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MINIREVIEWS

Radiation protection for the interventional cardiologist: Practical approach and innovations

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Abstract

Use of ionizing radiation during cardiac catheterization interventions adversely impacts both the patients and medical staff. In recent years, radiation dose in cardiac catheterization interventions has become a topic of increasing interest in interventional cardiology and there is a strong interest in reducing radiation exposure during the procedures. This review presents the current status of radiation protection in the cardiac catheterization laboratory and summarizes a practical approach for radiation dose management for minimizing radiation exposure. This review also presents recent innovations that have clinical potential for reducing radiation during cardiac interventions.

Key Words: Radiation; Cardiac catheterization; Quality improvement; Cathlab; Ionizing radiation

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Core Tip: Radiation safety is of concern to catheterization laboratory personnel. In recent years, radioprotection has become a priority in cardiac catheterization interventions and there is keen interest in reducing radiation exposure during the procedures. This review presents the current status of radiation protection in the cardiac catheterization laboratory and summarizes traditional protection mechanism and innovations.

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INTRODUCTION

Use of ionizing radiation during cardiac catheterization interventions adversely impacts both the patients and medical staff[1]. Radiation exposure can result in long-term health effects, including skin and eye damage, and may cause certain forms of cancer by interacting with and altering cellular DNA[1]. The deleterious effect that ionizing radiation has on human tissue may result in potential stochastic and deterministic sequels[2]. Deterministic effects such as ocular lens defects are characterized by a predictable dose-related increase in severity, which can be evaluated by means of air kerma (kinetic energy released per unit mass, AK)[2]. Stochastic effects follow a linear, no-threshold risk model, in which the risk of damage to the irradiated tissue increases linearly with the amount of exposure. The exposure to low-dose radiation induces a stochastic risk in various malignancies that can be measured by dose area-product (DAP)[2].

Interventional cardiologists, given their chronic radiation exposure in cardiac catheterization laboratories, are exposed to the highest cumulative radiation among health professionals. This issue has been magnified with increased exposure in the long duration of structural or complex coronary intervention like chronic total occlusion (CTO) cases. Cataracts, thyroid cancer, and disproportionate incidence of left-sided brain tumors have been reported in interventional cardiologists[1].

In recent years, radiation dose in cardiac catheterization interventions has become a topic of increasing interest in interventional cardiology and there is a strong interest to reduce radiation exposure during the procedures[1,2].

The level of protection should be the best possible under the prevailing circumstances, maximizing the margin of benefit over harm. Physician responsibilities with regard to radiation safety should be based on the ALARA radiation principle: "as low as reasonably achievable"[1].

RADIATION REDUCTION RECOMMENDATIONS IN THE CATHETERIZATION LAB

The hazards of radiation exposure are not limited to interventional cardiologists. Radiation safety is a multi-disciplinary approach, which should involve all catheterization lab (cathlab) personnel. Traditional lead personal protective equipment (LPPE) and radiation shields are mandatory to enhance the protection of all staff members during interventional procedures. The qualities of protective measures are summarized in Table 1.

Optimizing radiation protocols and implementing a radiation safety program to improve the safety of patients and medical staff should become a priority during interventional procedures. The primary goal is to reduce radiation doses wherever and whenever reasonably achievable, thereby reducing the health risk that is assumed to be proportional to the radiation dose[3,4]. Dose Limits Recommended by International Commission on Radiological Protection are presented in Table 2.

Traditional lead personal protective equipment

All staff members working in interventional x-ray rooms are required to wear lead-equivalent radiation protection garments. Traditional LPPE consists of the following. (1) Leaded glasses. A higher incidence of cataracts (specifically posterior subcapsular) has been reported in interventional cardiologists[1]. Leaded glasses reduce eye radiation by 35%-90%[5-7]. (2) Thyroid collar. The thyroid gland is a radiosensitive organ and thyroid cancer is a known consequence of radiation exposure. Consequently, a protective thyroid shield is mandatory during interventional procedures[8]. Thyroid shields should be quality-checked annually. And (3) Protective lead aprons. Lead aprons are very effective in reducing radiation exposure to the staff members. However, many lead aprons weigh more than 7 kg causing orthopedic problems[9]. An alternative is a two-piece wraparound apron consisting of a skirt and a vest. This type of garment is lighter potentially reducing the risk for musculoskeletal injury[9]. Lead aprons should be quality checked annually for any defects to ensure that no

Table 1 Qualities of protective measures

Protective measures	Evidence[1]	Reduction	Operator protection	Patient protection
Technical issues	A[2,3,13,14]	60%	Yes	Yes
Traditional LPPE	B[5-9,51]	35-95%	Yes	No
Surgical caps	D[44]	3.3%	Yes	No
Gloves	D[9]	20-50%	Yes	No
Radiation-blocking cream	D[46]	85%	Yes	No
Shield, curtain and TRPB	B[9,10-12]	30-70%	Yes	No
CathPax®	C[16,20-22]	70- 80%	Yes	No
Zero gravity®	C[19]	78-93%	Yes	No
RadPad®	A[26,29,30]	30-35%	Yes	No
Robotic systems	B[32,34,35,42]	96%	Yes	No

[1]Clinical evidence: A ≥ 1 randomized clinical trial; B ≥ 4 conclusive non-randomized clinical studies or safety/feasibility randomized trial; C < 4 conclusive non-randomized clinical studies or safety/feasibility randomized trial; D inconclusive clinical studies.
LPPE: Lead personal protective equipment; TRPB: Transradial radiation protection board.

Table 2 Regulatory limit on occupational radiation exposure and the current status with respect to the limit

Type of dose limit	Limit on dose from occupational exposure[1]
Effective dose	20 mSv/yr averaged over 5 consecutive years and 50 mSv in a single year
Effective dose on pregnancy	The dose to embryo/fetus should not exceed 1mV during remainder of pregnancy
Equivalent dose: Lens of the eye	20 mSv/yr averaged over 5 consecutive years and 50 mSv in a single year
Equivalent dose: Skin	500 mSv/yr
Equivalent dose: Extremities (hands and feet)	500 mSv/yr

[1]Occupational Exposure: Planned exposure situations where radiological protection can be planned in advance, and exposures can be reasonably predicted.
Dose limits recommended by international commission on radiological protection (ICRP)[52].

cracks in the radioprotective layer are forming.

