heart disease (CHD) who underwent a phase II CR programme, showed significant differences in mortality when comparing those who had improvements in pVO2 to those who did not. When assessing pVO2 as a continuous variable, a 1 mL/kg/min improvement in pVO2 was reported as being associated with a 10% reduction in mortality[67]. Recently, Carbone *et al*[68] also reported that among individuals with CHD undergoing CR, pVO2 at the end of the CR programme was a predictor of mortality. Notably, associations between pVO2 and CV events have also been reported in other settings, further reiterating the need for rigorous programme designs, namely in terms of exercise prescription[8,11,68,69]. Of mention, the timing of CR initiation (after an acute event) should also be taken into consideration as this can be associated not only with reduced uptake and completion but can also influence the response to ET[10,28,29,70].

Another issue which should be discussed pertains to the cost-effectiveness of CR[8,23]. Some studies have suggested the cost-effectiveness of CR among individuals with IHD, while an analysis by Hinde *et al*[70] also supports potential benefits in expanding overall CR coverage[71-73]. Though these data concur as to the relevance of CR, as discussed by Barradas-Pires, differences in terms of programmes and population under study should also be noted, as standardization of CR programmes (as discussed above) would allow further analysis of the best ways to optimize this intervention, while potentially streamlining patient care[71,74]. Beyond this, it should also be referred that differences in terms of overall policies (when comparing world regions) could also influence CR programmes (namely in terms of accessibility and uptake), a factor which should also be acknowledged[13,14].

While the abovementioned caveats should be kept under consideration, the wealth of data supporting the relevance of CR in individuals with IHD in terms of both morbidity and mortality reinforces its role in this group of patients. This is reflected by current guidelines by both the European Society of Cardiology and the American Heart Association/American College of Cardiology, which attribute these programmes high levels of recommendation in this setting, highlighting the paramount role of contemporary CR in the optimal management of IHD[4,6,7,75,76].

CHALLENGES TO CR

As stated above, CR programmes are endorsed as part of the standard management strategy of IHD[4,6,7,75]. Whilst this, data has shown that CR is often underutilized and that even in those who are referred for this intervention, many do not complete the pre-specified programme[8,13,14,77,78]. Notably, while the issue of CR underutilization can affect a substantial number of individuals, as illustrated by data from the ESC-EORP EUROASPIRE V study where less than half of individuals with CAD were referred for CR, this can particularly affect certain subgroups such as women and older patients[77-81].

A seminal work derived from the European Cardiac Rehabilitation Inventory Survey showed that asymmetries could affect different phases of CR, while also noting geographical differences[14]. This latter issue was also reported on a study assessing CR availability worldwide, showing important differences according to location[13]. Though outside the scope of the present report, several factors encompassing patient-related, physician-related, and system-related barriers can affect CR referral as well as completion[5,14,82-84] (Table 1). As such, and as reviewed by Chindhy *et al*[83], strategies directed at each of these components should be the focus of further tailoring, as to allow increased CR uptake. Strategies such as physician and patient education on the benefits of CR, automatic patient referral, flexible hours as well as optimization of expense coverage and early appointments after hospital discharge have been among some of the modalities postulated as to tackle some of these barriers[14,83,85]. Additionally, the potential utilization of alternative modalities should also be reflected upon, to mitigate some of these barriers[82,86-88]. Interestingly, and as discussed below, home-based CR (HBCR) as well as the incorporation of different technologies (such as sensors) could also be of interest, as to address some of these gaps[82,83,89,90]. As detailed in a statement concerning HBCR, this could be an option to overcome several barriers to CR such as scheduling, access, and transportation issues, as well as enrolment delays, though pitfalls such as less intensive training, monitoring and safety concerns related to higher risk patients have also been noted as some of its potential disadvantages[89,91,92]. Importantly, data has shown that this strategy can be performed safely while providing several benefits[89,91,93]. Whilst this, differences in programme designs (including patient characteristics as well as programme duration and frequency) should be considered when analysing comparisons with centre-based CR[89]. Interestingly, although older individuals have traditionally been less represented, a study has shown that a home-based programme was associated with significant functional benefits among the elderly, thus showcasing its possible relevance in this subgroup[92,94]. Notwithstanding the major advances facilitated by the growing digitalization of healthcare, adaptation of facilities as to provide the different facets of contemporary CR (including not only ET but also testing, educational sessions and other interventions) should also be reflected upon, as to maximize resource utilization[11,95].

One important aspect pertains to the presence of multiple comorbidities among individuals with IHD[8,96,97]. Indeed, as patients present with increasingly complex clinical contexts (such as in the elderly, as well as those with HF and polyvascular disease), tailoring of CR programmes can be particularly challenging[8,96-98]. Notably, ET can be associated with functional improvements such as walking distance in patients with peripheral artery disease (PAD), being recommended as an important part of the management of individuals with intermittent claudication[8,99]. Whilst this, studies have shown that functional benefits can differ when comparing patients with CAD with those who present with both CAD and PAD[96,98,100]. Another frontier field which is rapidly expanding relates to cardio-oncology rehabilitation[8,101]. Importantly, attending to the specificities related both to CV pathophysiology as well as to the potential impact of the oncologic disease and its associated treatments, the most adequate programme should be highly individualized and structured on a multidisciplinary setting[101-104]. Given these backgrounds, optimization of CR programmes in these frontier fields should be the focus of further research.

As mentioned above, the response to CR is an important aspect, as this has been shown in some studies to be associated with outcomes[67,68]. While some factors such as age and gender have been associated with modulation of the response to CR, several others have been postulated as having a role in explaining some of the differences in this response[17,25,67,81]. As expertly reviewed by Gevaert *et al*[25], the overall determinants to the complex individual response to CR should be further ascertained, as to allow improvements in its application. In this context, both clinical research as well as translational data, supplemented by the possible inclusion of insights gained from the application of novel instruments such as artificial intelligence

Table 1 Some of the challenges concerning cardiac rehabilitation uptake and completion

Suboptimal referral rates
Limited access (centre availability, geographical issues, transportation, *etc.*)
Challenges concerning programme design (working hours, participant characteristics, *etc.*)
Low participation of different subsets of patients (women, elderly, patients with multiple comorbidities, *etc.*)
Language barriers
Socio-economic issues
Low motivation and/or low self-efficacy
Challenges in the patient/provider relationship
Lack of knowledge concerning cardiac rehabilitation

and multi-omics technologies could improve current knowledge on the pathways involved in the response to CR in different individuals[25,105].

FUTURE PERSPECTIVE

As detailed in the current review, contemporary CR provides an ample secondary prevention framework, able to provide a comprehensive approach to the complex patient with IHD[4,6,8,10]. Nevertheless, questions related to the optimal application of CR among distinct subsets of patients (with a focus on those with different comorbidities) as well as the asymmetries in patient referral and completion still present highly important challenges.

The use of novel technologies has steadily made an impact across different fields of Medicine, including CR[25,90,105-107]. Though the interest in HBCR has been present over the years, with data showing that this could be an interesting option in different subsets of patients, the recent COVID-19 pandemic has markedly expanded the interest in novel models (including hybrid ones) of CR[89,90,108,109]. In this background, models which incorporate concepts of telehealth (namely encompassing different technologies) have been proposed as to allow continuity of care, while minimizing risk[110,111]. Of note, beyond this transitioning phase, these have been postulated as being of potential use to allow for future improvements in overall CR access[90]. Though the use of tele-rehabilitation has made great strides over the last years, as to mitigate some of the barriers associated with CR (particularly in terms of transportation, timing, and potentially cost), questions related to the relative role of hybrid models, as well as of the individuals who could benefit most from these, should be the focus of further study[90,94,109,112]. Moreover, the inclusion of digital tools such as mobile applications as well as sensors (to address not only data related to ET but also to different physiological facets including weight and diet as well as possible CVRF control) should also be a cornerstone of research[90,106,113,114]. Interestingly, some studies highlight the potential in the use of digital applications (often included in the broader concept of mHealth, as the use of wireless technologies with the aim of improving health outcomes) in CR[114]. These could improve access to CR (namely when applied in the framework of HBCR) and allow for more intensive monitoring of different parameters (such as CVRF and physical activity)[90,106,114]. Indeed, some reports have shown that telemonitoring could be of interest in IHD, namely being associated with benefits in functional capacity, whereas the integration of other modalities could allow additional options to address psychological parameters[113,115,116]. In this regard, a randomized study comparing the use of a wrist heart rate monitor with standard training showed that this could be associated with similar increases in pVO2 at twelve weeks, whereas another randomized study (the REMOTE-CR trial, assessing 162 individuals with CHD) showed that cardiac telerehabilitation could lead to comparable results in terms of pVO2[117,118]. While highly promising, questions related to the optimal application of mHealth in CR, particularly in terms of its inclusion across different moments in the CR continuum, should be the focus of additional research[110,114,118,119]. Beyond this, studies aimed at defining the most adequate platforms for a given programme (as well as their comparison to standard methodologies and subsequent validation) and further large, randomized trials would also be of importance, as to allow for an increasingly personalized approach[90,94,120-

122].

Another aspect worthy of mention pertains to the functional assessment methodology. While this point has been comprehensively reviewed in a position statement by the EAPC, novel insights (as discussed above) could also add interesting data[11,42,120,121]. While exercise testing (namely cardiopulmonary exercise stress testing) has a central role, other methods have also been described as of potential interest[11,42,90,123,124]. In this regard, the use of the 6-min walk test in assessing exercise progression has been proposed, whereas another recent study (albeit in a small number of individuals) reported on the use of the 200-m fast walking test in tailoring exercise in low to moderate risk CHD patients undergoing HBCR[123,124]. The relative role of these parameters (namely in the face of data derived from digital platforms) should also be further ascertained[121,125].

Finally, the concept of programme standardization will continue to have a central place when addressing the data for CR[8,11,12]. Data from different CVD shows that there are still variances across CR programmes in ET prescription, a fact which should be considered[126,127]. As mentioned above, standardization (and potential certification) of CR programmes could be of marked importance as to allow benchmarking and process optimization, across varied settings[11,12]. In this regard, also the evolution of preventive cardiology as a highly specialized area of Cardiology, as endorsed by the recently published core curriculum in Preventive Cardiology by the EAPC, could allow for further developments in this specific setting[11,128-130].

CONCLUSION

While substantial advances have been made in the management of IHD, this remains a major cause of morbidity and mortality. Contemporary CR programmes encompass a broad range of interventions, aimed at providing a comprehensive secondary prevention approach to these challenging individuals. Though differences in programme design and application should be considered, data has shown its relevance in improving outcomes, across different contexts. Importantly, the optimal strategy in different groups of patients (such as the elderly and other traditionally less represented individuals) remains an evolving field.

As the complexity of IHD in terms of patient characteristics and different therapeutic strategies (with an increasing focus on mitigating residual risk) grows, the central role of CR as a highly tailored intervention will grow ever more relevant, in the era of precision-based personalized medicine.

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MINIREVIEWS

Dabigatran in cardiovascular disease management: A comprehensive review

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Abstract

Dabigatran, a direct thrombin inhibitor, has robust data for the treatment of deep venous thrombosis and pulmonary embolism, stroke prevention in non-valvular atrial fibrillation, and the prophylaxis of venous thromboembolism (VTE) after knee and hip replacement. Recent studies have evaluated dabigatran to determine its safety and efficacy in such conditions as VTE in malignancy, coronary artery disease, mechanical and bioprosthetic valves, and antiphospholipid syndrome. This article provides a comprehensive review on the role of dabigatran in various cardiovascular diseases.

Key Words: Dabigatran; Anticoagulation; Thrombus; Bleeding; Atrial fibrillation; Deep venous thrombosis; Stroke

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Core Tip: Direct oral anticoagulants (DOACs) have plethora of data for the use in medical field and particularly in cardiovascular medicine. This review is focused on the dabigatran which is one of the DOAC and it is prudent for all the physicians to be familiar with this drug.

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INTRODUCTION

Warfarin, a vitamin K antagonist (VKA) and systemic anticoagulant, has been used for decades in clinical practice for a variety of clinical indications including nonvalvular atrial fibrillation, deep venous thrombosis (DVT) and pulmonary embolism (PE). Given warfarin's indirect mechanism of action, maintaining a goal international normalized ratio (INR) is a constant challenge. Patients often experience periods of over- and under-treatment and may therefore be exposed to increased risk for adverse outcomes. The two classes of direct-acting oral anticoagulants (DOACs) include direct thrombin inhibitors (DTI) and factor Xa inhibitors and both have emerged as attractive alternatives to warfarin[1,2]. Dabigitran, a DTI, and three factor Xa inhibitors including apixaban, edoxaban, and rivaroxaban are currently approved by the Food and Drug Administration (FDA) for ischemic stroke prevention in non-valvular atrial fibrillation (AF), treatment of venous thromboembolism (VTE) and the prevention of VTE after hip and knee arthroplasty[3]. Dabigatran etexilate is a small molecule prodrug that is rapidly converted by serum esterase to dabigatran, a competitive and reversible direct inhibitor of thrombin. Dabigatran is predominantly (80%) excreted through the kidneys and does not require INR[4]. The purpose of this review is to provide a comprehensive review of the current and potential indications for dabigatran use.

ANTICOAGULATION IN NONVALVULAR ATRIAL FIBRILLATION

Atrial fibrillation is a prothrombotic condition that may lead to thrombus formation in the left atrial appendage and with subsequent systemic embolization causing a cerebrovascular accident (CVA) or stroke[2,5]. The efficacy of dabigatran in non-valvular atrial fibrillation was studied in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) multicenter randomized controlled trial. In this study, patients were randomized to dabigatran 110 or 150 mg twice daily (BID) *vs* dose-adjusted warfarin. Compared to warfarin, dabigatran dosed at 150 mg twice daily was found to reduce the risk of systemic embolism and similar rates of major hemorrhage. Dabigatran was the first DOAC that received FDA approval in 2010 and by the European Medicines Agency (EMA) in 2011 for treatment of non-valvular atrial fibrillation. The recommended doses are 150 mg BID for patient with eGFR > 30 mL/min and 75 mg BID (not tested in the Re-LY trial) for patients with an eGFR of 15-29 mL/min[6]. In a meta-analysis, dabigatran was found to be associated with a lower risk of ischemic stroke, major bleeding, mortality, a similar risk of myocardial infarction, and a greater risk of gastrointestinal bleeding when compared to warfarin [7].

According to the 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Focused Update of the 2014 guidelines for the management of atrial fibrillation, dabigatran has a class 1 recommendation (level of evidence A) for the treatment of non-valvular atrial fibrillation and, similar to other DOACs, is recommended over warfarin. Dabigatran is associated with a lower risk of serious bleeding and has been proven to be either non-inferior or superior to warfarin in preventing stroke and systemic embolism[8].

TREATMENT OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Venous thromboembolism (VTE) includes the clinical entities of deep venous thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of morbidity and mortality. The role of dabigatran in the treatment of acute VTE was evaluated in the randomized, double-blind Phase III clinical trials of RE-COVER and RE-COVER II. These trials included patients with DVT and PE who were initially treated with a parenteral anticoagulant therapy for 5-10 d. Dabigatran at a dose of 150 mg twice daily was compared to dose-adjusted warfarin with an INR target of 2-3 for a 6-mo period. In both trials, dabigatran was found to be non-inferior to warfarin in reducing

recurrent VTE. In both trials, dabigatran and warfarin had similar bleeding rates and other adverse effects, while patients on dabigatran were more likely to have dyspepsia as compared to warfarin in the RE-COVER trial, presumably due to the tartaric acid component.

The extended treatment of VTE was studied in the RE-MEDY and RE-SONATE trials. The RE-SONATE trial included patients that had been previously treated for an acute DVT or PE with anticoagulant therapy for 6-18 mo. This trial found that dabigatran use had a significant reduction in symptomatic VTE and related deaths. While the RE-MEDY trial included patients, who had been previously treated for an acute DVT and PE with anticoagulant therapy for 3 to 12-mo, dabigatran 150 mg twice daily demonstrated noninferiority to dose-adjusted warfarin. An increased risk of acute coronary syndrome was observed in the RE-MEDY trial although there was no difference observed in the RE-SONATE trial[9]. In 2014, the FDA approved dabigatran 150 mg twice daily for the treatment of DVT and PE in patients with an eGFR > 30 mL/min while its use is not recommended for patients with a GFR < 30 mL/min.

The American College of Chest Physicians 2016 guidelines recommend dabigatran, along with other DOACs, over warfarin for the treatment of acute VTE in patients without cancer (Grade 2B) and recommend 3 mo of treatment for the management of DVT and PE (Grade 1B)[10]. The American Society of Hematology 2020 guidelines for VTE recommend DOACs over VKAs (conditional recommendation based on a moderate certainty in evidence) and this recommendation does not apply to a patient with low creatinine clearance, moderate to severe liver disease, or antiphospholipid syndrome. This panel does not suggest one DOAC over another (conditional recommendation based on low certainty in evidence)[11].

POSTOPERATIVE VTE PROPHYLAXIS AFTER HIP AND KNEE SURGERY

VTE is the third most common cause of cardiovascular death after myocardial infarction and stroke and has high morbidity and mortality. Major orthopedic surgeries such as total hip and knee arthroplasty are responsible for 50% of thromboembolic events in the absence of VTE prophylaxis[12]. Oral dabigatran (220 mg or 150 mg once daily) was compared to subcutaneous enoxaparin for the primary prevention of VTE in patients undergoing elective total hip or knee arthroplasty in four randomized, double-blind, non-inferiority trials[13].

Prevention of postoperative thromboembolism after knee replacement

RE-MODEL was a randomized, double-blinded trial conducted in Europe and included patients undergoing total knee replacement. In this trial, the patients were assigned to oral dabigatran 150 mg or 220 mg once daily and were compared to enoxaparin 40 mg subcutaneously once daily. Enoxaparin was given the evening before surgery while dabigatran was administered 1–4 h after completion of surgery. Treatment was continued for a total of 6–10 d and patients were assessed for 3 mo after surgery. The primary outcome (total VTE and mortality during treatment) and safety outcome (bleeding events) showed no difference between the two therapies. Dabigatran (150 mg or 220 mg) was as effective as enoxaparin and had a similar safety profile for the prevention of VTE after total knee replacement surgery[14].

RE-MOBLIZE was a double-blind, randomized trial conducted in the United States and Canada and used enoxaparin 30 mg twice daily as compared to the 40 mg daily dose used in the RE-MODEL trial. Patients with unilateral total knee arthroplasty were randomized to receive dabigatran 220 or 150 mg once daily starting 6 to 12 h after the surgery, or enoxaparin 30 mg subcutaneously twice daily starting the morning after surgery. The treatment was continued for 12-15 d. Dabigatran showed inferior efficacy to enoxaparin 30 mg twice daily while major bleeding rates were found to be similar [15].

Prevention of postoperative thromboembolism after hip surgery

The RE-NOVATE randomized phase III, double-blinded trial was conducted in Europe. This trial compared dabigatran 150 mg and 220 mg once daily to enoxaparin 40 mg subcutaneously once daily for the prevention of VTE in patients undergoing total hip replacement. The treatment duration was 28-35 d. Both dabigatran doses were found to be non-inferior to enoxaparin and the incidence of major bleeding was not significantly different[16]. The RE-NOVATE II randomized phase III, double-blinded trial was the follow-up study to further evaluate the efficacy and safety of the dabigatran 220 mg dose in a more diverse population. This trial compared dabigatran

220 mg to enoxaparin 40 mg once daily in patients undergoing total hip arthroplasty. Patients were randomized to 28–35 d of treatment of dabigatran 220 once daily or enoxaparin 40 mg subcutaneously. Subcutaneous enoxaparin was given the evening before surgery while dabigatran 110 mg was given 1–4 h after completion of surgery followed by a full dose of dabigatran 220 mg the morning after surgery. Dabigatran was as effective as enoxaparin for preventing VTE and superior to enoxaparin for reducing the risk of major VTE and major bleeding risk while adverse effects were the same for both groups[17].

In 2015, the FDA approved dabigatran 110 mg on the day of surgery followed by 220 mg the next day for prophylaxis of DVT and PE in patients undergoing hip replacement surgery. The recommended duration of prophylaxis is a minimum of 10-14 d and can be extended up to 35 d. The same dose is being used off-label for the prophylaxis of VTE after knee replacement[18]. The American College of Chest Physicians' guidelines recommend using antithrombotic prophylaxis over no prophylaxis in patients undergoing total hip and knee arthroplasty and suggest extending thromboprophylaxis for up to 35 d (Grade 1B recommendation)[19]. The American Society of Hematology 2019 guidelines also recommends using pharmacological prophylaxis for patients undergoing hip fracture repair (conditional recommendation based on very low certainty in evidence) and recommend using aspirin or a systemic anticoagulant, preferably DOACs, for prophylaxis in patients undergoing total hip or knee arthroplasty (conditional recommendation based on low certainty in evidence)[20].

ROLE IN CORONARY ARTERY DISEASE

The randomized controlled RE-DUAL and RE-DEEM trials assessed the efficacy and safety of DOACs in patients with coronary artery disease (CAD) including acute coronary syndrome (ACS) and stable CAD in patients with atrial fibrillation. RE-DUAL was a noninferiority trial that showed dual-pathway therapy with dabigatran 150 mg or 110 mg twice daily plus clopidogrel or ticagrelor reduced the risk of the primary bleeding outcome compared to triple therapy in patients with atrial fibrillation undergoing PCI. This dual-pathway regimen also demonstrated noninferiority for the secondary efficacy outcome (thromboembolic events, death), although there was an increase in MI and stent thrombosis in dual pathway therapy when compared to triple therapy[21]. The RE-DEEM phase II trial investigated the safety and efficacy of dabigatran in ACS. Patients with STEMI and NSTEMI were randomly assigned to dabigatran 50 mg twice daily, 75 mg twice daily, 110 mg twice daily, 150 mg twice daily or placebo. Patients already on DAPT were continued on this regimen until the end of the study. Dabigatran was found to have no association with ischemic benefit and showed a dose-dependent increase in the rate of the primary safety outcome (bleeding rate) when compared to placebo. A Phase III investigation was not conducted following the RE-DEEM trial[22].

ROLE IN TREATMENT OF VTE WITH CANCER

Patients with cancer are at four-to-seven fold higher risk of developing VTE than those without cancer. Therefore, VTE is an important cause of morbidity and mortality in patients with cancer. The role of dabigatran in the treatment of acute VTE was evaluated in the RE-COVER and RE-COVER II trials as reported above. Data from these two randomized trials were pooled to determine the primary efficacy (recurrent VTE and related death) and safety (major and non-major bleeding) outcomes of dabigatran in active cancer patients who were diagnosed with cancer in the previous 5 years. No significant difference in efficacy between dabigatran and warfarin was found. Although major bleeding and non-major bleeding events were more frequent in patients with cancer than without cancer, there were no differences in the safety outcomes between dabigatran and warfarin[23].

DABIGATRAN USE IN MECHANICAL AND/OR BIOPROSTHETIC VALVE REPLACEMENT

In the Dabigatran phase III clinical trials for atrial fibrillation, patients with mechanical heart valves were excluded. The RE-ALIGN study randomized patients with recent mechanical aortic or mitral valve replacement in a 2:1 ratio to receive dabigatran or warfarin. The patients received dabigatran doses of 150 mg, 220 mg or 300 mg twice daily based on creatinine clearance. The study was discontinued early due to more bleeding and thromboembolic events in the dabigatran-treated group. The DAWA study was initiated to evaluate the efficacy and safety of dabigatran in patients with bioprosthetic mitral and/or aortic valve replacement but the study was terminated early due to limited enrollment[24,25].

ROLE IN TREATMENT OF LEFT VENTRICULAR THROMBUS

Although DOACs have been used off-label for the treatment of left ventricular thrombus, there are currently no randomized controlled trials evaluating the safety and efficacy for this indication. There is conflicting evidence based on various observational studies and a recent systematic review recommended against DOACs for the treatment of left ventricular thrombi[26].On the other hand, a single centered, retrospective, small observational study carried out at tertiary care center found that dabigatran use in patients with left ventricular thrombus is both safe and effective[27]. Additional studies are needed the clarify the role of dabigatran in the treatment of left ventricular thrombus.

USE AFTER LEFT ATRIAL APPENDAGE OCCLUSION

Left Atrial Appendage Occlusion (LAAO) is an established alternative to oral anticoagulation in patients with atrial fibrillation and a contraindication to oral anticoagulation to prevent the risk of stroke. LAAO device placement is associated with increased postoperative stroke risk and requires anticoagulation after device implantation[28]. There is no randomized clinical trial to compare the safety and efficacy of anticoagulants after LAA occlusion. Although warfarin was used after LAAO in landmark trials DOACs have been used in the real-world setting[29].

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia leading to arterial, venous, and microvascular thrombosis. Post hoc analyses compared dabigatran with warfarin in patients with APS for the treatment and prevention of VTE and found no significant difference in symptomatic VTE or VTE-related deaths between groups. The dabigatran group showed fewer bleeding events, but differences did not reach statistical significance. The EMA recommends against the use of DOACs in patients with APS, especially those with triple positive (lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein antibodies) disease[30].

CONSIDERATION IN KIDNEY DISEASE

A meta-analysis published by some researchers evaluated the safety and efficacy of dabigatran, apixaban and rivaroxaban in patients with renal insufficiency. DOAC use was compared to warfarin in patients with mild (defined as eGFR 50–79 mL/min) and moderate (defined as eGFR of 30–49 mL/min) renal impairment and found that DOAC use reduced the risk of stroke, systemic embolism and major and non-major bleeding[31]. Dabigatran 150 mg twice daily was approved by the FDA for atrial fibrillation for patients with eGFR > 30 mL/min and 75 mg twice daily for patients with eGFR 15-29 mL/min[6]. Based on real-world data, the use of DOACs is strongly discouraged in patients with end-stage renal disease (ESRD)[31]. After RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, the FDA approved dabigatran 150 mg BID (after 5-10 d of parenteral anticoagulation) for the treatment of DVT and PE in

patients with eGFR > 30 mL/min and recommends against the use in patients with eGFR < 30 mL/min[9]. In 2015, based on the RE-SONATE and RESONATE II trials, the FDA approved dabigatran 220 mg once daily for VTE prophylaxis in patients undergoing hip arthroplasty. This dose is used off-label in patients with knee arthroplasty; dabigatran is contraindicated for VTE prophylaxis in patients with eGFR < 30 mL/min[32]. The doses of dabigatran for various indications are shown in Table 1.

CONSIDERATION IN LIVER DISEASE

As all approved DOACs undergo some degree of hepatic metabolism, liver dysfunction may increase the risk of bleeding. Patients with liver disease have been excluded from the trials of DOACs, therefore, unlike guidelines for DOAC use in renal disease, no guidelines are available for patients with liver impairment. Dabigatran has 3%-7% bioavailability and a small fraction is metabolized in the liver while 80% is excreted through the kidney. Based on pharmacokinetic and pharmacodynamics studies, the FDA does not recommend dose adjustments for patients with mild or moderate hepatic impairment. The EMA recommends against dabigatran use in patients with elevated liver function tests (twice the upper limit of normal)[33].

CONSIDERATION IN OBESITY

The efficacy and safety of DOACs in the obese population have not been investigated in any large randomized controlled trial. DOACs are as effective as warfarin in phase III randomized trials of atrial fibrillation and VTE, however, patients weighing ≥ 100 kg were underrepresented and accounted for 20% of enrolled patients. The Scientific and Standardization Subcommittee of the International Society on Thrombosis and Hemostasis recommends against the use of DOACs in patients with a BMI > 40 kg/m^2 or a weight >120 kg[3,34].

COST-EFFECTIVENESS ANALYSIS

There is no consensus on the most cost-effective DOAC agent and future head-to-head clinical studies among DOACs are needed. One Canadian study demonstrated dabigatran to be highly cost-effective among patients with atrial fibrillation for the prevention of stroke and systemic embolism as compared to other alternatives[35]. Similarly, in the United Kingdom, Belgium, Denmark, and Taiwan studies have demonstrated dabigatran to be cost-effective in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism[35-39]. Dabigatran was found to be a cost-effective alternative compared to both warfarin and rivaroxaban for the treatment of acute VTE in the United Kingdom[40]. In one study comparing rivaroxaban and dabigatran with enoxaparin, dabigatran was found to be more cost-effective than enoxaparin and less cost-effective than rivaroxaban for thromboprophylaxis in patients undergoing total hip and knee replacements[41].

SAFETY

Dabigatran is associated with a high risk of gastrointestinal bleeding when used at higher doses. Similarly, bleeding risk increases with in treatment with concomitant aspirin use or in those with a history of bleeding[42]. According to the Beers criteria, Dabigatran should be used with caution in patients age 75 and above given an increased risk of gastrointestinal bleeding[43]. Due to the mechanism of absorption, dabigatran use is not recommended in patients with a history of gastrointestinal or bariatric surgery[44,45].

REVERSAL AGENT

Idarucizumab is a humanized monoclonal antibody fragment approved by the FDA and EMA to reverse the anticoagulant effects of dabigatran. The recommended dose of

Table 1 Indications and dosage of dabigatran

Indication	Renal function	Doses
Non-valvular atrial fibrillation	CrCl > 30 mL/min	150 mg BID
	CrCl 15-30 mL/min	75 mg BID
	CrCl < 15 mL/min	Avoid use
Venous thromboembolism treatment	CrCl > 30 mL/min	150 mg BID
	CrCl < 30 mL/min	Avoid use
Venous thromboembolism prophylaxis following hip/knee replacement surgery	CrCl > 30mL/min	110 mg one dose followed by 220 mg daily
	CrCl < 30 mL/min	Avoid use

BID: Twice daily.

idarucizumab is 5 g administered as two separate 2.5 g doses intravenously for rapid reversal of uncontrolled bleeding in dabigatran-treated patients[46]. Glund *et al*[47] conducted a randomized, controlled, phase I study in which patients received idarucizumab 20 mg to 8 g as 1-hour intravenous infusion or 1, 2, or 4 g as 5 min infusion and was found to be safe and well-tolerated in all administrated doses. In the multicenter, prospective cohort study, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial, Idarucizumab was found to reverse the anticoagulant effect of dabigatran in 88% to 98% of the patients[48].

CONCLUSION

Dabigatran has strong data supported by randomized-controlled trials, observational studies, systemic reviews, and meta-analysis for its role in stroke prevention in non-valvular atrial fibrillation, treatment and prophylaxis of VTE, and treatment of VTE in cancer patients. It has also been used off-label for the treatment of left ventricular thrombus and post LAAO, but further randomized trials are needed to determine the safety and efficacy of dabigatran in these indications. Current data do not support the use of dabigatran in patients with mechanical or bioprosthetic valves and acute or chronic CAD.

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MINIREVIEWS

Pulmonary artery catheterization in acute myocardial infarction complicated by cardiogenic shock: A review of contemporary literature

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Abstract

Acute myocardial infarction (AMI) with left ventricular (LV) dysfunction patients, the most common cause of cardiogenic shock (CS), have acutely deteriorating hemodynamic status. The frequent use of vasopressor and inotropic pharmacologic interventions along with mechanical circulatory support (MCS) in these patients necessitates invasive hemodynamic monitoring. After the pivotal Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial failed to show a significant improvement in clinical outcomes in shock patients managed with a pulmonary artery catheter (PAC), the use of PAC has become less popular in clinical practice. In this review, we summarize currently available literature to summarize the indications, clinical relevance, and recommendations for use of PAC in the setting of AMI-CS.

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Grade C (Good): 0
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Core Tip: The unstable hemodynamic status in acute myocardial infarction-cardiogenic shock patients and frequent use of vasopressor and inotropic medications along with mechanical circulatory support devices, may suggest a role for invasive hemodynamic monitoring with a pulmonary artery catheter (PAC) to help improve outcomes. In this review, we summarize the currently available literature to summarize the indications, clinical relevance, and recommendations for use of PAC in the setting of acute myocardial infarction-cardiogenic shock.

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INTRODUCTION

Cardiogenic shock (CS) is a high-acuity hemodynamically diverse state of end-organ hypoperfusion that is frequently associated with multisystem organ failure. Acute myocardial infarction (AMI) with left ventricular (LV) dysfunction remains the most frequent cause of CS[1,2]. AMI related CS (AMI-CS) continues to be associated with high mortality (30%-40%) even in the contemporary era of early reperfusion, increasing use and availability of MCS devices and multidisciplinary shock teams[3-5]. In contrary to conventional teaching, the hemodynamic profile of CS patients is dynamic across a wide clinical spectrum depending on its stage of development[6]. The acutely deteriorating hemodynamic status in AMI-CS patients and nearly ubiquitous use of vasopressor and inotropic medication along with mechanical circulatory support (MCS) devices, underscore the importance of invasive hemodynamic monitoring to help in providing optimal therapies for these patients.