Equipment-mounted shielding

The main shield mounted on the equipment consists of shields suspended from the ceiling and curtains suspended from the table. Radiation shields must be discreetly placed and actively managed both before and during the procedure to be effective[4].

Ceiling-mounted shields are made of leaded clear plastic that is adjustable during the procedure and if positioned correctly can reduce the radiation dose to the operator's head and neck[4,9]. The shield should be as close as possible to the patient to stop the scatter at the source for the greatest degree of attenuation.

The lower region of the operator receives the most exposure during a procedure. Protecting the pelvic region containing the reproductive organs is essential due to their radiosensitivity. Table suspended lead drapes between the X-ray tube and the operator provide a significant lower radiation dose to operators at pelvic and thorax level[4,9,10]. Recently, a clinical trial showed that the combination of pelvic drapes and under-table shields on top of the standard protective measures of the cathlab reduced the operator radiation exposure at thorax to negligible levels[11].

Transradial radiation protection board (TRPB) is a grooved arm board with a detachable 0.5 mm lead equivalent shield designed to rest between the patient's arm and side. TRPB reduces radiation operator dose during radial approach procedures in addition to standard protection[12].

Mobile leaded shield consists of a 200 cm x 80 cm lead-equivalent mobile shield with a thickness of 2 mm positioned between the patient and the operator. A transparent 2-mm lead-equivalent window offers a permanent view of the patient. A

mobile leaded shield, combined with standard preventive measures, significantly reduces operator exposure to ionizing radiation during interventional procedures.

Technical approach

The guiding principle with regard to radiation safety should be based on the ALARA radiation principle. ALARA stands for "as low as reasonably achievable." This principle means that even if it is a small dose, if receiving that dose has no direct benefit, it should be avoided. Effective strategies to minimize patient and operator exposure during interventions are based on four principles (Figure 1)[2,3,11,13-15].

Utilize radiation only when imaging is necessary to support clinical care and limit fluoroscopy time to only when the operator is looking at the monitor.

Keep the image receptor as low as possible on the patient's chest. Optimal table positioning can reduce patient radiation dose. The patient is ideally placed as close as possible to the image receptor and further away from the X-ray source.

Minimize use of steep angles of the X-ray beam. Extreme angulations are associated with high air kerma values. Paying close attention to the angulation and placing the C-arm in 0° to 20° angulation will result in a more than 3-fold reduction in the amount of radiation scattered during fluoroscopic acquisition. The left anterior oblique view cranial angulation has the highest degree of scatter exposure to the operator (Figure 2)[3].

Minimize use of cine and shorten each cine acquisition as much as possible.

Minimize the use of magnification modes. Most modern systems have software magnification algorithms that allow for magnification without additional radiation. Nevertheless, hardware magnification should still be used when clinically indicated.

Utilize collimation to the fullest extent possible.

Monitor radiation dose in real time to assess the operator's and patient's risk/benefit ratio during the procedure. Use of real-time radiation monitoring devices that provide auditory feedback can significantly reduce radiation exposure during cardiac catheterization (Figure 3).

Adjust the fluoroscopy frame rate. Fine-tuning radiation safety protocols could reduce radiation doses without compromising the effectiveness of catheterization procedures in patients. Frame rate is typically set at 15 frames-per-second and decreasing it to 7.5 frames-per-second results in significant radiation dose reduction[2,13].

Increase the distance between the operator and radiation source. Radiation exposure is inversely proportional to the square of the distance from the X ray source. Increasing the distance between the cardiologist and the patient to 1 m can decrease a physician's occupational radiation dose by about a half.

Educate in radiation protection. Training and education in radiation protection is widely recognized as one of the basic principles of optimization programs for medical exposures. These provide practitioners of interventional cardiology adequate theoretical and practical training in radiation safety to help minimize occupational radiation dose.

INNOVATIONS

Traditional LPPE with lead aprons, thyroid shields and lead glasses are only partially effective. This protection equipment leaves body parts such as arms, hands and heads unprotected[16-18]. In recent years, new concepts in individual or semi-individual radioprotection were being marketed to reduce scatter radiation.

Suspended radiation protection system: Zero Gravity®

The Zero-Gravity suspended radiation protection system is designed to increase the level of radiation protection while at the same time eliminating the weight burden for the operator. Compared to conventional lead aprons with under-table or ceiling-mounted shields, Zero-Gravity provides superior operator protection during fluoroscopy. This system reduces fatigue and orthopedic injuries resulted from routinely wearing heavy protective apparel as well as allowing clinicians freedom of movement, especially during challenging procedures (Figure 4A and B)[19].

Mobile radiation protection cabins: CathPax®

In the last decade, radiation protection cabins (RPCs) have become used in interventional procedures. RPCs significantly reduce radiation exposure in different interventional procedures[16,17,20-23]. The cathpax® cabin (Lemer Pax, Carquefou, France) is a

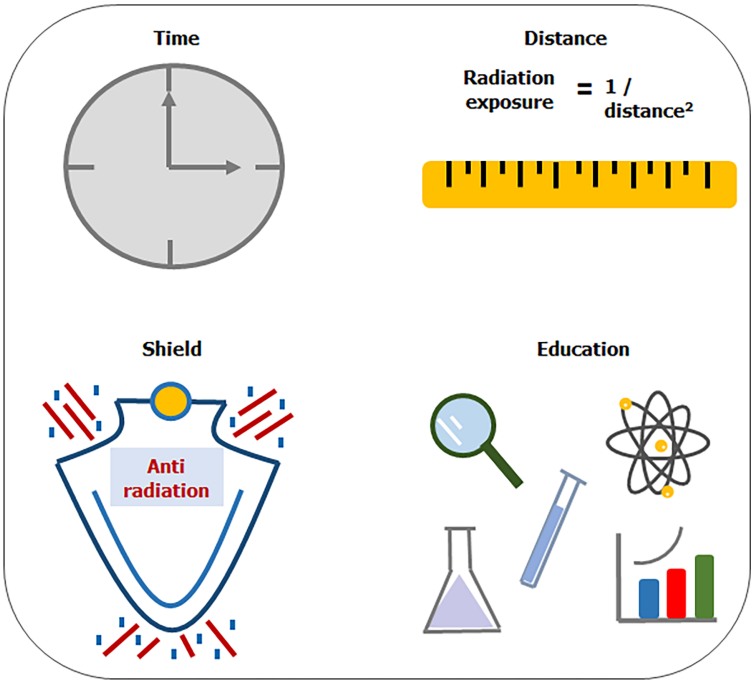


Figure 1 Radiation protection in the catheterization lab should be based on four principles. Time: radiation dose depends linearly on the exposure time. Distance: The amount of radiation exposure depends on the distance from the source proportionally to the inverse of the distance squared from the X-ray source, so staff can lower their exposure levels by a factor of four by doubling their distance from the source. Shielding: barriers of lead protection can be accomplished with different forms such as personal protective equipment or mobile shields. The greater the shielding around the source, the smaller the exposure. Education: training and education in radiation protection is one of the basic components of radiation protection programs.