Although earlier randomized clinical trials (RCTs) including the pivotal Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial failed to show a significant improvement in clinical outcomes in shock patients managed with a pulmonary artery catheter (PAC), this data may not be representative of AMI-CS patients as it involved hemodynamically stable patients with heart failure and specifically excluded CS patients[7].

Earlier data from RCTs also failed to show mortality benefit in CS with use of PAC [8-11]. But CS is not a homogeneous disorder and AMI-CS being a distinct entity with markedly different therapeutic/interventional options and management protocols were grossly under-represented (5%-20%) in those studies. Extrapolation of data from these prior studies in the realms of heart failure and critical care and applying it to AMI-CS population may warrant caution and further deliberation[12]. Recent registry-based data allude to improved mortality especially in patients with heart failure and CS with use of PAC[13]. The 2016 European Society of Cardiology guidelines for treatment of heart failure also suggest use of PAC in patients with refractory CS despite pharmacological treatment LOE IIb [C] or being considered for MCS or heart transplantation LOE I [A][14].

Although there are a few earlier reviews on PAC use, they were focused on diagnosis and management of CS patients undergoing MCS[15,16]. However, the use of PAC in AMI-CS subset of patients requires more critical discussion due to multiple recent studies in this arena and addition of intriguing new data regarding its clinical utility. In this review, we intend to explore the indications and recommendations for use of PAC in the setting of AMI-CS and review the recent literature supporting it.

Epidemiological trends of PAC use in AMI-CS

After the data from ESCAPE trial was published, there was a notable decrease in PAC use for hemodynamically unstable patients except for AMI-CS. A recently published studies of a nationally representative population of AMI-CS and HF showed up to 75% decrease in PAC use between 2000 and 2014 despite a concomitant increase in patient acuity[13,17]. Significantly higher PAC use was seen in younger patients, patients of white race and those with higher baseline comorbidity, non-cardiac organ failure, and on MCS[17]. Interestingly, PAC was utilized 10 times more frequently in patients with HF and CS as compared to HF patients without CS between 2004 and 2014[13]. Another study involving medicare beneficiaries looked at 457193 hospitalized patients with PACs and showed that the use of PAC decreased by about 2/3^{rds} from 6.28 per 1000 admissions in 1999 to 2.02 per 1000 admissions in 2013 ($P < 0.001$). The study also noted that the decrease use of PAC was more pronounced in patients with respiratory failure [29.9 PACs placed per 1000 admission in 1999 to 2.3 in 2013 (92.3% reduction), $P < 0.001$ for trend] as compared to PAC use for AMI [20.0 PACs placed per 1000 admissions in 1999 to 5.2 in 2013 (decreased by 74.0%) $P < 0.001$]. Interestingly, the study also noted a nadir in 2009 followed by a subsequent increase in use of PAC for heart failure patients (9.1 PACs placed per 1000 admissions in 1999 to 4.0 in 2009 to 5.8 in 2013) and this was also associated with improved in-hospital mortality, 30-d mortality, and reduced length of stay[18]. A study by Khera *et al*[19] looking at the trends in PAC use among HF patients in the United States from the National Inpatient Sample (NIS) data, 2001 to 2012 showed a decrease in PAC use in CS from 8.2% in 2001 to 6.7% in 2007, but then there was an upward trend up to 14% in 2012 and its use was more common in the larger academic facilities with advanced HF therapies. Similarly, more recent studies using NIS data from 2000-2014, looking at 364001 admissions with AMI-CS showed that PAC was used in 8.1% of patients but there was a 75% decrease during over the study period (13.9% to 5.4%)[17]. While another NIS based study looking at more recent data of 1531878 hospitalized patients with CS (0.3% of total hospital admissions) from January 1, 2004-December 31, 2018, showed a significant increase in the trend for utilization of PAC in CS patients (both AMI-CS and non AMI-CS) reaching up to 17% in 2018 as compared to 10% utilization in the immediate post-ESCAPE trial era (P-trend < 0.001)[20].

In the European literature, a study by Sionis *et al*[6] using an observational, prospective, multicenter, European registry showed that CS patients treated in aca-demic centers noted PAC use 82 (37.4%) of the 219 patients over a course of 2 years. Rossello *et al*[21] noted that a PAC was used in 64% of patients with CS from 2005-2009. In Japan, the use of PAC was seen in 16.8% of patients[22]. Overall, the use of PAC is more common in European countries than in United States and other non-European countries. Earlier studies also noted higher use of PAC in patients with higher socio-economic status and with insurance coverage, large urban hospitals and in patients with MCS which may relate to social disparities in care among this population and paradigm shift in the management of AMI-CS using newer per-cutaneous MCS devices that may require constant hemodynamic data feedback for effective and safe utilization[17].

Pathophysiology of CS and the role of PAC

Regardless of the etiology, CS is a primary pump failure (increased residual volume and intracardiac pressures in one or both ventricles), which could be from right ventricular, LV or biventricular dysfunction, resulting in hemodynamic compromise and multi-organ failure[23-25]. PAC measures direct and indirect parameters which can be used to differentiate right-sided, left-sided, or biventricular dysfunction. For instance, a high central venous pressure (CVP) to pulmonary capillary wedge pressure (PCWP) ratio indicates right-ventricular (RV) failure[26]. Similarly, low pulmonary artery pulsatility index (PAPi), a more accurate measure of RV function, is associated with high CVP, PCWP, mean PA pressure and low cardiac index (CI). In contrast, these parameters measured with other non-invasive parameters such as echocardiography are not as accurate as with PAC[27]. The Society for Cardiovascular Angiography and Interventions (SCAI) recently proposed a five-stage classification system for CS: A – at risk – at risk of developing symptoms of CS but currently asymptomatic; B – beginning – patient who has relative hypotension but no signs of hypoperfusion; C – classic – patients require inotropic or MCS; D – deteriorating – C getting worse with failure to respond to aforementioned therapies; and E – extremis – circulatory collapse and refractory cardiac arrest (Figure 1)[28]. SCAI classification is used for prognostication purposes as the in-hospital mortality has been shown to rise progressively with each advancing SCAI stage[29,30]. Use of PAC measured para-



Figure 1 Stages of cardiogenic shock classified by the Society of Cardiovascular Angiography and Intervention. CPR: Cardiopulmonary resuscitation; ECMO: Extracorporeal membrane oxygenation. Citation: Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, van Diepen S, Naidu SS. SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1): 29-37. Copyright© The Authors 2021. Published by John Wiley and Sons. The authors have obtained the permission for figure using from the Wiley Periodicals Inc.

meters and prognostication through SCAI classification can facilitate clinical decision making in deciding the therapy and its clinical utility[31].

Untreated or sub-optimally treated CS results in a state of persistent tissue hypoperfusion with accumulation of lactic acid metabolites which transitions the early potentially reversible hemodynamic insult of CS to a more complex 'hemo-metabolic' cascade with refractory CS (Figure 2)[32]. All aspects of hemodynamic support including adequate circulatory support, optimal LV unloading, restoring myocardial perfusion and achieving significant decongestion must be fulfilled in a timely manner to effectively treat and reverse the hemodynamic compromise of CS[32,33].

Adequate circulatory support is defined by an increase in mean arterial pressure (MAP) and enhanced microvascular blood flow resulting in adequate organ perfusion. Ventricular unloading, which is defined as a reduction in myocardial work and wall stress, is best achieved by reducing native ventricular pressure and volume[32,33]. Myocardial perfusion, increased epicardial and microvascular coronary blood flow, often improves with adequate circulatory and ventricular support. Decongestion refers to a reduction in total body volume resulting in decreased venous filling pressures [32]. The importance of aforementioned aspects of CS is crucial to highlight, since selective therapies such as inotropes and vasopressors although may increase MAP, but they do not improve microvascular organ perfusion[32]. In addition, inotropes and vasopressors disproportionately increase LV afterload, myocardial work/wall stress, and myocardial ischemia eventually culminating refractory CS and increased in-hospital mortality[32].

Clinical utility of hemodynamic parameters from the PAC

The use of hemodynamic parameters obtained through the PAC are essential indicators for decision-making during the selection, initiation, titration and weaning of pharmacological as well as MCS support in AMI-CS patients. Emerging new evidence suggests that the use of PAC among patients with CS is associated with lower mortality and lower in-hospital cardiac arrest possibly by improved patient selection and better utilization of hemodynamic data to guide management[13]. Early acquisition of hemodynamic data like cardiac output (CO), cardiac filling pressures and systemic vascular resistances (SVR) and pulmonary vascular resistances (PVR) would

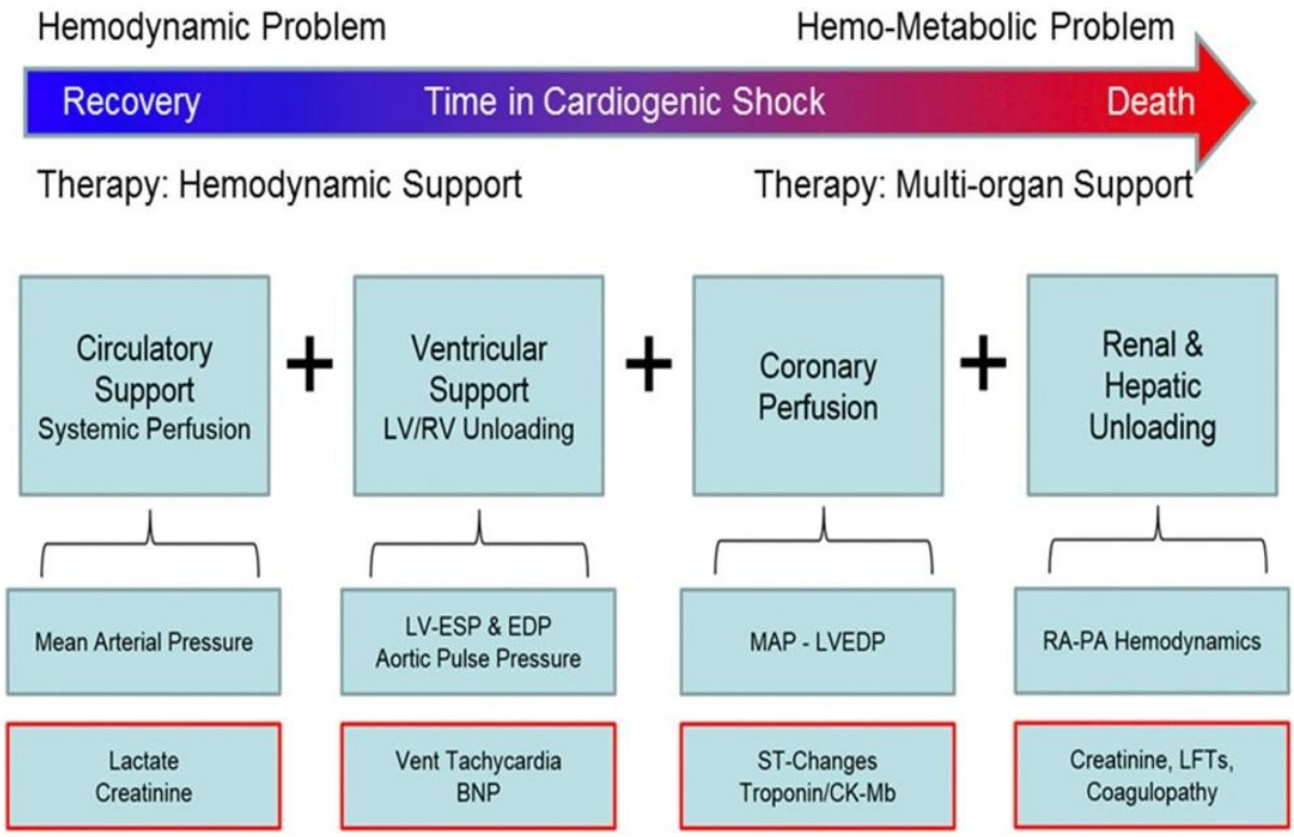


Figure 2 Hemo-metabolic cascade of acute myocardial infarction with cardiogenic shock. BNP: B-type natriuretic peptide; CK: Creatinine kinase; ESP: End-systolic pressure; LFT: Liver function tests; LV: Left ventricular; LVEDP: Left ventricular end-diastolic pressure; MAP: Mean arterial pressure; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular. Citation: Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the "door to support" time. F1000Res. 2017 May 22; 6: 737. Copyright© The Authors 2021. Published by Taylor and Francis Group. The authors have obtained the permission for figure using from the Taylor and Francis Group.

help not only to define the nature of CS (univentricular or biventricular) but also to evaluate the patient's response to various advanced therapies[32]. For instance, the use of PAC in such patients would be indispensable in assessing response to therapies, guiding management and optimize device settings especially when escalating or de-escalating MCS and is supported by the current heart failure guidelines (Table 1)[14, 16]. In patients with CS, continuous hemodynamic feedback from a PAC can guide management by helping to optimize volume status, titrate vasoactive medications in a more targeted fashion as well as detect any complications such as pump thrombosis which usually manifests as recurrence of CS with sudden elevation of PA and PCWPs [33,34]. A more recent reanalysis of the ESCAPE trial data published in 2016 showed that advanced heart failure patients with a PAC who achieved a post-treatment goal of PCWP + right atrial pressure (RAP) < 30 mmHg was associated with a 6-mo mortality rate of 8.7%, as compared to 45.3% (P-value < 0.0001) in patients who have failed to achieve that target[35]. A recently released scientific statement from the American Heart Association does endorse use of PAC in difficult clinical scenarios such as when treating patients with cardiorenal syndrome as the real-time hemodynamic data obtained through PAC will help to identify and treat subclinical congestion and avoid over diuresis and intravascular underfilling and thereby improving the hemodynamics and subsequent end organ perfusion to the heart and kidneys[36] (Table 2).

Several algorithms have been proposed to help manage and potentially improve outcomes in patients with AMI-CS and early acquisition of hemodynamic data using a PAC and prompt action remain a central theme across all the various protocols. According to the National Cardiogenic Shock Initiative, in order to achieve four aspects of hemodynamic support equation, it is important to maintain thrombolysis in myocardial infarction - 3 flow, CPO > 0.6 (CPO = MAP × CO/451) and PAPi > 0.90 [PAPi = (systolic pulmonary artery pressure – diastolic pulmonary artery pressure/CVP][37-39]. Four different management pathways could be evaluated from CPO and PAPi. Therefore, the hemodynamics obtained from the use of a PAC are crucial in determining further management.

Table 1 Studies evaluating outcomes with use of pulmonary artery catheter in patients with cardiogenic shock

Author (year)	Study type	Region/sites	Time period	*n*	Study population	Outcomes	Conclusion
Sotomi *et al*[22] (2014)	Prospective observational	Japan-multicenter	2007-2011	1004	ADHF	All-cause mortality	Decreased all-cause mortality in PAC cohort on ionotropic support or lower SBP
Sionis *et al*[6] (2020)	Prospective observational	Europe-multicenter	2010-2012	219	CS, hypotension or severe LCOS	30-d mortality	No mortality difference. CI, CPI, and SVI-predictors of 30-d mortality
Rossello *et al*[21] (2017)	Prospective observational	Spain-single center	2005-2009	179	CS	Short- and long-term mortality	Lower long-term and short-term mortality
Hernandez *et al*[13] (2019)	Retrospective observational	United States-multicenter	2004-2014	9431944	ADHF and CS	Mortality	Lower mortality
Doshi *et al*[54] (2018)	Retrospective observational	United States-multicenter	2005-2014	842369	CS	In-hospital mortality	Lower mortality
Cohen *et al*[55] (1)(2005)	Retrospective observational	International-multicenter	–	26437	ACS	30-d mortality	Higher mortality
Gore *et al*[56](1987)	Retrospective observational	United States-multicenter	1975, 1978, 1981, 1984	3263	AMI	In-hospital and long-term mortality	No mortality difference
Vallabhajosyula *et al*[17](2020)	Retrospective observational	United States-multicenter	2000-2014	364001	AMI-CS	In-hospital mortality	No mortality difference
Zorzi *et al*[52] (2019)	Retrospective observational	Switzerland-single center	2008-2011	91	CS	Mortality	Increase in PAC in first 24 h
Garan *et al*[34] (2020)	Retrospective observational	United States-multicenter	2016-2019	1414	CS	In-hospital mortality	Lower mortality
Cooper *et al*[57] (2015)(3)	Retrospective observational	United States-single center	2002-2008	217	AMI	CS diagnosis	Echocardiography-based criteria can be used to accurately diagnose CS

ACS: Acute coronary syndrome; ADHF: Acute decompensated heart failure; AMI: Acute myocardial infarction; CI: Cardiac index; CS: Cardiogenic shock; CPI: Cardiac power index; HF: Heart failure; LCOS: Low cardiac output syndrome; PAC: Pulmonary artery catheterization; SBP: Systolic blood pressure; SVI: Stroke volume index.

The INOVA Heart and Vascular Institute algorithm adopts a similar 'combat' approach to managing CS and primarily relies on 5 key areas of focus which include rapid identification of shock, early right heart catheterization, expedited initiation and early escalation of percutaneous MCS as appropriate, minimization of vasopressor and inotrope use, and, meaningful patient recovery and survival[40,41]. In addition to the routinely measured hemodynamic parameters using a PAC, the INOVA pathway emphasizes on measurement of CPO (< 0.6), right atrial (RA): PCWP (> 0.63) and PAPi (< 1.5) as well as other metrics such as serum lactate (> 2 mmol/L) and tricuspid annular plane systolic excursion (< 14 mm) to help diagnose the presence of RV failure and need for RV mechanical support in CS as well as guide management including initiating or escalating/de-escalating percutaneous MCS[40].

In another prospective study by Garan *et al*[42] comparing outcomes of veno-arterial extracorporeal membrane oxygenation and a percutaneous ventricular assist device an institutional CS algorithm was used to guide selection of MCS. Of the 51 patients, 31 (76.4%) underwent invasive hemodynamic assessment with a PAC before the first device initiation and both groups had very similar hemodynamic parameters as measured by the PAC including, RA pressure, PCWP, CPO and CI[42]. The Utah Cardiac Recovery Shock Team also emphasizes the importance of multidisciplinary shock team approach and early use of PAC to guide MCS selection and improve in-hospital mortality (61.0% for shock team *vs* 47.9% for control; $P = 0.041$) and 30-d all-cause mortality [hazard ratio (HR): 0.61, 95% cumulative incidence (CI): 0.41-0.93] in refractory AMI-CS[41]. The University of Ottawa Heart Institute adopted a multidisciplinary code shock team approach to CS and demonstrated improved long-term survival[43]. In their study as well, hemodynamic monitoring with a PAC was done in 62% of patients (66% for treatment *vs* 50% for control, $P = 0.13$) for a median duration of 4 d (IQR, 2-6)[43].

Table 2 Current guidelines on pulmonary artery catheterization in cardiogenic shock

Guideline	Recommendation
2011 ACCF/AHA CABG[51]	Invasive hemodynamic monitoring with PAC is required before induction of anesthesia in patients with CS undergoing CABG (Class 1; level of evidence C)
2013 ACCF/AHA HF [52]	Invasive hemodynamic monitoring should be performed in patients with respiratory distress or impaired perfusion – when intracardiac filling pressures could not be determined from clinical assessment (Class 1; level of evidence C)
	Invasive hemodynamic monitoring is also recommended for patients with persistent acute HF symptoms despite empiric HF therapy adjusts and with one of following: (1) Systemic or pulmonary vascular resistance; or fluid status or perfusion is uncertain; (2) Low systolic blood pressure despite initial therapy; (3) Worsening renal function; (4) Candidate for pressor support; and (5) Candidate for MCS or heart transplant (Class IIa; level of evidence C)
The 2013 ISHLT MCS [53]	Patients undergoing procedure MCS device placement should have insertion of large-bore intra-venous line, arterial line, and pulmonary catheter for monitoring and intra-venous access (Class I; level of evidence B)
2016 ESC HF[11]	Routine invasive hemodynamic evaluation is not indicated for diagnosis of HF – PAC could be used in hemodynamically unstable patients with unknown mechanism of deterioration
	PAC could be used for acute HF who have refractory symptoms despite pharmacological treatment (Class IIb; level of evidence C)
	PAC along with right heart catheterization is recommended for evaluation of patients for MCS or heart transplantation (Class I; level of evidence C)
2017 SCAI/HFSA Invasive Hemodynamics[54]	Continuous hemodynamic monitoring is required for patients receiving MCS
	Continuous hemodynamic monitoring is used for withdrawal of MCS and pharmacologic support

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; CABG: Coronary artery bypass grafting; CS: Cardiogenic shock; ESC: European Society of Cardiology; HF: Heart failure; HFSA: Heart Failure Society of America; ISHLT: International Society of Heart and Lung Transplantation; MCS: Mechanical circulatory support; PAC: Pulmonary artery catheter; SCAI: Society of Cardiovascular Angiography and Intervention.

The ratio between the RA pressure and PCWP (RA:PCWP ratio) could help us gain insight into the possibility of RV failure in AMI and prognosis in patients with CS[32]. The RA:PCWP ratio can be used analogous to the classic 2 × 2 table in HF patients to classify patients as hypovolemic, LV-, RV-, or BiV dominant congestion (Figure 3)[44, 45]. Prior studies have successfully demonstrated PAPi as a simple and reliable hemodynamic measure to predict in-hospital mortality after acute inferior wall MI with high sensitivity and specificity as well as predict RV failure after left ventricular assist devices implantation[46,47].

A recent review on AMI-CS emphasizes the need for systems of care with early recognition and transportation of AMI-CS patients to level I dedicated cardiac shock care centers along with use of pre-PCI implantation of MCS devices with "door-to-support" time ≤ 90 min and consistent use of PAC for accurate hemodynamic monitoring to help improve survival and outcomes in these patients[48]. It is important to recognize that PAC does not have any intrinsic therapeutic effect and by itself would not improve outcomes but rather facilitates decisions that could translate to favorable outcomes by prompt and appropriate action guided by the real-time monitoring of hemodynamic data. For instance, escalation of device therapy from a primarily LV support to biventricular device support with Bipella (right and left sided Impella) may be warranted if hemodynamic monitoring with PAC suggests biventricular failure with CPO < 0.6 and PAPI < 0.9 to help reverse the progression of AMI-CS[25].

Differentiating AMI-CS from CS in chronic congestive heart failure

Although CS is often referred to as one homogenous entity the CS phenotype in AMI patients may be very distinct from that in end stage heart failure patients and such early distinction could have significant prognostic and therapeutic implications. There are also considerable differences between CS from AMI *vs* heart failure – chronicity in heart failure along with neurohumoral dysregulation (especially shock) and changes stemming from heart failure therapy[49]. CS from AMI has low filling, lower pulmonary artery pressures, higher oxygen delivery (DO_2), lower oxygen-hemoglobin affinity (P50), and more severe metabolic acidosis in comparison with CS from end-stage heart failure (ESHF)[49]. Further, there is higher inpatient mortality in patients with acute HF related *vs* acute on chronic HF related CS even with similar hemodynamic characteristics such as MAP, CO, cardiac power index (CPI)[50].

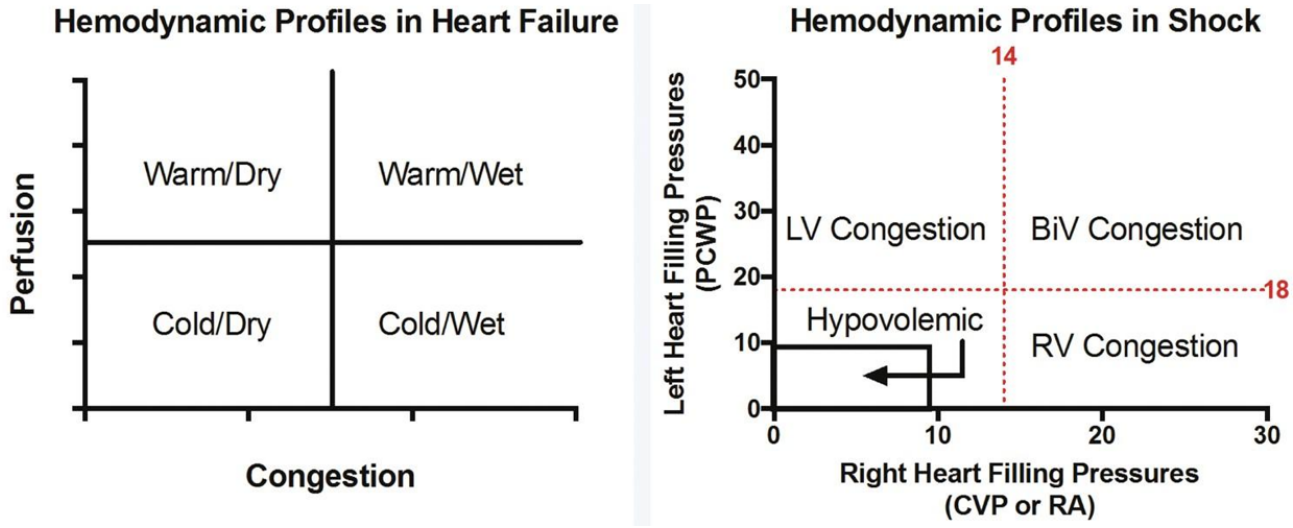


Figure 3 Congestive profiles in cardiogenic shock. Clinical assessment of hemodynamic conditions in decompensated heart failure is traditionally categorized into four groups based on systemic perfusion and congestive status using a two-by-two table. Cardiogenic shock is categorized as having LV-, RV-, or BiV-dominant congestion or hypovolemia. Treatment approaches may be tailored to each of these four categories. BiV: Biventricular; CVP: Central venous pressure; LV: Left ventricular; PCWP: Pulmonary capillary wedge pressure; RA: Right atrial; RV: Right ventricular. Citation: Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the "door to support" time. F1000Res. 2017 May 22; 6: 737. Copyright© The Authors 2021. Published by Taylor and Francis Group. The authors have obtained the permission for figure using from the Taylor and Francis Group.

A recent single-center study by Lim *et al*[49] looking at patients with CS due to AMI (n = 26) and ESHF (n = 42) who underwent MCS (extracorporeal life support, Impella or temporary ventricular assist devices) suggested that the ESHF-CS patients had higher filling and pulmonary artery pressures but lower oxygen delivery, greater anaerobic metabolism with less severe metabolic acidosis as compared to the AMI-CS patients.

Clinical outcomes in CS patients with PAC and hemodynamic monitoring

More recent data from the CS literature have shown potential short- and long-term mortality implications of invasive hemodynamic data. In the CardShock study, which used an observational, prospective, multicenter, European registry, the CI, CPI and stroke volume index were the strongest 30-d mortality predictors in addition to the previously validated CardShock risk score (Table 1)[6]. Similarly, an earlier study looking at 541 patients with CS who were enrolled in the Should we emergently revascularize Occluded Coronaries for CS (SHOCK) trial registry suggested that CP [odd ratio (OR): 0.60, 95%CI: 0.44-0.83, P < 0.002; n = 181] and CPI (OR: 0.65, 95%CI: 0.48-0.87], P < 0.004; n = 178) are the strongest independent hemodynamic correlate of in-hospital mortality in patients with CS[37], but this was not shown to be predictive in a more recent study involving a large multi-center registry[34]. Data from this large multicenter registry study representing real-world patients with CS in the contemporary acute MCS era suggested that decreased MAP along with an increased RAP significantly associated with higher mortality but PCWP, CPO and CI did not appear to impact mortality consistently[34].

The Nursing Students Competence Instrument shock team protocols used cardiac power output[37], and PAPi[39,51] as hemodynamic criteria for MCS patient selection, assessing response to therapy and for escalation/de-escalation of MCS. In this study, CPO (> 0.6 or < 0.6 W) and lactate (> 4 or < 4 mg/dL) at 12-24 h was shown to have the best prognostic value in predicting survival as patients with persistently higher lactate levels (> 4 mmol/L) and low CPO (< 0.6 W) at 12-24 h while on Impella support will have a higher mortality (50%) and such patients should be evaluated for escalation of MCS[38].

Another retrospective single center study looking at 91 consecutive patients with CS due to primary LV failure, who had PAC within the first 24 h showed that a reduced compliance of the pulmonary artery (CPA), worsened right ventricular dysfunction and was independently associated with increased mortality in patients with CS and increased from 4.5% in the quartile of patients with highest CPA to 43.5% in the lowest CPA quartile[52].

Literature has shown beneficial, non-significant, and deleterious effects of PAC in CS patients (Table 1). In a study by Hernandez *et al*[13] utilizing the NIS database, patients with CS and PAC use had lower mortality (35.1% *vs* 39.2%, OR: 0.91; $P < 0.001$) and lower in-hospital cardiac arrest (14.9% *vs* 18.3%, OR: 0.77; $P < 0.001$) which persisted even after propensity score matching. The Acute Decompensated Heart Failure Syndromes registry which was an prospective, multicenter observational study in which 813 patients (16.8%) were managed with PACs, of which 502 patients (PAC group) were propensity core-matched with 502 controls (control group) showed that PAC guided management in advanced HF patients with CS requiring inotropes (HR: 0.22; 95%CI: 0.08-0.57; $P = 0.002$) and are hypotensive (systolic blood pressure ≤ 100 mmHg; HR: 0.09; 95%CI: 0.01-0.70; $P = 0.021$) had an in-hospital mortality benefit compared to those managed without PAC derived hemodynamic data[22]. Another recent study from the Cardiogenic Shock Working Group looking at 1414 patients with CS showed that use of complete PAC-derived hemodynamic data prior to MCS initiation in 1190 (84%) patients with advanced CS stages was associated with improved survival from CS ($P < 0.001$). Patients with no PAC assessment had worse in-hospital mortality as compared to patients who were assessed with PAC (OR: 1.57; 95%CI: 1.06-2.33)[34]. Another recent study involving 15259 AMI-CS patients treated rapidly with an Impella for MCS along with use of invasive hemodynamic monitoring with a PAC as the first strategy had significantly better survival rates (63%) as compared to the controls (49%) ($P < 0.001$)[53].

Interestingly, a single center study with 129 patients admitted with CS and followed for 5 years showed that the use of PAC in patients with CS was associated with lower short-term (HR: 0.55, 95%CI: 0.35-0.86, $P = 0.008$) and long-term mortality rates (HR: 0.63, 95%CI: 0.41-0.97, $P = 0.035$) even after adjustment for age, gender and the presence of shock upon admission but this benefit was only significant in those patients without acute coronary syndrome (ACS)[21]. This merits future studies on outcomes of PAC in ACS *vs* non-ACS patients.

In contrast, CardShock study was an observational, prospective, multicenter, European registry study in which more than one-third of patients were managed with a PAC. The findings from this study suggest that use of PAC was associated with a more aggressive treatment strategy but did not increase the 30-d mortality[6]. Similarly, a retrospective single center study looking at 91 consecutive patients with CS due to primary LV failure, who had PAC within the first 24 h showed with increased mortality in patients with CS[52]. The discrepancy in the outcomes of mortality with PAC invites future multi-center and international trials as deciding factors to assess the efficacy of PAC in comparison with PAC in AMI-CS sub-set of population.

Limitations

This review is based on the results of currently available observational, single/multicenter, and national cohorts. However, the contribution of confounding factors in these studies in unknown. For instance, use of PAC could be significantly higher in critically ill patients thus confounding the results of in-hospital, 30-d mortality and other relevant clinical outcomes. Therefore, the role of PAC in AMI-CS patients may need to be further explored through well-designed future RCTs.

Future directions

As PAC by itself has no intrinsic therapeutic benefit, future studies focused on testing the workflows and appropriate interventions that would allow prompt acquisition and action on hemodynamic information from the PAC including the timing, selection, management, and weaning of temporary MCS. There is also an ongoing clinical trial looking at whether PAC guided LV mechanical unloading after PCI for acute anterior wall MI will attenuate post-infarct scar and cardiac remodeling. The data from this study may further define the clinical utility of PAC in guiding the need for mechanical LV unloading to help improve clinical outcomes in the setting of AMI-CS.