mobile and height-adjustable RPC that comes in three ranges of radiation protection tailored to the specific needs of cardiac interventional operators. The CathPax® AF and the Cathpax® CRM cabins are particularly adapted for electrophysiology procedures and for cardiac devices implantations respectively. The Cathpax® AIR (Figure 4C and D) shielded with 2 mm lead-equivalent is adapted to all interventional cardiology procedures, (coronarography, complex percutaneous coronary interventions (PCIs) as well as structural ones like TAVI or left appendage closure).

One of the main concerns regarding RPCs is its comfortability and workability in a real-world setting, especially in complex scenarios such as CTOs. Recently, the Cathpax® AIR confirmed its feasibility and efficacy in a real-world setting by reducing first-operator relative radiation exposure by 78%. This effect was consistent during different types of procedures including emergent procedures, complex PCIs and structural procedures[24].

Disposable radioprotective drapes

Disposable radioprotective drapes can be particularly useful in complex interventional procedures associated with higher radiation exposure, such as CTO interventions[25,26]. They contain metallic elements (bismuth, barium, and tungsten-antimony) and are placed over the patient during fluoroscopically guided interventions. Radioprotective drapes reduce attenuate scatter radiation 12-fold for the eyes, 25-fold for the thyroid, and 29-fold for the hands[27].

The Radpad® is a disposable drape lead-free shield (Worldwide Innovations and Technologies Inc, Lenexa, KS) (Figure 5) that reduces operator radiation exposure in several studies by 20%-59% including a real-world randomized trial[16-18,26,28-30].

However, the disposable drapes shield should not be placed within the imaging field during radial angiography as such an action may trigger an automatic increase in dose rate, significantly increasing patient dose[25,26].

Robotic percutaneous systems

Robotic PCI (R-PCI) is an emerging technology with significant potential for transforming PCI[31]. In 2006, Beyar *et al*[32] developed and reported the first remote controlled robotic system to address the occupational hazards of interventional cardiology[31,32]. Five years later, Granada and colleagues reported the first in-human experience in a series of eight patients with the CorPath® 200 robotic system (Corindus,

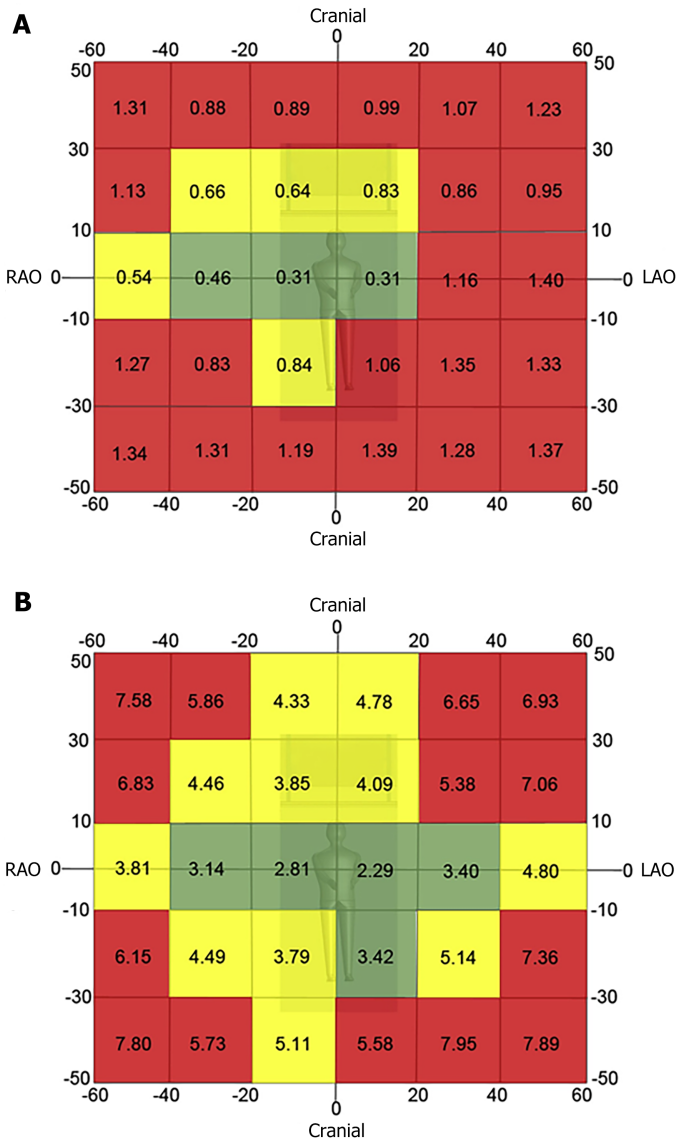


Figure 2 Two-dimensional radiation map for fluoroscopy (A) and acquisition imaging (B). The red zone denotes projections where < 26% of the image procurement occurred in the lowest tertile of Air Kerma rate. The yellow zone denotes projection where 26% to 40% of the images were procured in the lowest tertile of air kerma rate the value in each cell represents the median Air Kerma rate for the respective projection. Reproduced with permission from reference 8[3]. LAO: Left anterior oblique view; RAO: Right anterior oblique view.

Inc., Natick, Massachusetts, United States)[33]. At present, the second generation of CorPath is available. The CorPath GRX system (Figure 6) has new features that further facilitate R-PCI in complex anatomies, including remote manipulation of the guide catheter to help augment support after engagement or incorporation of wiring algorithms such as "rotate on retract and simplified device exchanges." The new system achieves tremendous reduction in radiation exposure to operators with high rates of clinical and technical success even in complex PCI scenarios such as laser atherectomy or left main stem disease[31,34,35]. The R-One (Robocath) is a new R-PCI platform that recently received regulatory approval for use in Europe. This new system has functional capabilities similar to those of the CorPath 200 system.