CONCLUSION

In conclusion, PAC has shown to be useful in monitoring treatment parameters, tailoring treatments, and predict prognosis in AMI-CS patients. Several hemodynamic parameters acquired using PAC are critical to not only defining the etiology of AMI-CS (univentricular or Bi-ventricular) but also vital to the selection, initiation, titration of both pharmacological and MCS devices in these patients that may help better

outcomes. Early identification of CS with a targeted shock to device time of < 90 min along with dedicated multidisciplinary shock teams and designated shock centers will be critical to favorably affecting mortality outcomes in this extremely sick patient population. However, the contradicting benefits of in-hospital and 30-d mortality in AMI-CS requires further understanding of the processes and treatment strategies using larger RCTs.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic value of left atrial size in hypertensive African Americans undergoing stress echocardiography

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Abstract

BACKGROUND

Left atrial (LA) enlargement is a marker of increased risk in the general population undergoing stress echocardiography. African American (AA) patients with hypertension are known to have less atrial remodeling than whites with hypertension. The prognostic impact of LA enlargement in AA with hypertension undergoing stress echocardiography is uncertain.

AIM

To investigate the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography.

METHODS

This retrospective outcomes study enrolled 583 consecutive hypertensive AA patients who underwent stress echocardiography over a 2.5-year period. Clinical characteristics including cardiovascular risk factors, stress and echocardiographic

(HRPP) and does not replace any other approvals that may be required.

Informed consent statement: This was a retrospective study that the IRB deemed as exempt and so we did not need informed consent forms signed by patients.

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data were collected from the electronic health record of a large community hospital. Treadmill exercise and Dobutamine protocols were conducted based on standard practices. Patients were followed for all-cause mortality. The optimal cutoff value of antero-posterior LA diameter for mortality was assessed by receiver operating characteristic analysis. Cox regression was used to determine variables associated with outcome.

RESULTS
The mean age was 57 ± 12 years. LA dilatation was present in 9% (54) of patients (LA anteroposterior ≥ 2.4 cm/m^2). There were 85 deaths (15%) during 4.5 ± 1.7 years of follow-up. LA diameter indexed for body surface area had an area under the curve of 0.72 ± 0.03 (optimal cut-point of 2.05 cm/m^2). Variables independently associated with mortality included age [P = 0.004, hazard ratio (HR) 1.34 (1.10-1.64)], tobacco use [P = 0.001, HR 2.59 (1.51-4.44)], left ventricular hypertrophy [P = 0.001 , HR 2.14 (1.35-3.39)], Dobutamine stress [P = 0.003, HR 2.12 (1.29-3.47)], heart failure history [P = 0.031, HR 1.76 (1.05-2.94)], LA diameter ≥ 2.05 cm/m^2 [P = 0.027, HR 1.73 (1.06-2.82)], and an abnormal stress echocardiogram [P = 0.033, HR 1.67 (1.04-2.68)]. LA diameter as a continuous variable was also independently associated with mortality but LA size ≥ 2.40 cm/m^2 was not.

CONCLUSION
LA enlargement is infrequent in hypertensive AA patients when traditional reference values are used. LA enlargement is independently associated with mortality when a lower than "normal" threshold (≥ 2.05 cm/m^2) is used.

Key Words: Mortality; Hypertension; African American; Left atrial enlargement; Stress echocardiography

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Core Tip: In hypertensive African American patients referred for stress testing, left atrial (LA) enlargement was infrequent when using the established references values for the general population. Indexed LA Antero-posterior diameter has a superior area under the curve compared to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a lower reference value derived from our population.

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INTRODUCTION

Left atrial (LA) enlargement is a known predictor of adverse cardiovascular events including atrial fibrillation, stroke and heart failure[1-3]. Hypertension can induce left ventricular (LV) remodeling resulting in increased LV mass and concentric hypertrophy, both of which are associated with LA enlargement[4,5]. In the general population of patients undergoing stress echocardiography, LA enlargement [defined by an anteroposterior (AP) dimension ≥ 2.4 cm/m^2] has been shown to be predictive of myocardial infarction and death[6,7]. LA enlargement has also been shown to be predictive of an abnormal stress echocardiogram[8]. African Americans (AA) have a high burden of cardiovascular disease as well as risk factors including hypertension and diabetes mellitus. Although morbidity and mortality risk in this population is well established, pharmacotherapy is less commonly utilized and AA have higher mortality relative to other ethnicities[9]. The prognostic value of LA enlargement in AA patients

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undergoing stress echocardiography is less clear. Additionally, it is unclear if reference values for LA enlargement established in white populations should be applied in AA. In African American patients, LA remodeling appears reduced relative to whites even when controlling for risk factors such as obesity, age, increased LV mass, and hypertension[10-12]. The lower incidence of atrial fibrillation in AA may be attributed to their smaller LA size and may be related more to inter-racial differences in antero-posterior diameter rather than volume[10,13,14]. Despite less LA remodeling, AA are at increased for cardiovascular events and mortality compared to white patients[15]. However, LA size may also have prognostic value in this racial group[7,16]. The purpose of this study was to assess the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography and to determine a threshold value of LA enlargement associated with mortality.

MATERIALS AND METHODS

The Indiana University Institutional Review Board approved this study. The study population comprised of 583 consecutive AA patients with a history of hypertension referred for stress echocardiography at an urban community hospital in Indianapolis over a 2.5-year period.

Clinical characteristics

Clinical characteristics were extracted from the electronic health record. Patients were considered to have a smoking history if they were currently using tobacco or were a former smoker. Hypercholesterolemia was defined as total cholesterol greater than 200 mg/dL or if the patient was receiving lipid-lowering therapy. Obesity was defined as a body mass index ≥ 30 kg/m^2. Patients were considered to have a history of coronary artery disease if they previously suffered a myocardial infarction, underwent a revascularization procedure, or had at least 50% diameter stenosis in one or more major epicardial coronary arteries by angiography. A history of heart failure was noted if there was a previous hospitalization for heart failure or a clinical diagnosis made in an outpatient setting with ongoing medical treatment for heart failure.

Two-dimensional echocardiographic measurements and stress echocardiography

LA diameter was measured as the maximum end-systolic anterior-posterior diameter in the parasternal long- or short-axis views. LA enlargement was defined as a dimension ≥ 2.4 cm/m^2 when indexed to body surface area (BSA) based on studies in the general population[7,17]. LA volume index was not routinely assessed because only a minority of subjects had apical views visualizing the entire LA. In a small subset of patients with apical views that included the entire left atrium, LA volume index was also measured using the biplane Simpson's method. LV diameters and wall thickness were obtained in the parasternal long- or short-axis views at the level of the mitral leaflet tips. LV mass was calculated using linear measurements with the following formula:

LV mass = 0.8 × {1.04 [(LVIDd + PWTd + SWTd)^3 – (LVIDd)^3]} + 0.6 g where:
LVIDd = maximum internal diameter at end-diastole.
PWTd = end-diastole posterior wall thickness.
SWTd = end-diastole septal wall thickness.

Left ventricular hypertrophy (LVH) was defined as an LV mass indexed to BSA greater than or equal to 96 g/m^2 for women and 116 g/m^2 for men[18,19]. Relative wall thickness (RWT) was calculated by the formula (2 × PWTd/LVIDd). LVH was further differentiated into concentric and eccentric hypertrophy if RWT was > 0.42 or ≤ 0.42, respectively. Concentric remodeling was defined as a normal LV mass with RWT > 0.42. Ejection fraction was calculated with either the area length method or with the modified Simpson's method for patients with regional wall motion abnormalities.

Treadmill exercise was performed with protocols chosen based on the patient's age and expected exercise ability. Standard end-points were used[20]. The Dobutamine protocol was conducted with a step-wise infusion using previously described methods and endpoints[21]. Images were obtained in the apical four- and two-chamber views and parasternal long- and short-axis views at rest, low-dose (5-10 μg/kg/min), peak dose and recovery in patients undergoing Dobutamine stress. Baseline and immediate post-stress images were obtained in patients undergoing exercise. Experienced echocardiographers blinded to the clinical data and follow-up interpreted the stress echocardiograms. An abnormal stress echocardiogram was defined by the presence of resting or stress-induced wall motion abnormalities in one or more of 16 myocardial

segments[22].

Follow-up

Follow-up data was obtained retrospectively by review of the electronic health records and the Social Security Death Index database[23]. The end-point for the study was all-cause mortality.

Statistical analysis

Continuous variables were reported as mean ± SD. Patient groups were compared using the Student *t*-test for continuous variables and Chi-square test for categorical variables. A two sided *P*-value < 0.05 was considered significant. Receiver-operating characteristic (ROC) curve analysis was used to determine the best cut-point of LA diameter for predicting mortality. The area under the curve (AUC) was calculated for both LA diameter and LA diameter indexed to BSA. The difference between the two AUC values was compared using the correlated area test statistic. Kaplan-Meier analysis of survival was performed using the best cut-point from ROC analysis. Cox proportional hazards model was used to assess predictors of mortality. Variables with *P* value < 0.05 were included in a multivariate analysis employing a forward conditional method. LA diameter was tested on multivariate analysis both as a continuous variable and as a categorical variable using the cut-point of 2.4 cm/m^2 previously established in the general population and the best cut-point determined from ROC analysis in our study population. The relationship between LA diameter index and LA volume index was assessed by linear regression.

Statistical analysis was performed using SPSS version 18 (SPS, Chicago, IL, United States) and the software package ROCKIT[24].

RESULTS

Patient characteristics

Table 1 shows the clinical and stress echocardiographic characteristics of the patient population. Of the 583 patients, 32% were male and the mean age was 57 ± 12 years. A history of heart failure or coronary atherosclerosis was present in 11% and 19%, respectively. Ninety percent of the patients were on anti-hypertensive therapy and the mean resting systolic blood pressure was 140 ± 17 mmHg. An abnormal stress echocardiogram was noted in 17% of patients. Eleven percent had an ejection fraction less than 50%. LVH was present in 25% and concentric remodeling was present in 52%. Only 9% of the study population had an elevated LA diameter index, using the cut-point of 2.4 cm/m^2 as defined in the general population.

LA size and mortality

During follow-up of 4.5 ± 1.7 years (max 6.9 years), 85 patients (15%) died. ROC analysis showed that LA diameter referenced to body surface area had a larger AUC compared to LA diameter alone (AUC of 0.72 ± 0.03 *vs* 0.66 ± 0.03, *P* = 0.002) for distinguishing survivors and those who died. Figure 1 demonstrates a plot of sensitivity and specificity of LA diameter for death during follow-up at 0.05 cm/m^2 intervals. LA size above the reference value (2.4 cm/m^2) had sensitivity and specificity for mortality during follow-up of 24% and 93%, respectively. The best cut-point for predicting death during follow-up (maximum of sensitivity and specificity) was 2.05 cm/m^2, which produced a sensitivity and specificity of 61% and 72%, respectively.

LA size and survival

Figure 2 shows a Kaplan-Meier analysis of cumulative survival using the best cut-point of 2.05 cm/m^2. Overall, survival was 92% if LA diameter index was ≤ 2.05 cm/m^2 and 72% if LA diameter index was > 2.05 cm/m^2 (*P*-value < 0.001).

Predictors of mortality

Table 2 shows univariate predictors for all-cause mortality. There were six independent predictors of mortality by multivariate analysis using the reference cut-point for LA enlargement (2.4 cm/m^2, see Table 3). These included age, smoking history, heart failure, the need for Dobutamine stress, an abnormal stress echocardiogram, and LVH (Chi-square 102). LA enlargement was not a predictor. In a second multivariate analysis using the ROC defined cut-point of 2.05 cm/m^2 for LA size, LA enlargement was found to be an additional independent predictor (Chi-square 107). A

Table 1 Baseline clinical and echocardiographic characteristics

Clinical		Echocardiographic	
Age (yr)	57 ± 12	Ejection fraction (%)	59 ± 10
Male	32%	Reduced EF	11%
Tobacco	60%	LA Diam (cm)	3.7 ± 0.6
Family history of CAD	34%	LA Diam index (cm/m^2)	1.9 ± 0.4
Hyperlipidemia	50%	Abn LA Diam index	9%
Diabetes mellitus	38%	LV mass (g)	172 ± 59
Obesity	45%	LV mass index (g/m^2)	89 ± 29
CAD	19%	LV hypertrophy	25%
Heart failure	11%	Relative wall thickness	0.51
Atrial fibrillation	3%	LV remodeling pattern	
CKD (GFR < 60)	17%	Normal geometry	22%
Systolic BP (mmHg)	140 ± 17	Concentric remodeling	52%
Hypertensive therapy	90%	Concentric hypertrophy	21%
Diuretic	56%	Eccentric hypertrophy	4%
Calcium channel blocker	33%	Dobutamine study	40%
ACE-I/ARB	55%	Abnormal stress echo	17%
Beta-blocker	46%		

Data are presented as the mean value + standard deviation or percent baseline prevalence. CAD: Coronary artery disease; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; BP: Blood pressure; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; EF: Ejection fraction; LA: Left atrial; LV: Left ventricular.

third multivariate analysis considering LA diameter index as a continuous variable rather than a categorical variable also found LA diameter index to be independently predictive in addition to the other six predictors (Chi-square 109).

Comparison of LA anteroposterior diameter and la volume index

In the 57 patients (10%) in whom LA volume index could be assessed, the *R*-value for the correlation of LA diameter index and LA volume index was 0.76. Fourteen subjects (25%) were identified as having LA enlargement by volume index based on a cut-point of 34 mL/m^2 established in the general population[6].

DISCUSSION

Our study had three main findings. LA enlargement in the AP dimension was infrequent in AA with hypertension using reference values established in the general population. LA diameter indexed for BSA had a superior AUC to LA diameter alone. LA size was an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or using the cut-point of 2.05 cm/m^2 for enlargement derived from our population but not when using the cut-point of 2.4 cm/m^2 derived from the general population.

LA remodeling in AA

In this study, only 9% of hypertensive AA were found to have LA enlargement. This is a lower than expected frequency of LA enlargement when compared to the general population. Among a broad sample of the Framingham study used to validate reference values of LA diameter, 22% of men and 29% of women had LA diameters that exceeded reference limits[2]. Compared to the Framingham study cohort, our population had a higher prevalence of hypertension (100% *vs* 33%), heart failure (11% *vs* 1%), and older age (mean age 57.4 years *vs* 50.8 years), which are all variables associated with LA enlargement[3,25,26]. Multiple studies have shown a higher

Table 2 Univariate predictors of all-cause mortality

Characteristic	Event	No event	Hazard ratio (95%CI)	*P* value
Clinical				
Age	62.9	56.5	1.04 (1.02-1.06)	< 0.001
Male sex	40%	32%	1.43 (0.92-2.20]	0.109
Tobacco	79%	57%	2.55 (1.51-4.29)	< 0.001
Fam. History of CAD	28%	35%	0.73 (0.45-1.28)	0.194
Hyperlipidemia	48%	51%	0.91 (0.59-1.40)	0.662
Diabetes mellitus	52%	36%	1.77 (1.16-2.71)	0.008
Obesity	32%	47%	0.56 (0.35-0.88)	0.010
CAD	33%	17%	2.15 (1.37-3.38)	0.001
Heart failure	27%	9%	3.44 (2.13-5.56)	< 0.001
Atrial fibrillation	7%	2%	2.70 (1.18-6.19)	0.019
CKD (GFR < 60)	29%	15%	2.37 (1.48-3.78)	< 0.001
Systolic BP (mmHg)	141.5	140.0	1.01 (0.999-1.02)	0.438
Echocardiographic				
Reduced EF	25%	9%	2.89 (1.76-4.72)	< 0.001
Abn. LA index (2.40 cut-point)	24%	7%	3.16 (1.91-5.22)	< 0.001
Abn. LA index (2.05 cut-point)	61%	28%	3.35 (2.17-5.18)	< 0.001
LV hypertrophy	52%	21%	3.62 (2.36-5.54)	< 0.001
Relative wall thickness	0.51	0.51	0.94 (0.19-4.57)	0.941
LV diastolic diameter	4.54	4.34	1.57 (1.15-2.13)	0.005
LV systolic diameter	3.24	2.98	1.54 (1.20-1.99)	0.001
Fractional shortening	0.30	0.32	0.05 (0.00-0.57)	0.017
IV septum thickness	1.20	1.11	2.51 (1.19-5.33)	0.016
LV post. wall thickness	1.13	1.07	2.48 (1.04-5.92)	0.040
Dobutamine study	68%	35%	3.55 (2.25-5.60)	< 0.001
Abnormal stress	35%	14%	2.76 (1.77-4.31)	< 0.001

CAD: Coronary artery disease; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; BP: Blood pressure; EF: Ejection fraction; Abn. LA index: Abnormal left atrial diameter indexed to body surface area (cm/m^2); LV: Left ventricular; IV: Intraventricular; Post.: Posterior; See text for further explanation of variables.

prevalence of LA enlargement in white patients with hypertension (weighted average 37.3%)[27-30].

AA have a higher burden of hypertension and cardiovascular mortality with lower rates of pharmacologic interventions[9]. However, when traditional reference values for LA size are used, AA patient mortality risk may be underappreciated. Several studies have shown reduced LA remodeling in AA patients. In a cohort of men with hypertension (58% AA), investigators found that as age increased white patients had a greater mean LA diameter than AA patients[12]. Similarly, in a cohort of 3882 elderly subjects, AA men had significantly smaller mean LA diameter (1.9 mm LA dimension)[11]. Additionally, in a study evaluating the effect of race on the prevalence of atrial fibrillation, AA subjects were demonstrated to have significantly smaller LA diameters (2 mm smaller AP LA dimension)[10].

A more recent evaluation of 129 AA compared with 326 whites showed that in the presence of hypertension, the former had significantly smaller LA size despite similar ventricular relative wall-thickness, diastolic function, and 6-min walk test[31]. Why LA remodeling might be reduced in AA remains unclear although there is speculation that genetic and environmental factors influence the structure of the hearts of AA patients

Table 3 Multivariate predictors of all-cause mortality

	Reference cut-point for Abn. LA Diam			Best cut-point for Abn. LA Diam		
	Chi-square 102			Chi-square 107		
Predictor	Wald	HR (95%CI)	*P* value	Wald	HR (95%CI)	*P* value
Age (per 10 yr)	11.4	1.40 (1.15-1.71)	0.001	8.2	1.34 (1.10-1.64)	0.004
Tobacco	11.9	2.61 (1.51-4.49)	0.001	11.9	2.59 (1.51-4.44)	0.001
Heart failure	6.4	1.92 (1.16-3.20)	0.012	4.7	1.76 (1.05-2.94)	0.031
LVH	17.6	2.54 (1.64-3.93)	<0.001	10.5	2.14 (1.35-3.39)	0.001
Abnormal stress	5.9	1.79 (1.12-2.86)	0.015	4.6	1.67 (1.04-2.68)	0.033
Dobutamine study	8.5	2.09 (1.27-3.43)	0.004	8.9	2.12 (1.29-3.47)	0.003
LA index ≥ 2.40	–	–	NS	[1]	[1]	[1]
LA index ≥ 2.05	[1]	[1]	[1]	4.9	1.73 (1.06-2.82)	0.027

[1]Variable not included in calculation.

Column (Reference cut-point for Abn. LA Diam) demonstrated a multivariate analysis using the reference cut-point of 2.40 cm/m^2 for defining an abnormal left atrium and column (Best cut-point for Abn. LA Diam) demonstrates a multivariate analysis using the best cut-point of 2.05 cm/m^2. ABN: Abnormal; DIAM: Diameter, LVH: Left ventricular hypertrophy; LA index: Left atrium diameter index (cm/m^2).

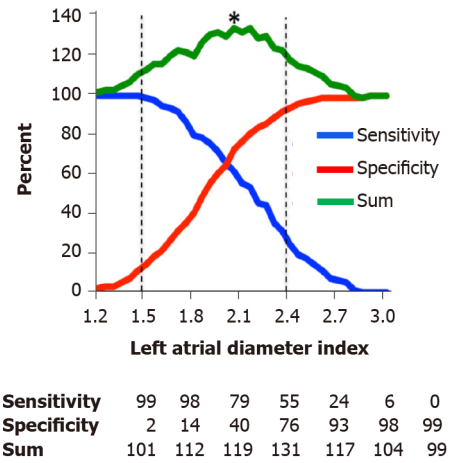


Figure 1 Comparison of sensitivity and specificity of left atrial diameter index cut-points. Sensitivity, specificity, and the summation of sensitivity and specificity are plotted for left atrial diameter index at 0.05 cm/m^2 intervals. Sensitivity is shown in blue, specificity is shown in red, and the summation of the two is shown in green. The reference upper and lower limits of normal (2.4 cm/m^2 and 1.5 cm/m^2, respectively) are indicated with dashed lines. The optimal cut-point that maximizes sensitivity and specificity was 2.05 cm/m^2 and is indicated with an asterisk (*) on the graph.

compared to hearts of white patients. Badertscher *et al*[31] found that AA have lower levels of collagen 1 telopeptide and higher levels of collagen 1 propeptide suggesting that different collagen homeostasis may contribute to atrial remodeling. While AA have a similar average LV mass index as whites, they have significantly smaller LV cavities and thicker LV walls, with a high percentage demonstrating the "concentric remodeling" pattern of cardiac structure[33-35]. This pattern was seen in a majority of our population with 52% displaying concentric remodeling. Similar genetic and environmental factors that produce differences in LV remodeling may also contribute to race related differences in LA remodeling. Gottdiener *et al*[12] proposed the possibility that in parallel with an increased LV wall thickness, there might also be a similar increase in LA wall thickness, which might reduce wall compliance and the resultant cavity size of the LA.

An additional possibility is that reduction of anterior-posterior LA dimension in AA is due to differences in chest and mediastinal structures rather than a consequence of true differences in LA remodeling. The LA is a relatively low-pressure chamber and its size and configuration is influenced by its surrounding structures. Manolio *et al*[11] reported that racial differences in LA dimensions were partially mitigated when

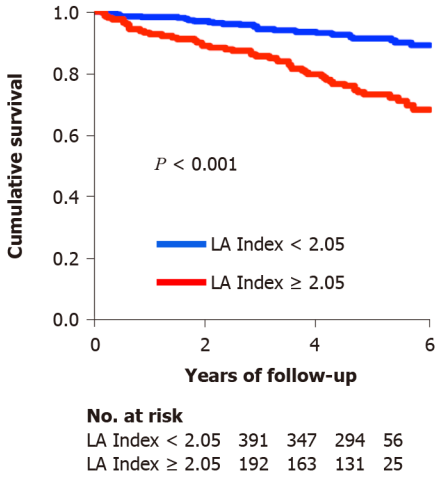


Figure 2 Kaplan Meier curve. Cumulative survival estimates are compared between patients with left atrial (LA) diameter index values above (blue line, LA index < 2.05) and below (red line, LA index ≥ 2.05) the optimal cut-point that maximizes sensitivity and specificity for death. LA: Left atrial.

accounting for chest dimensions and spirometric lung volumes. Given the close proximity of the ascending aorta to the LA, enlargement of the aortic root might limit the ability of the LA to expand in the antero-posterior direction. AA patients are known to have a higher than expected prevalence of aortic regurgitation, which was independently predicted by aortic root size[35]. In the small cohort of patients in our study who had LA volume measurements, the proportion (25%) that had enlargement remained lower than expected.

Prediction of mortality by LA dimension

From ROC analysis, the optimal cut-point for an abnormal LA diameter that predicts mortality in AA was well within the normal reference range. In contrast, the guidelines-defined cut-point had very low sensitivity for predicting mortality in our study population. While LA dilation is infrequent in AA, LA diameter does hold prognostic significance in this population when a lower threshold for abnormal is used.

LA diameter indexed to BSA improved prediction of mortality over LA diameter alone. Indexing of echocardiographic measurements to BSA is currently recommended by the American Society of Echocardiography but it has been argued that correcting for body size inappropriately "forgives" for obesity[36]. Our population included a large proportion of AA females, a population known to have a high prevalence of obesity[37]. Forty-five percent of our population was obese. Therefore, use of indexed LA diameters raises the potential of overcorrection for obesity in our study. However, we found that indexed LA diameter had superior prognostic value over LA diameter alone suggesting that the correction is appropriate in our population. To our knowledge, this is the first study to demonstrate superiority of indexed LA diameter over LA diameter alone.

Comparative long term prognostic value of la dimension

Our data found LA diameter index to be an independent predictor of all-cause mortality in addition to heart failure, age, smoking history, LVH, an abnormal stress echocardiogram, and the requirement for Dobutamine stress. Our study demonstrated that LA diameter predicted long-term outcome as survival curves continued to separate at 6 years of follow-up. Similar to our finding, data from the Framingham study found LA diameter to be predictive of death during 8 years of follow-up[2]. Within an AA cohort of the Atherosclerosis Risk in Communities study, those with the highest quintile of LA diameter had a higher risk of mortality during a median follow-up of 9.8 years[38]. Several investigations have suggested that LA enlargement serves as a marker of chronic diastolic dysfunction over time and thus accounts for the accumulated risk of elevated cardiac filling pressures for cardiovascular events[39]. Our results suggest different reference values are needed for AA patients to accurately evaluate their cardiovascular risk. This may also improve treatment in hypertensive AA patients which may translate to decreased mortality.

Limitations of this study

The primary limitation of this study is our use of LA diameter as opposed to LA volume index. LA volume is currently recommended by the American Society of Echocardiography as the most accurate measure of true LA size[6]. Unfortunately, majority of the patients in our study had truncated apical images utilized for stress echocardiography so we were unable to derive information on LA volume except in a minority of patients. In the small subset of patients there was a reasonable correlation between LA diameter and volume index. While LA volume is clearly a more accurate measure of true LA size, LA volume may be only marginally superior at identifying cardiovascular disease[26,40]. For patients undergoing stress echocardiography, LA diameter index has shown to offer adequate prognostic value and is probably acceptable for those with difficult visualization of the complete LA[7].

An additional limitation of our study was the large percentage of female subjects. Sixty-eight percent of our population was female. How this might affect the applicability of our data for predicting mortality in AA men is unknown, but previous data have suggested that indexing for body size nearly completely accounts for gender differences in LA dimensions[41].

CONCLUSION

LA enlargement is infrequent in AA with hypertension referred for stress testing when using the established references values for the general population. Indexed LA AP diameter has a superior AUC to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a cut-point derived from our population.

ARTICLE HIGHLIGHTS

Research background

African Americans (AA) have higher cardiovascular (CV) risk factors including hypertension and mortality compared to other races. Left atrial (LA) size has shown prognostic value in white patients.

Research motivation

Prior research has suggested AA have smaller LA volumes and standard references values may not apply.

Research objectives

We investigated the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography.

Research methods

In this retrospective cohort study, we evaluated 583 consecutive AA patients with a history of hypertension referred for stress testing and evaluated LA diameter in the Antero-posterior window.

Research results

LA dilatation was present in 9% (54) of patients [LA anteroposterior (AP) ≥ 2.4 cm/m^2]. There were 85 deaths (15%) during 4.5 ± 1.7 years of follow-up. LA diameter indexed for body surface area had an AUC of 0.72 ± 0.03 (optimal cut-point of 2.05 cm/m^2). Variables independently associated with mortality included age (P = 0.004), tobacco use (P = 0.001), left ventricular hypertrophy (P = 0.001), need for pharmacologic dobutamine stress (P = 0.003), heart failure history (P = 0.031), LA diameter ≥ 2.05 cm/m^2 (P = 0.027), and an abnormal stress echocardiogram (P = 0.033). LA diameter as a continuous variable was also independently associated with mortality but LA size ≥ 2.40 cm/m^2 was not.

Research conclusions

LA enlargement is infrequent in AA with hypertension referred for stress testing when using the established references values for the general population. Indexed LA AP

diameter has a superior prognostic value to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a cut-point derived from our population.

Research perspectives

References values for LA size in AA patients may need to be adjusted to more accurately reflect CV risk and which may translate to more aggressive pharmacologic management.

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ORIGINAL ARTICLE

Observational Study

Highly sensitive troponin I assay in the diagnosis of coronary artery disease in patients with suspected stable angina

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Author contributions: Ramasamy I was responsible for the conception, design and analysis and presentation of the data and writing the manuscript.

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Data sharing statement: The raw data is stored in the Laboratory Quality Management System of The Worcester Royal Hospital, and is available following anonymization of patient identifiable information. The full data set can be requested from the corresponding author upon approval of the paper proposal using the data.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

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Abstract

BACKGROUND

Evaluation of suspected stable angina patients with probable coronary artery disease (CAD) in the community is challenging. In the United Kingdom, patients with suspected stable angina are referred by community physicians to be assessed by specialists within the hospital system in rapid access chest pain clinics (RACPC). The role of a highly sensitive troponin I (uscTnI) assay in the diagnosis of suspected CAD in a RACPC in a "real-life" setting in a non-academic hospital has not been explored.

AIM

To examine the diagnostic value of uscTnI (detection limit 0.12 ng/L, upper reference range 8.15 ng/L, and detected uscTnI in 96.8% of the reference population), in the evaluation of stable CAD in a non-selected patient group, with several co-morbidities, who presented to the RACPC.

METHODS

One hundred and seventy two RACPC patients were assigned to either functional or anatomical testing according to the hospital protocol.

RESULTS

The investigations offered to patients were exercise tolerance test 7.6%, 24 h ECG 1.2%, Echocardiogram 14.5%, stress echocardiogram 8.1%, coronary computed tomography angiography (CCTA) 12.8%, coronary angiogram 13.4%, 17.4% were diagnosed with non-cardiac chest pain, 3.5% treated as stable angina, 8.2% reviewed by cardiologists, electronic medical records were not available in 10.4%. Receiver operating characteristic curves for CAD used uscTnI values measured in patients who underwent functional testing, angiogram or CCTA. Values > 0.52 ng/L showed 100% sensitivity and at > 11.6 ng/L showed 100% specificity. In the range > 0.52-11.6 ng/L, uscTnI may not have the same diagnostic potential. In patients assigned to coronary angiogram higher concentrations of uscTnI was

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associated with severe CAD. Low levels of uscTnI and low pre-test probability of CAD (QRISK3) may decrease patient numbers assigned to CCTA.

CONCLUSION
The uscTnI diagnostic cut-off values in a RACPC will depend on patient population and their presenting co-morbidity. In the presence of clinical comorbidities and previous CAD the uscTnI needs to be used in conjunction with clinical assessment.

Key Words: Rapid access chest pain clinic; Suspected stable angina; Troponin I; Coronary artery disease; Coronary angiogram; Coronary computed tomography angiography

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Core Tip: In the United Kingdom, patients with suspected stable angina are referred to rapid access chest pain clinic (RACPC) by community physicians for assessment by hospital specialist medical practitioners. We evaluated the value of a new highly sensitive cardiac troponin I assay in the management of patients with suspected coronary artery disease (CAD) in a RACPC. Patients admitted for further assessment and preselected for either coronary computed tomography angiography or coronary angiogram the assay may indicate the severity of CAD. The diagnostic cut-off values of the assay is determined by the patient population and existing co-morbidities.

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INTRODUCTION

Chest pain is a common presenting symptom in primary care, of which there are many possible causes. The most important of these in terms of subsequent morbidity and mortality are the acute chest pain coronary syndromes (acute coronary syndrome, ACS) comprising unstable angina and acute myocardial infarction (AMI). Current medical practice in the United Kingdom is to transfer patients with ACS urgently to hospital emergency care. In contrast, the differential diagnosis of chronic chest pain is wide and includes cardiac pain as exertional chest pain or stable angina. The diagnosis of coronary heart disease (CHD) may be missed in these patients[1].

New models of assessment have been introduced. In the United States, chest pain observation units provide short stay inpatient care where chest pain is monitored and investigated prior to either formal admission or discharge[1]. In England, the government's National Service Framework guideline recommended outpatient rapid access chest pain clinic (RACPC) in which people who develop new symptoms that their community physician thinks might be due to stable angina can be assessed by a specialist within 2 weeks of referral[2]. Unlike patients with ACS, who are investigated in emergency care units, evaluation of patients with stable symptoms and suspected CHD (stable angina) in a RACPC may be a challenge. The ability to recognise the high-risk patient with stable angina and an increased risk of progression to AMI may be difficult on clinical grounds alone and may require further functional testing.