A key potential advancement that R-PCI could bring is in the field of tele-R-PCI. This will allow for the treatment of patients who are in geographically distant locations[36]. Performing long distance tele-R-PCI in type A coronary lesion is currently feasible with predictably successful outcomes if reliable network connectivity and local cardiac catheterization facilities are available[37].

In addition to mitigating occupational hazards for interventional cardiologists, R-PCI offers the potential advantages of more precise measurements of lesion length and more stable deployment of angioplasty balloons and stents[38].

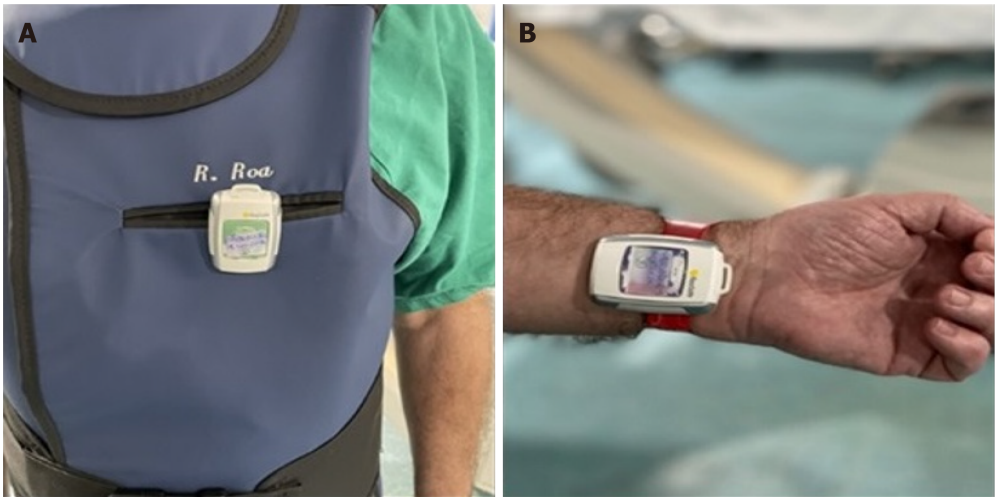


Figure 3 Real time electronic personal dosimeters placed over the apron (A) and on the left wrist of the operator (B).

Finally, the ongoing worldwide coronavirus disease 2019 (COVID-19) pandemic has imposed severe restrictions on such an interventional environment. In this setting, R-PCI can provide an additional layer of protection to the healthcare personnel participating in the management of COVID patients[39].

The current robotic systems are in the early stages of development compared to standard manual PCI. Despite being a promising technology, there are still some important issues to address before its use spreads beyond a few limited centers. Most importantly, there is a need for clinical evidence from large-scale randomized clinical trials showing improved radiation safety for the operators and non-inferior angiographic and clinical results[40]. Additionally, the initial CorPath 200 system had several limitations; the subsequent version, the CorPath GRX, has overcome some of these limitations but there are still multiple technical limitations to current R-PCI technology compared to manual PCI. These include the need for operators to obtain arterial access and manually engage guide catheters prior to utilization of R-PCI systems; current R-PCI systems are limited to 0.014″ wires and rapid exchange devices; thus, rotational atherectomy or two stent deployment cannot currently be performed [41]. The absence of tactile feedback is another important issue in complex PCIs, where the interaction among the wire, lesion, and operator is key to subsequent technical success[40]. Finally, at least one team member needs to remain at the bedside for equipment exchanges and the procedure duration is significantly increased compared to traditional interventions[32,35,42].

Others

The effectiveness of other radiation safety innovations, such as radiation-blocking hats, gloves, or radiation-blocking cream, still remain uncertain[17,20,43].

A recent study showed that radiation scattering comes predominantly from under the head of the operator and surgical radio-absorbing caps do not cover this area, so the brain protection demonstrated by a surgical lead cap is minimal. It has been shown to decrease radiation dose to the brain by only 3.3%[4,44].

The hands of the fluoroscope operator should only be placed in the field of view when required by the procedure. The best way to protect the hands is to keep them away from the direct radiation beam whether protective gloves are used or not[9]. Notably, the use of protective gloves when the hands are placed in the field may trigger an automatic increase in dose rate, significantly increasing patient dose. Nevertheless, the use of radio protective gloves to reduce the exposure of the hands to scattered radiation when the hands remain outside the field is not contraindicated[45].

Radiation-blocking cream (BloXR®) is a hand lotion designed to offer radiation protection from X-rays[46]. The cream is applied prior to donning gloves, or over a glove with another glove on top. However, the commercially available cream comes with an United States Food and Drug Administration black box warning. The radiation-blocking cream could pose a radiation exposure risk to healthcare professionals due to the lack of radiation attenuation, which can occur due to inadequate or inconsistent cream formulation.



Figure 4 Zero Gravity® and Cathpax® AIR. A: Two hinged swing arm zero gravity systems installed in a hybrid room. This system consists of a single fixation point of the hinged swing arm. It can be used on both sides of the table if there is a fixation point available; B: A floor zero gravity unit. The suspended body and face shield can be repositioned for a broad range of procedures and room configurations; C, D: Photographs of the radiation protection cabin (Cathpax® AIR) in use during a coronary chronic total occlusion intervention.

PREGNANCY

Women are particularly underrepresented in cardiology procedural subspecialties, and account for < 10% of the physician workforce in interventional cardiology[47]. However, currently, the proportion of women who choose intervention cardiology as a career is increasing. The Women in the Innovations group of Cardiologists aim to provide guidance by describing the risk of radiation exposure to pregnant physicians and cardiac catheterization personnel[48].