There can be considerable variation in which possible stable angina is assessed in RACPC. The American College of Cardiology (ACC)/American Heart Association (AHA)[3,4] and European Society of Cardiology (ESC) recommend clinical risk scores [5] which incorporate age, sex and chest pain presentation to calculate pre-test probability. Pre-test probability is determined by the Diamond-Forrester Coronary Artery Surgery Study[3,4] and the updated version the Coronary Artery Disease consortium (CADC) clinical risk scores. NICE guidelines, United Kingdom[6] suggest a symptom based clinical assessment followed by coronary computed tomography angiography (CCTA) for those in the possible angina group. CCTA identifies obstructive and nonobstructive coronary artery disease (CAD) and allows the quanti-

fication of coronary artery calcium[7]. Guidelines recommend a stepwise approach for decision making in suspected stable CAD. A clinical assessment of the probability of stable CAD is followed by non-invasive testing, based usually on the availability of non-invasive tests. Characteristics of tests, sensitivity and specificity, used to diagnose CAD are given in the ESC guidelines[5]. Some of the functional tests available are: Exercise electrocardiogram (ECG), exercise stress echocardiography, dobutamine stress echocardiography and coronary CCTA. A variety of factors affect test choice which include local availability of specific tests, local expertise in test performance and interpretation, or the presence of diagnostic or prognostic questions addressed better by one form of test. Local availability and tariff may make clinicians choose one particular test. Current literature either suggest that CCTA and functional tests can serve equally well as first-line tests for patients with suspected CAD[8,9] or that CCTA may have a benefit over more standard testing[10].

An elevated cardiac troponin (cTn) has long been a pre-requisite for the diagnosis of AMI and has become a diagnostic gold standard for AMI[11]. The value of cTnI in stable angina patients, in contrast to those with ACS and myocardial infarction, is not well understood. The high sensitive troponin assays were able to measure troponin in approximately 50% of normal, healthy individuals. In the most very highly sensitive troponin assays (uscTnI) the cTnI is measurable in almost all healthy individuals[12]. Studies have investigated the use of uscTnI in the early diagnosis of CAD in selected groups of patients without known clinically relevant heart disease. In stable symptomatic patients undergoing coronary computed tomography angiography (CCTA) elevated concentrations of uscTnI was associated with CAD[7,13]. The studies suggest that though uscTnI was not sufficient to use the test as a single standalone test, the test may improve the selection of patients for further investigation and treatment [14,15]. The clinical utility of uscTnI is not fully defined in a RACPC either in (1) differentiating non acute chest pain of uncertain origin; or (2) detecting patients with functionally relevant CAD at risk of progression to AMI. Further, the role of uscTnI in the management of patient with established CHD presenting to a RACPC is yet to be evaluated.

In the United Kingdom, QRISK3 calculations are used in the assessment of 10 year risk of cardiac events. In Worcester, RACPC are staffed by specialist cardiac nurses, in a service led by a specialist cardiologist. Currently they use QRISK3 as part of their initial clinical evaluation of patients, prior to stratifying patients into non-invasive techniques or to identify patients requiring further invasive testing or immediate angiography. In this report we describe the use of uscTnI in the investigation of patients, presenting to the RACPC with probable stable angina. Cardiac troponin assays are not currently used in the investigation of patients with suspected stable CAD in the RACPC. The current study, to our knowledge for the first time, describes the use of uscTnI in the investigation of stable CAD in a RACPC in a non-teaching "district general" hospital in the United Kingdom. Unlike previous studies, this study has been carried out in a non-selected group of patients, and included those with previously known cardiac disease, who presented with suspected stable angina to the RACPC.

MATERIALS AND METHODS

Study population

We investigated 172 patients referred to the RACPC at the Worcester Royal Hospital between the period September 2018 and March 2019. Blood samples were taken at the community physician surgery prior to review by RACPC, which was within 2 wk of referral by the community physician. The patients were outpatients whose physicians believed that non urgent cardiovascular testing was necessary for suspected CAD. Patients with stable chest pain or chest pain equivalent and those with previous history of CAD who presented with chest pain were included in the study. Seven patients with previous cardiac pathology were referred to RACPC by their physicians. A sixty two year old male with a prior history of CAD and cardiac stent placement who presented with increasing chest pain was assigned to coronary angiography. Three patients with previous coronary artery bypass graft or stent insertion were classified as non-cardiac chest pain or were already under the care of cardiologists. The mean age of all patients was 62.1 years (range 23-88 years) of which 51.1% were women. The proportion of patients (given as percentage of the study patients) with cardiovascular risk factors were, with hypertension (51%), current or ex-tobacco users (44%), dyslipidemia (48%), diabetes (27%), family history of CAD (68%); increased

BMI was recorded in 29% of the patients. Calculated QRISK3 ranged from 1-88%, mean 16%. Patient electronic medical notes both inpatient and outpatient notes were reviewed and followed for major adverse cardiac events for a period of six months following the end of the study. Receiver operating characteristic curves (ROC), statistical analysis were performed using GraphPad Prism (United Kingdom) and graphs were constructed using the same software.

In addition, the patients had routine tests (renal function, liver enzymes, serum calcium, HbA1c) to which uscTnI was added as part of the performance assessment of pathway that included uscTnI in the clinical evaluation of the patient. The study was carried out according to the Declaration of Helsinki and the NHS data protection policy. Patients were excluded if they required urgent evaluation for suspected ACS.

Patient follow up care

Following clinical assessment the patients with suspected stable CAD were assigned to 24 h monitoring ECG, exercise tolerance test (ETT), echocardiogram (echo), exercise or pharmacological stress echo, CCTA, coronary angiogram and percutaneous coronary intervention (PCI), medical treatment for angina, or were discharged as clinical assessment suggested non-cardiac chest pain. More complex patients were designated for review by specialist cardiologists.

The results of the uscTnI test were not provided to the RACPC staff and subsequent care of the patient was dependent on his or her clinical assessment of the subject, which was independent of uscTnI value.

Diagnostic testing

The patient sera were collected within 24 h of phlebotomy, stored and transported frozen in dry ice (quality controlled by the courier) to Barcelona prior to measurement of uscTnI. uscTnI was measured by the Singulex Clarity (United States) assay. The detection limit of the assay was 0.12 ng/L. The assay CV was 10% at 0.53 ng/L. Imprecision was 3.16% to 12% for the assay. uscTnI was detectable in 96.8% of healthy individuals. The 99th percentile for healthy individuals was 8.15 ng/L. The assay was stated as outperforming other high sensitivity cTnI assays in terms of analytical sensitivity[12,16].

For the exercise tolerance test the Bruce protocol was followed with ECG recording. A semi-supine bike was used for exercise stress echocardiogram (increasing the workload by 25 Watts every 2 min until the 85% or more of target (heart rate) HR is achieved. Target heart rate was calculated by 220 - age). For dobutamine stress echocardiogram with ischaemia the protocol used was: 10 μg/kg/min and infused up to a maximum 40 μg/kg/min in 10/μg/kg/min increments at every 3-5 min according to HR response (to achieve a minimum. of 85% of the target HR for the test to be diagnostic). If target HR was not achieved at 40 μg/kg/min, iv atropine was given. CCTA was done on a 64-slice CT scanner (Toshiba Acquilion Cx or Acquilion Prime, Toshiba). All scans are reported by specialist cardiologists or radiologists. The stenosis was graded as mild (< 50%), moderate (50%-70%) or severe (> 70%).

Following coronary angiogram degree of stenoses was graded as normal, mild (< 50% stenosis), moderate (50%–74% stenosis), severe (> 75%-99% stenosis), and critical (> 99% stenosis). The angiogram was reported by specialist cardiologists.

RESULTS

Patient demographics following clinical assessment by RACPC is shown in Table 1. The flow chart of patients according clinical assessment is given in Figure 1 and the uscTnI values according to further testing carried out for functional CAD is summarised in Table 2. The investigations offered to patients were ETT 7.6%, 24 h ECG 1.2%, Echo 14.5%, stress echo 8.1%, CCTA 12.8%, coronary angiogram 13.4%, 17.4% were discharged with the diagnosis of non-cardiac chest pain, 3.5% were diagnosed and treated as stable angina, 4.1% were further referred to specialist cardiologists, 4.1% were known cardiology patients, electronic medical records were not available in 10.4%, 2.9% were admitted with ACS during the study. The diagnostic conundrum presented by individual patients is summarised according to outcome measures, prior to analysis of the data by ROC curves.

Outcome measures

The patients are divided into follow-up testing subgroups. Clinical details of patients presenting with uscTnI > upper quartile of the reference range (6 ng/L) are described

Table 1 Patient characteristics

	Non-cardiac chest pain	ETT	ECG	Angina	Review	Lost to follow-up	Previous cardiac problems	Stress Echo (negative)	Stress Echo (positive)	Echo (negative)	Echo (pos)	CCTA (negative)	CCTA (positive)	Angiogram (negative)	Angiogram (positive)	ACS
Age (yr)	57 (23-88)	54 (36-66)	66 (62-69)	73 (66-79)	66 (43-84)	64 (41-84)	71 (67-87)	63 (49-82)	68	67 (43-84)	72 (55-83)	53 (34-63)	62 (51-77)	59 (50-65)	58 (46-81)	69 (62-86)
Sex (M/F)	15/15	11/2	0/2	1/5	5/2	4/14	3/4	4/9	1/0	10/9	5/1	4/8	5/5	3/3	12/5	2/3
BMI (> 25 kg/m$^{2)}$ (*n*)	9	4	1	2	4	8	0	2	1	4	0	4	5	1	6	2
Diabetes (*n*)	2	4	0	1	2	1	0	2	0	2	2	2	1	0	4	3
Hyperlipidmia (*n*)	11	8	1	2	4	6	4	6	1	11	5	5	7	2	11	3
Hypertension (*n*)	10	7	2	4	4	7	3	7	1	13	5	4	8	3	11	2
Family History of CAD (*n*)	6	5	1	0	3	7	0	3	0	5	2	8	6	3	10	0
Smoker (*n*)	11	5	0	4	5	9	1	6	0	10	4	3	9	1	8	0
Past History MI/stent/CABG (*n*)	2	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
Aspirin (*n*)	7	2	0	2	1	6	3	4	0	4	2	4	5	2	6	2
Statin (*n*)	5	3	0	2	1	3	5	3	1	7	4	1	2	0	10	1
ISMN/Nitroglycerin (*n*)	9	1	1	5	3	6	4	7	1	7	3	4	5	3	8	2
Anti-hypertensive (*n*)	7	7	1	2	3	2	5	4	1	8	4	2	1	1	14	2
Creatinine (μmol/L) (*n*)	83 (52-122)	79 (54-100)	77 (71-82)	83 (70-103)	82 (51-98)	75 (47-109)	71 (36-95)	72 (56-88)	84	78 (52-102)	83 (63-103)	71 (52-88)	72 (52-99)	78 (56-98)	81 (46-134)	76 (65-86)
QRISK3%	2-> 88	12 (7-40)	9 (5-13)	22 (6-34)	22-41	19 (2-58)	NA	13 (3-36)	32	1 to > 40	12 to 45	9.4 (1-35)	22 (6-37)	8 (2-16)	8 to > 40	
n	30	13	2	6	7	18	7	13	1	19	6	12	10	6	17	5

ETT: Exercise tolerance test; CCTA: Coronary computed tomography angiography; ISMN: Isosorbide mononitrate; ACS: Acute coronary syndrome; CABG: Coronary artery bypass graft; MI: Myocardial infarction; ECG: Electrocardiogram.

in each group.

Patients classified as non-cardiac chest pain: Thirty patients were classified as non-cardiac chest pain and not investigated further by the RACPC. Seventy one year old

Table 2 uscTnI values by patient subgroup according further testing following clinical review

Subgroup	uscTnI ng/L (minimum value)	uscTnI ng/L (average value)	uscTnI ng/L (maximum value)	*n*	*P* value
Referred back to the community practitioner (non-cardiac chest pain)	0.71	2.9	17	30	
Exercise test	0.97	2.6	9.7	13	
24 h ECG	1.9	2.3	2.6	2	
Diagnosed angina, treated with medication	1.8	5.0	9.2	6	
Advised further review by specialist cardiologist	1.0	12	70	7	
Lost to follow up	0.8	2.6	7.5	18	
Previously diagnosed with cardiac problems and under the care of a cardiologist	1.5	7.2	33.2	7	
Echo (normal)	0.46	3.0	8.6	19	
Echo (mild abnormalities)	2.47	6.44	17.0	6	
Stress echo (negative)	0.98	2.1	3.9	13	
Stress echo(positive)	3.1	3.1	3.1	1	
CCTA (negative)	0.58	2.8	9.3	12	NS
CCTA (positive)	1.1	2.7	8.7	10	
Angiogram(negative)	1.1	1.8	2.2	6	< 0.05
Angiogram(positive)	0.94	7.3	49	17	

ECG: Electrocardiogram; CCTA: Coronary computed tomography angiography; NS: Not significant.

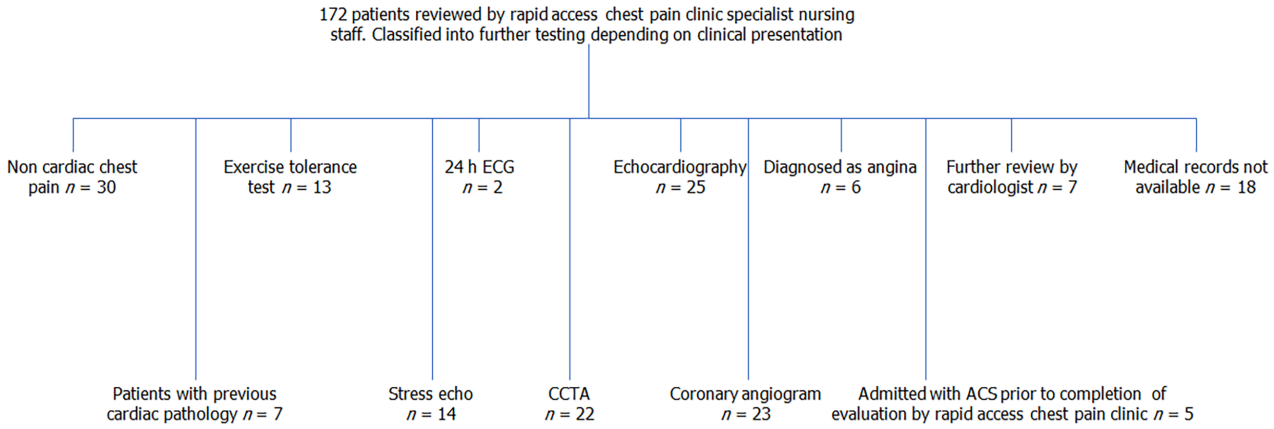


Figure 1 Patient flow chart according to further investigation.

female patient with a past history of AMI, coronary artery bypass surgery and uscTnI = 16.6 ng/L, was referred to the heart failure clinic with severe left ventricular systolic dysfunction. Two patients with uscTnI at the upper quartile of the reference range: 71year old female with persistent gastric reflux and uscTnI = 8.2 ng/L, QRISK3 score = 12%, and 89 year man with a history of pulmonary embolism, idiopathic pulmonary fibrosis and osteoarthritis with a uscTnI=7.7 ng/L, QRISK3 score rated as high, were categorised as non-cardiac chest pain.

Exercise tolerance test: Thirteen patients had a negative exercise tolerance test. A 55 year old male with constant chest pain and an uscTnI value of 9.7 ng/L and QRISK3 score of 9% assigned to ETT developed a non-limiting chest pain during exercise and was described as low risk.

Three patients with ECG changes suggestive of ischemia and a further patient with a normal exercise tolerance test and typical angina pain underwent cardiac catheterisation and coronary angiogram. These patients are included in the section with the group assigned to coronary angiography.

24 h ECG monitoring: Twenty four hour ECG monitoring detected ectopic activity with ventricular and supraventricular ectopics in two patients.

Echocardiography: Twenty five patients were designated for investigation with echocardiography. One 78 year old female with an uscTnI = 8.6 and QRISK3 = 20% was diagnosed with atrial fibrillation. A further 78 year old male with uscTnI at the upper quartile of the reference range, 6.2 ng/L, QRISK3 = 54% and normal systolic and ventricular function was diagnosed with angina and his medication was changed to a beta-blocker. He was diagnosed with adenocarcinoma of the prostate 12 years previously and treated with androgen blockade and radiotherapy. He was referred for further review by cardiology specialists.

Echocardiography diagnosed mild abnormalities in six patients. Two patients were diagnosed with recent onset atrial fibrillation (71 year old male with uscTnI = 9.3 ng/L) and pre-existing left bundle branch block (79 year old male with uscTnI = 17.0 ng/L).

Angina: Six patients were diagnosed with and treated as stable angina. Two patients had measured uscTnI values of 7.9 and 9.2 ng/L.

Review by a specialist in cardiology: Seven patients were further reviewed by a medical specialist in cardiology. A 63 y old male patient with a prior history of cardiovascular accident, subarachnoid haemorrhage and alcohol dependence and uscTnI value of 70 ng/L was treated with beta-blockers and placed under surveillance.