Radiation exposure during pregnancy poses a risk to the fetus leading to two types of adverse effects: deterministic and stochastic effects. Deterministic effects consist of intrauterine growth retardation, pregnancy loss, mental retardation, small head size, reduced intelligence quotient and congenital malformations. Stochastic effects consist of risk of childhood cancer and hereditary diseases in the descendants[49]. The risk of each effect depends on the gestational age at the time of exposure with the first trimester being the period of greatest risk. Doses below 50 mGy have not been associated with an increase in fetal anomalies or pregnancy losses[50]. The fetal radiation exposure for most women who work in the cardiac catheterization laboratory is extremely low, and is much lower than the recommended limit. Protective garments specifically for pregnant women must provide at least 0.5 mm lead-equivalent protection throughout the entire pregnancy with a double thickness protective garment, specific maternity lead apron or maternity bib (for an additional lead protection layer). Additionally, an extra dosimeter at waist level under the lead apron to monitor fetal radiation exposure monthly is also recommended[48].

Although perceptions of radiation exposure risk remain widespread, with standard radiation safety measures practiced routinely, there is no statistically significant or

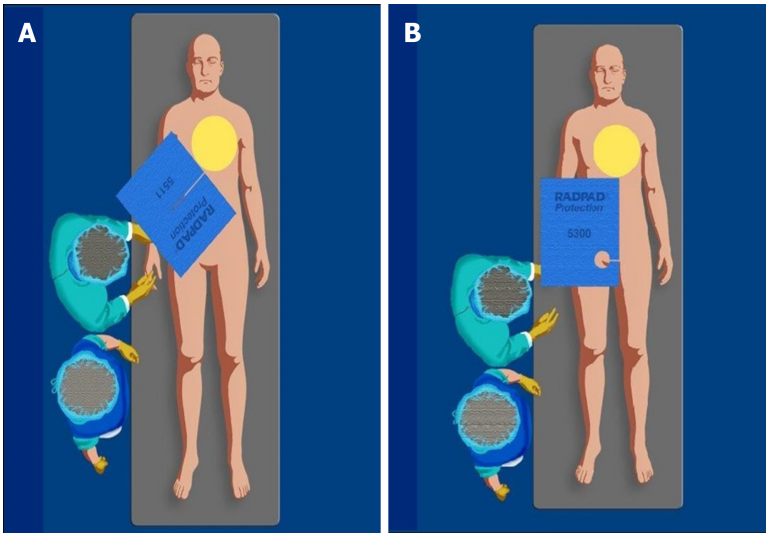


Figure 5 Correct positioning of the RadPad radioprotective drapes. A-B: The radioprotective drapes should be placed on the patient, between the image intensifier and the operator during (A) femoral and (B) radial procedures.

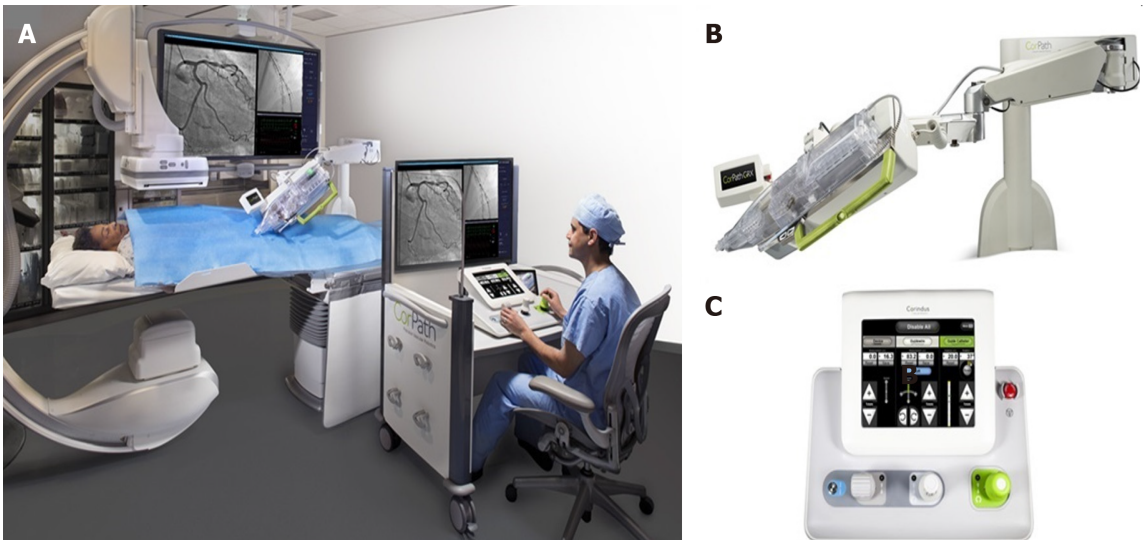


Figure 6 During robotic-assisted intervention, the interventional cardiologist sits in a radiation-shielded workstation and uses a set of joysticks and touchscreen controls that translate the physician's movements into device control. A: Control console; B: Extended-reach arm; C: CorPath cassette of the robotic system.

convincing evidence of an increased risk of pregnancy-related complications for female cardiologists exposed to radiation. This suggests that female interventionists can integrate pregnancy safely into their careers. All operators should follow common sense measures under the ALARA principle[47].

CONCLUSION

Optimal use of ionizing radiation in cardiovascular interventions is the responsibility of the healthcare professionals working in the cathlab. Efforts to reduce radiation exposure and participation in radiation safety educational programs should be encouraged by all the professionals involved in interventional procedures exposed to radiation. Professionals endeavor should be focused on the correct use of LPPE, optimal positioning and distancing to the table, the image intensifier and the operator. It is vitally important to optimize the X-ray settings, use fluoroscopy judiciously, and ensure appropriate shielding. Proper use of personnel dosimeters ensures correct radiation monitoring limiting exposure.

Based on the ALARA radiation principle, a priority should be to minimize radiation exposure in every clinical circumstance reducing radiation hazards.

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MINIREVIEWS

Chronic total occlusion revascularization: A complex piece to "complete" the puzzle

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Abstract

Treatment of coronary chronic total occlusion (CTO) with percutaneous coronary intervention (PCI) has rapidly increased during the past decades. Different strategies and approach were developed in the recent past years leading to an increase in CTO-PCI procedural success. The goal to achieve an extended revascularization with a high rate of completeness is now supported by strong scientific evidences and consequently, has led to an exponential increase in the number of CTO-PCI procedures, even if are still underutilized. It has been widely demonstrated that complete coronary revascularization, achieved by either coronary artery bypass graft or PCI, is associated with prognostic improvement, in terms of increased survival and reduction of major adverse cardiovascular events. The application of "contemporary" strategies aimed to obtain a state-of-the-art revascularization by PCI allows to achieve long-term clinical benefit, even in high-risk patients or complex coronary anatomy with CTO. The increasing success of CTO-PCI, allowing a complete or reasonable incomplete coronary revascularization, is enabling to overcome the last great challenge of interventional cardiology, adding a "complex" piece to "complete" the puzzle.