Lost to follow up: Medical notes following RACPC evaluation were not available for eighteen patients. A 74 year old female with an uscTnI = 7.5 ng/L and QRISK3 of 46% was diagnosed with stable angina and referred by RACPC staff for review by specialist cardiologists. Further follow-up of this patient was not recorded in the medical electronic notes.

Patients with previous cardiac pathology: Seven patients with previous cardiology pathology were reviewed by cardiologist. A 72 year old male with prior history of coronary artery bypass graft 9 years previously presented with a uscTnI of 32.2 ng/L. His medication was changed to include statins and ISMN (Isosorbide mononitrate). A further 76 year old female with known AF presented with an uscTnI=6.1 ng/L.

Stress echocardiography: Thirteen patients categorised to stress echocardiography, were classified as normal. A single patient showed mild inducible ischemia.

CCTA: Of the twenty two patients allocated to CCTA 12 were classified as normal, and 6 with mild CAD and 4 with severe disease. The mean uscTnI concentration in patients with obstructive CAD was 2.7 (range 1.1-8.7) ng/L and without CAD was 2.8 (range 0.6-9.3) ng/L. There was considerable overlap between the values. Fifty nine year old female with no relevant previous history and uscTnI = 9.3 ng/L and QRISK3 score 5%, and a 42 year old female with a history of gastroesophageal reflux and uscTnI = 7.1 ng/L and QRISK3 < 2% had normal CCTA. Sixty one year old male with uscTnI = 8.7 ng/L and QRISK3 score of 25% demonstrated severe obstructive disease. A further 62 year old female with a QRISK3 of 17% and uscTnI = 1.2 ng/L demonstrated severe CAD following CCTA and presented with ACS and Non-ST segment elevation myocardial infarction (NSTEMI) prior to completion of investigation. A plot of QRISK3 scores and uscTnI (Figure 2) suggested that 3/22 patients with an uscTnI < 1 ng/L and QRISK3 score < 10% showed a normal CCTA.

Coronary angiography: Twenty three patients underwent coronary angiography. Six patients showed normal coronary arteries. Fifty nine year old male, with definite angina pain, uscTnI = 2.23 ng/L and QRISK3 = 8%, underwent ETT which showed ventricular bigeminy. Investigative echo and coronary angiogram were classified as normal.

Coronary angiography detected severe disease in two patients: 58 year old male with uscTnI = 3.2 ng/L, QRISK3 13%, 53 year old male with uscTnI = 48.5 ng/L and QRISK3 10%. ETT detected ischemic changes in both patients. A further patient, 49 year old male with uscTnI = 1.4 ng/L and QRISK 23%, and normal ETT, and referred for further investigation for 'typical' angina pain, developed NSTEMI prior to

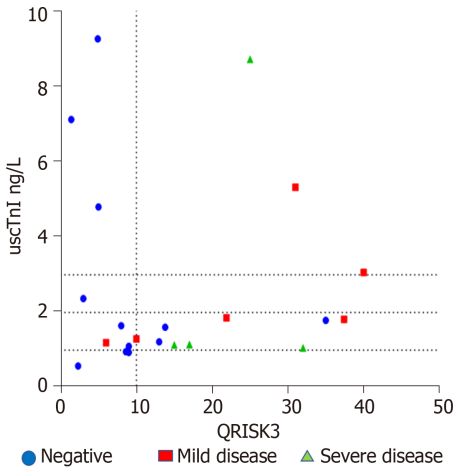


Figure 2 QRISK3 and uscTnI profile in patients assigned to coronary computed tomography angiography. Vertical dotted line represent QRISK3 values of 10%, and the horizontal dotted lines represent uscTnI values of 1, 2 and 3 ng/L. The lower left hand quadrant represents a QRISK value of < 10% and uscTnI values < 1 ng/L. Three patients classified as negative by computerized tomography coronary angiogram fall within the quadrant.

completion of investigation. A 60 year old female uscTnI = 2.9 ng/L and QRISK3 score 8% presented with crescendo angina and a troponin change of 26 ng/L, Coronary angiogram showed severe CAD in both patients. uscTnI increased in patients with the increasing severity of coronary artery occlusion (Table 3). Higher uscTnI was more likely to be associated with severe occlusion of CAD. A plot of QRISK3 and uscTnI in this group showed that patients were not classified within lower quartile (< 1 ng/L uscTnI and QRISK3 score < 10%).

ACS: Two patients presented with ACS and troponin changes prior to assessment by RACPC. A fifty eight year old male with a baseline uscTnI = 1.9 ng/L presented to the emergency department with a cardiac troponin change of 42 ng/L. Coronary angiogram showed mild occlusion. A 63 year old female who was admitted, prior to RACPC assessment, to the hospital with pyelonephritis showed a cardiac troponin change of 23.6 ng/L; coronary angiogram showed severe disease. Baseline uscTnI taken prior to hospital admission was not available in this patient. One 73 year old male and 86 year old female were classified as recent acute cardiac events, a review suggested uscTnI levels of 2290 and 221 ng/L, respectively, prior to review by RACPC. A further 62 year old female with a past history of breast cancer and uscTnI = 3.6 ng/L died of cardiac arrest prior to review by RACPC staff. Patient follow-up over a period of 6 mo after RACPC review did not result in further admissions with ACS.

uscTnI and receiver operating characteristic curves

We examined whether uscTnI can predict the presence or exclude the presence of coronary artery stenosis in patients assigned to ETT, Echo, Stress Echo, CCTA and coronary angiogram using ROC, Figure 3. The analysis included 63 patients who tested negative and 34 patients who tested positive. ROC analysis showed an AUC of 0.63 (95%CI: 0.51-0.73). At a value of uscTnI value > 0.52 ng/L, sensitivity was 100% and specificity 1.6%. At a value of uscTnI > 11.6 ng/L, sensitivity was 10.7% and specificity 100%. We found a single patient (84 year old male) with an uscTnI = 0.46 ng/L with a normal echo. Ten patients with uscTnI > 11.6 ng/L were detected within the study. Three with severe CAD disease following coronary angiogram (uscTnI = 13.4 ng/L, 18.3 ng/L, 48.5 ng/L), one with moderate disease (uscTnI = 22.3 ng/L), left bundle branch block (uscTnI = 17.0 ng/L), known ischemic heart disease (uscTnI = 33.2 ng/L), chronic morbidity for monitoring by cardiologist (70.4 ng/L), a further patient diagnosed with non-cardiac chest pain (uscTnI = 16.6 ng/L), and two with recent previous ACS events (uscTnI = 221 and 2290 ng/L).

DISCUSSION

Early detection of CAD remains an important task as effective treatments are available to relieve symptoms and reduce mortality[5]. Suspected stable angina remains a common presenting complaint. The challenge remains to identify those with CAD and

Table 3 Patients assigned to coronary angiogram

Group	Normal	Mild disease	Moderate disease	Severe disease
Mean uscTnI ng/L	1.8	3.3	7.3	10
Min uscTnI ng/L	1.1	2.0	1.0	0.94
Max uscTnI ng/L	2.2	3.9	22	49
n	6	5	5	7

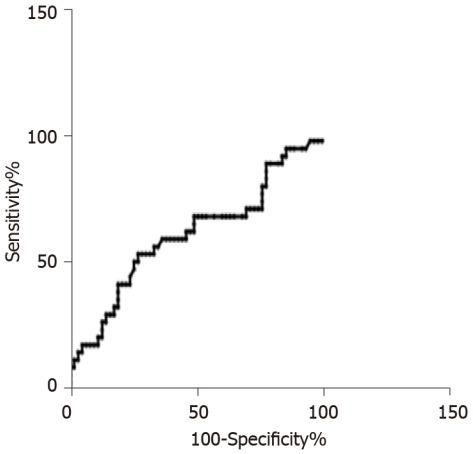


Figure 3 Receiver operating characteristic curves for uscTnI in patients allocated to functional testing (Exercise tolerance test, Echocardiogram, Stress echocardiogram), coronary computed tomography angiography and coronary angiogram. Patients were diagnosed with coronary artery disease based on patient follow-up tests.

those with intermediate pre-test probability who need further functional testing. The pre-test probability of stable CHD is determined by the presence of cardiovascular risk factors, age, sex and the nature of the presenting chest pain[5]. NICE guidelines, United Kingdom suggest that the diagnosis of stable angina is based on clinical assessment alone or clinical assessment and diagnostic testing[6]. In the United Kingdom, RACPC is the first place of referral in the investigation of suspected stable angina. In Worcester specialist nursing staff triage patients using clinical assessment which include among others, detailed clinical history, physical examination, QRISK3 as well as typicality of chest pain. In this study we investigated the use of a very highly sensitive troponin assay, an assay that can detect cTnI in 98% of healthy individuals, in the diagnosis and management of stable angina in the RACPC. In previous studies, uscTnI to rule out functionally relevant CAD was investigated in patients without known previous CAD; in this study we aimed to investigate the application of the assay in an unselected group of patients who presented to the RACPC.

Previous reports have stated that levels of uscTnI were significantly higher in patient with exercise induced ischemia, Using a combination of pre-ETT clinical assessment and uscTnI, the authors suggest a cut-off value of 1.54 ng/L to rule out 15% of patients from further testing, but acknowledge that further refinement is required because even when used with clinical judgement uscTnI provided only moderate diagnostic accuracy[17,18]. This value may be influenced by other structural cardiac abnormalities. In our patient series, the patient co-morbidity included congestive cardiac failure, history of breast cancer and sarcoidosis. In this study, investigation on two patients with uscTnI 3.2, and 48.5 ng/, and abnormal ETT which showed ischemic changes, showed severe CAD. A further patient with a normal ETT, uscTnI = 1.4 ng/L and classified for a coronary angiogram because of "typical angina pain" developed NSTEMI prior to further investigation. Coronary angiogram showed severe CAD. This study suggests overlap in uscTnI values in patients assigned to ETT and classified as with and without CAD. Strategies used to stratify patients into different investigation methods, as well as patient selection for RACPC assessment may influence cut-off levels used for uscTnI.

An additional study, included patients referred for investigation of functionally relevant CAD by rest/stress myocardial perfusion single-photon emission tomography/computer tomography. The patients with clinically relevant cardiac

disease were excluded. An uscTnI value of < 0.5 ng/L ruled out functionally relevant CAD in 10% of patients[15]. The SCOT-HEART trial investigated patients with suspected stable angina assigned to CCTA for obstructive CAD. The median concentration of uscTnI assay in patients without CAD was 1.2 ng/L and with CAD was 1.9 ng/L. Addition of uscTnI to the CADC risk model reduced the number of patients determined to be at intermediate or high risk by the CADC model by 10%[14]. The authors suggest that the study demonstrates that the use of uscTnI as a biomarker can improve the diagnosis of stable obstructive CAD. In the current study there was considerable overlap in uscTnI values between patients with and without obstructive CAD. However a plot of QRISK3, a risk evaluation of cardiac events at 10 years and uscTnI showed that at QRISK3 < 10% and uscTnI < 1 ng/L, 14% of patients with normal CCTA scan were within this quartile. This study confirms previous studies that the assessment of stable angina in patients referred for CCTA may be improved by the addition of uscTnI. Cardiac imaging remains a valuable tool for the assessment of CAD and the early detection of CAD remains an important task, CCTA has recently come under scrutiny due to increased cost, limitations such as increased radiation or user dependent interpretation or used inappropriately in patients with very low pre-test probability of CAD[4,5]. Additional studies are mandatory to elucidate if the rule out of 14% of patients is applicable to a larger cohort of patients pre-selected for CCTA.

Increase in uscTnI occurred in patients referred for coronary angiogram and increased with degree of severity of CAD. Given that previous studies suggest an association between high sensitive cTnI and the presence of CAD without ACS[19], this study confirmed an association between uscTnI and severity of CAD in the patient group referred for coronary angiogram. Further, the use of troponin assays in an RACPC setting may identify patients with recent ACS events and result in earlier assessment and treatment of these patients.

The question remains how these findings and uscTnI can be applied in clinical practice in the RACPC in the United Kingdom. A comparison of ROC curves for patients who underwent both functional testing, CCTA and coronary angiogram did not identify a single uscTnI value with a high enough sensitivity and specificity (and negative and positive predictive value) for stable CAD. In the population referred to the RACPC for further evaluations a low level of uscTnI ≤ 0.52 ng/L may decrease the number of patients required for further investigation and high levels > 11.6 ng/L may identify those who require further evaluation. It is unlikely that uscTnI within the range > 0.52-11.6 ng/L will be a standalone test for suspected stable angina. The cohort we studied included patients with several comorbidities and previous history of CHD that often pose a diagnostic and prognostic challenge as to the cause and significance of the presenting chest pain. This study suggests uscTnI as a sensitive marker of cardiac damage would perform best when combined with clinical assessment of the patient. It must be emphasized that the findings of this study would not mean that in the RACPC clinical judgment can be substituted with uscTnI. Should a single uscTnI be performed in either primary care or at presentation to RACPC, it needs to be interpreted with clinical evaluation.

These findings complement previous data on the use of uscTnI in the diagnosis of CAD in suspected stable angina. To our knowledge this is the first study to investigate the use of a "highly" sensitive cardiac troponin assay in a RACPC. The limitations of this study are that this is a single-centre study and bias may have been introduced due to referral characteristics. We do not believe that lack of access to patient medical records, which was not based on patient demographics led to sample bias. We also need to emphasise that in this institution myocardial ischemia was investigated by several methods in patients with a wide range of clinical probability of CAD based on clinical evaluation.

The study suggests that in the presence of clinical comorbidities and previous CHD the uscTnI needs to be used in conjunction with clinical assessment. Diagnostic cut off values of uscTnI in an RACPC setting depend on patient population and comorbidities. Further work is required to investigate the use of "highly sensitive" cardiac troponin values in the selection of patients suspected with CAD for further investigation and treatment.

CONCLUSION

The study suggests that in the presence of clinical comorbidities and previous CHD the uscTnI needs to be used in conjunction with clinical assessment. Diagnostic cut off

values of uscTnI in an RACPC setting depend on patient population and comorbidities. Further work is required to investigate the use of "highly sensitive" cardiac troponin values in the selection of patients suspected with CAD for further investigation and treatment.

ARTICLE HIGHLIGHTS

Research background

In the United Kingdom rapid access chest pain clinics (RACPC) have been set up in hospital centers to address the problem of non-acute chest pain of uncertain origin. The early detection of coronary artery disease (CAD) in these patients can lead to effective treatment. In this study we looked at the value of a highly sensitive troponin I assay in the rule out of functionally relevant CAD in patients referred for further assessment and investigation in a RACPC. To our knowledge this is the first study to be carried out in a non-teaching hospital in patients who presented with several clinical co-morbidities.

Research motivation

While functional studies and imaging techniques are valuable in the evaluation of patients with suspected CAD, highly sensitive troponin I which detects even minute concentrations of troponin I in the serum may provide further information on cardiac injury that may be associated with CAD.

Research objectives

The aim was to assess the role of troponin in assisting clinical decision making in the setting of a RACPC in a non-teaching hospital. This has not been explored previously.

Research methods

One hundred and seventy two patients admitted to the rapid access clinic were studied. Unlike previous studies, patients with a previous history of CAD were included in the study. Following clinical assessment the patients with suspected stable CAD were assigned to 24 h monitoring electrocardiogram, exercise tolerance test, echocardiogram, exercise or pharmacological stress echo, coronary computed tomography angiography, coronary angiogram and percutaneous coronary intervention, medical treatment for angina, or were discharged as clinical assessment suggested non-cardiac chest pain. More complex patients were designated for review by specialist cardiologists.

Research results

Receiver operating characteristic curves suggest that patients with troponin I ≤ 0.52 ng/L were less likely to present with CAD and values > 11.6 ng/L required further evaluation. In the range > 0.52-11.6 ng/L troponin I was not a standalone test. In all cases troponin was best used in conjunction with clinical assessment. In patients assigned and preselected for coronary computed tomography angiography and coronary angiogram troponin I was an indicator of the severity of CAD. Cut-off levels of troponin I were determined by the patient population cohort.

Research conclusions

The study suggests that in unselected patients presenting with suspected stable angina to a rapid access clinic troponin I is best used in conjunction with clinical evaluation of the patient. Diagnostic cut-off levels are dependent on patient population.

Research perspectives

What is now required is further work with different population groups.

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