Key Words: Chronic total occlusion; Percutaneous coronary intervention; Complete revascularization; Prognosis; Coronary artery disease

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Core Tip: The application of "contemporary" revascularization strategy in coronary chronic total occlusion percutaneous interventions, allowed a high procedural success rate and to achieve a complete or reasonable incomplete coronary revascularization. From a procedural and clinical management point of view, an improved accuracy in

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Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

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clinical decision making process and a state-of-the-art revascularization, led to a long-term clinical benefit, even in high-risk patients or complex coronary anatomy.

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INTRODUCTION

Treatment of coronary chronic total occlusion (CTO) with percutaneous coronary intervention (PCI) has rapidly increased during the past decade, driven by technical and technological advancements involving drug-eluting stents (DES), antithrombotic drugs management, procedural strategies and interventional cardiologists' expertise. "Contemporary" revascularization strategies include: novel and dedicated techniques, use of 2nd and 3rd generation DES and intracoronary imaging, "tailored" antithrombotic therapy management. Strategies aimed to achieve an extended revascularization with a high rate of completeness have led to an exponential increase in the number of successful CTO-PCI procedures, which translates in a long-term clinical benefit. However, CTO-PCI is still underutilized, accounting for only 5%-15% of elective PCI, despite a reported prevalence of CTO in up to one-third of patients with coronary artery disease, and 10%-18% of patients with STEMI[1,2] The presence of a CTO, compared with non-occlusive coronary lesions, greatly affects the therapeutic strategies of patients with atherosclerotic ischemic heart disease, with a more frequent referral to surgical revascularization [coronary artery bypass graft (CABG)] or medical therapy rather than percutaneous solution.

CLINICAL BENEFITS OF CTO REVASCULARIZATION: STILL AN OPEN DEBATE?

The expected benefits from the revascularization of a CTO can be summarized in: (1) Improved quality of life; (2) Improved left ventricular (LV) function; (3) Increased long-term survival; (4) Increased tolerance to potential subsequent coronary events; and (5) Reduced risk of life threatening-arrhythmias.

The available evidence in support of a favorable prognostic impact, mostly comes from observational studies (high volume single-center registries or multi-center registries), with the recognized limitations of selection and publication bias and possible residual confounders[3-6]. On the other side, such registries have the undoubted advantage to offer a view of clinical and therapeutic practice in the real world. At present, there are also extensive meta-analyses to consolidate this evidence [7-9]. Contemporary randomized clinical trials are small, and often investigate surrogate prognostic end points or non-inferiority analyses[10,11] (Table 1).

The Korean multicenter randomized DECISION-CTO trial, which was discontinued because of slow enrollment (out of 1.284 planned patients, only 834 were enrolled), showed how CTO-PCI, combined with optimal medical therapy, was not superior to medical therapy alone in reducing cardiovascular events in patients with CTO at 3-year follow-up; the primary end point, a composite of all-cause mortality, myocardial infarction, stroke, and repeat of any coronary revascularization, was 20.6% *vs* 19.6% (P = 0.008 for non-inferiority of optimal medical therapy). Five years follow-up data, published in 2019, confirmed no differences in term of primary end point (22.3% *vs* 22.4%; HR 1.03; 95%CI: 0.77 to 1.37; P = 0.86); notably, the 19.6% of the patients assigned to the no CTO-PCI strategy arm, crossed over to receive staged CTO-PCI[10]. In the Korean study, the mean age of patients was approximately 62 years, LV function 57%, and two thirds of patients had a stable coronary artery disease. It is estimated that for an adequate statistical power to detect a difference in outcome in terms of mortality between CTO-PCI and optimal medical therapy, an ideal trial would require more than 5000 patients, a figure not even remotely represented in

Table 1 Chronic total occlusion study results and clinical outcomes according to hierarchical levels of evidence-based medicine: Registries, meta-analyses, and randomized clinical trials

Studies		Patients (*n*)	CTO-PCI success	Follow-up	PCI success *vs* PCI failure	
					MACE	Death
Registries	OPEN-CTO 2020 (12) (Hybrid approach)	1000	90%	1 yr	3.4% *vs* 3.7%	0.9% *vs* 0%
	EXPERT-CTO 2019 (2) (New generation DES)	250	96.4%	1 yr	18.5% *vs* 24.4%	NR
	Valenti *et al* 2019 (3) (Elderly ≥ 75 yr)	460	72%	5 yr	9.6% *vs* 17%	84% ± 3% *vs* 72% ± 6%
	Sudhakar *et al* 2014 (4)	13443	70.6%	2.65 yr	NR	HR 0.72, 95%CI: 0.62-0.83
Metanalyses	Christakopoulos *et al* 2015 (5)	28486	71%	3.11 yr	29.1%	6.4% *vs* 9.5%
	Hoebers *et al* 2015 (6)	15459	71.7%	1-10 yr	NR	10.4% *vs* 14.9%
	Chenmin *et al* 2021 (7) (Elderly ≥ 75 yr)	4693	70.4%-78.36%	20 mo-5 yr	16.8% *vs* 28.9%	HR: 0.51, 95%CI: 0.34-0.77
RCTs	DECISION CTO 2019 (8)	834	90.6%	4 yr	22.3% *vs* 22.4%	3.6% *vs* 5.3%
	EURO CTO 2018 (9)	396	86.6%	1 yr	5.2% *vs* 6.7%	0.8% *vs* 0%

RCT: Randomised controlled trial; CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; DES: Drug-eluting stents; NR: Not reported.

current studies.

The multicenter randomized EURO-CTO trial enrolled 450 patients, randomized to CTO-PCI *vs* medical therapy with a 2:1 ratio; procedural success in the PCI arm was 86.7%; at 12 mo follow-up, CTO-PCI group showed greater improvement in the angina frequency score (P = 0.003) and the quality-of-life score (P = 0.007) compared with optimal medical therapy; causative classification system (CCS) improved considerably more in the PCI group than in the optimal medical therapy group (P < 0.001). No differences in the primary safety end points evaluated at 36 mo were found. Major cardiovascular and cerebrovascular events (MACCE) during 12 mo follow-up were similar between the two groups (P = 0.55)[11].

The lack of positive results in terms of clinical outcomes in randomized trials may be explained, at least partially, by the exclusion of patients at higher risk of events, for whom, on the basis of a perceived or demonstrated therapeutic benefit, an interventional attitude is preferred, effectively excluding the possibilities of randomization to conservative therapy for ethical reasons. Accordingly, Galassi *et al*[12] in their study reported how, even in the absence of statistically significant differences in MACCE at a median follow-up of 16.3 ± 8.2 mo, the group of patients with severely depressed left ventricular ejection fraction (LVEF) (< 35%), showed a significantly improvement of LVEF when a successful CTO-PCI was performed.

Convincing positive results from randomized trials are still awaited to conclusively legitimize the potential benefits of CTO-PCI in patients with indication for revascularization. The lack of unequivocal answers from randomized trials, however, does not preclude the possibility of choosing a therapeutic strategy: "evidence-based medicine" is still "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"[13] and the current evidence points in favor of CTO-PCI attempts.

A meta-analysis published in 2015, conducted on more than 28000 patients, showed the association of successful CTO-PCI with improved long-term survival when compared with procedural failure (OR 0.52, 95%CI: 0.43-0.63)[7]. Another meta-analysis, conducted on 2243 patients with successful CTO-PCI, found a LVEF significant increase, with 4.4 percentage points over baseline comparison in absolute terms (P < 0.01), as well as a reduction in negative ventricular remodeling[8].

Clinical benefit of successful CTO-PCI was found also in large registries[3-6]. In the OPEN-CTO registry (1), which enrolled 1000 patients, investigators reported in the group of successful CTO revascularization a statistically significant improvement in Seattle Angina Questionnaire (SAQ) from 49.4 ± 0.9 to 75.0 ± 0.7 (P < 0.01), and, after adjusting for baseline differences, the mean group difference in SAQ between successful and unsuccessful CTO-PCI was 10.8 (95%CI: 6.3 to 15.3; P < 0.001)[3]. At 1

year, the unadjusted MACCE rate was lower in patients with successful index CTO-PCI compared to patients with unsuccessful CTO-PCI (9.4% *vs* 14.6%; $P = 0.04$)[14].

Nowadays, despite results from perspective randomized controlled trials are conflicting, and the survival benefits are still debates, the indications to drive a CTO-PCI according to guidelines of the most important scientific societies are refractory angina symptoms despite optimal medical therapy or patients with documented large ischemic area in the territory of occluded vessel[15]. Furthermore, current evidence and guidelines support the use of viability imaging to assist decision-making in patients with ischemic heart failure and coronary artery disease[15]. Distinguishing hibernating myocardium from non-viable myocardium is particularly important to select patients that are more likely to benefit from myocardial revascularization and to reduce the risk of inappropriate treatment. Despite lack of longitudinal outcome benefit in the previous clinical trials, myocardial viability assessment plays an important role on a personalized level of clinical decision making for patients with CTO and LV dysfunction. The different noninvasive modalities available to assess myocardial viability interrogate distinct pathophysiologic myocyte and myocardial processes. The single photon emission computed tomography radionuclide tracers) examine myocyte cell membrane integrity, positron emission tomography myocardial blood flow and metabolism, cardiac magnetic resonance (CMR) with late gadolinium enhancement identifies scarred myocardium, whereas dobutamine echocardiography or CMR assesses regional ventricular contractile reserve. The imaging modality of choice needs to be individualized according to each clinical scenario, technology availability and institution expertise.

CMR is a versatile imaging modality to assess multiple interrelated features of both ischemia and viability in a single test without the use of ionizing radiation. It provides accurate and reproducible assessment of global and regional ventricular function, myocardial perfusion at rest and at stress, myocardial scar and the identification of viable but dysfunctional hibernated myocardium, being able to predict its recovery after successful revascularization[16]. Previous studies showed that the use of CMR may help to select patients who could derive significant LV reverse remodeling, ischemic burden relief, and quality of life improvement after CTO recanalization[17, 18]. Nevertheless, randomized trials with larger patient numbers are warranted to explore whether CMR-guided CTO revascularization is indeed superior to other available functional imaging, and is an independent predictor of long-term improved clinical outcome. Two ongoing trials, NOBLE-CTO (the nordic-baltic randomized registry study for the evaluation of PCI in chronic total coronary occlusion; NCT03392415) and ISCHEMIA-CTO (revascularization or optimal medical therapy of CTO; NCT03564317), employing CMR and nuclear imaging are eagerly awaited. Meanwhile according to current evidences, CTO PCI should be considered in symptomatic patients despite optimal medical therapy.

PERCUTANEOUS INTERVENTION OF CHRONIC OCCLUSION AS PART OF CORONARY REVASCULARIZATION: A COMPLEX PIECE TO "COMPLETE" THE PUZZLE

Rarely, CTO presents as single vessel coronary disease. More often, the interventional cardiologist is confronted with a multivessel coronary artery disease in which CTO represents an additional element of complexity. In this scenario, it is appropriate to analyze the potential prognostic impact of percutaneous revascularization of CTO in the broader perspective of a complete or reasonable incomplete revascularization.

Pioneering studies have shown that complete coronary revascularization, achieved following PCI of at least one CTO, results in a significant reduction in long-term cardiac mortality in the setting of multivessel atherosclerotic disease[19]. Even in patients undergoing PCI for multiple CTOs, 2-year survival was significantly better in patients with a complete revascularization by PCI[20]. Further confirmation came from the publication of the subanalysis of the Synergy Between Percutaneous Coronary Intervention with Taxus And Cardiac Surgery (SYNTAX) trial, which evaluated the prognostic impact of complete revascularization achieved after PCI or CABG and its association with the presence of CTO[21]. Incomplete revascularization was found to be conditioned by the complexity of the coronary anatomy and patient comorbidities and correlated with increased mortality and MACCE at 4-year follow-up in both groups. The presence of CTO represented the strongest independent predictor of incomplete percutaneous revascularization, at a time in history still burdened by

limited procedural proficiency, as demonstrated by the lower rate of successful revascularization of CTO in the group undergoing PCI, compared with the group undergoing CABG. To emphasize the importance of these results, it is worth mentioning that they derive from analyses conducted on patients in the SYNTAX trial, with stable coronary artery disease, without previous revascularizations, in whom first-generation DES were implanted, stent associated with more frequent events of restenosis and reocclusion than current second- or third-generation DES[22]. In addition, the success rate of CTO-PCI was significantly lower (approximately 49%) than the current rate, and complete revascularization was achieved in slightly more than half of the patients undergoing PCI and in only 63% of the patients undergoing CABG. Also in the study of Jang *et al*[23] published in 2017, data showed that in patients with CTO, achieving a complete revascularization (residual SYNTAX Score = 0) or a reasonable incomplete revascularization (residual SYNTAX Score = 12) guarantees a significantly lower risk of cardiac death and all-cause death compared with incomplete revascularization (residual SYNTAX score > 12), and these results were comparable with the CABG revascularization group at a median follow-up of 42 mo.

The favorable prognostic impact of a complete coronary revascularization has also been confirmed by large meta-analyses[5,24,25]. Among nearly 90000 patients from 35 randomized clinical trials and observational studies, completeness of revascularization, most often achieved by CABG, was found to be associated with approximately 30% reduction in long-term mortality[24]. Thus, it is not the surgical or percutaneous strategy that makes the difference, but the achievement of complete coronary revascularization. Another meta-analysis published in 2016, conducted on 156240 patients undergoing PCI for multivessel coronary artery disease, confirmed the strong prognostic benefit of the association between completeness of revascularization and reduced mortality and MACCE[25]. Notably, these benefits were maintained both in the subanalysis conducted on the cohort of 5 studies with CTO (OR 0.69; 95%CI: 0.53-0.80), and in the subanalyses that took into account the different definitions of complete revascularization[25]. Also of note, complete coronary revascularization by PCI was achieved in slightly less than half of the cases. Even in the pooled-analysis of Ahn *et al*[26] published in 2017, patients with incomplete revascularization by PCI had a higher risk of all-cause mortality respect to the patients treated with CABG. Conversely, no significant differences were found between patients undergoing CABG and those undergoing PCI with complete revascularization regarding the risk of death (aHR: 1.16; 95%CI: 0.83 to 1.63; $P = 0.39$) and the composite of death, myocardial infarction, and stroke (aHR: 1.14; 95%CI: 0.87 to 1.48; $P = 0.35$).

The favorable prognostic impact of successful CTO-PCI and complete revascularization on survival was also confirmed in elderly population. Valenti *et al*[5] collected data from 460 elderly patients (> 75 years) in the Florence real world CTO registry. Patients were stratified according to success or failure of CTO-PCI. Results showed improved five-year cardiac survival in the successful CTO-PCI group ($P = 0.006$) and a further improved survival benefit if complete coronary revascularization was achieved (90% ± 3% *vs* 68% ± 5%; $P < 0.001$) (Figure 1). Moreover, multivariate analysis demonstrated that increasing age, diabetes, chronic kidney disease, LVEF < 0.40 and complete revascularization resulted independently associated with long-term cardiac survival. Even in the meta-analysis of Cui *et al*[9] published in 2020, data derived from 8 studies showed how successful CTO-PCI was associated with reduction in long-term mortality and major adverse cardiovascular events (MACE) as compared to failed PCI in elderly.

Most of the elderly patients in these studies had high prevalence of comorbidities, complex coronary anatomy and concomitant LV dysfunction and heart failure, so they are consistent to the current setting definition of "complex higher-risk and indicated patients"[27]. In this context of patients with several comorbidities and severely reduced LV function, the execution of a percutaneous CTO revascularization is considered at very high risk, both for the technical difficulty of the procedure and for the clinical characteristics of the patient. Even if data regarding use of LV assist devices for hemodynamic support during CTO-PCI procedure are still lacking, initial experiences of small retrospective studies and case reports/series seem to show encouraging results[28].

Nowadays, the application of a "contemporary" revascularization strategy, in addition to the technical and procedural aspects, involves an optimal management of antithrombotic therapy. Patients who undergo a CTO-PCI are at high risk of clinical ischemic and thrombotic events. Antiplatelet therapy could play a leading role in reducing clinical event rates. Recent data from Valenti *et al*[19] has shown that a "tailored" approach based on platelet reactivity test results and clinical aspects could

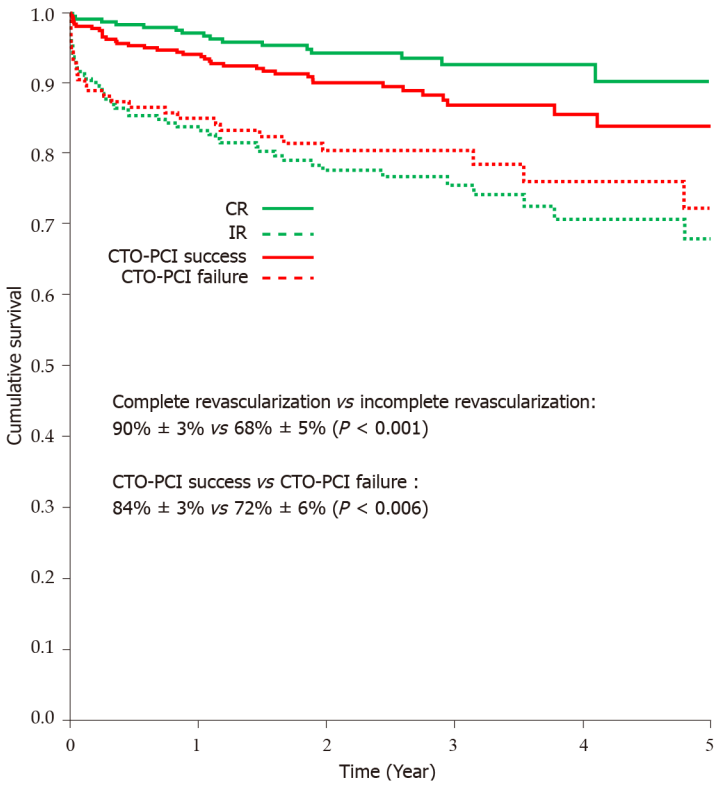


Figure 1 Long-term survival according to chronic total occlusion-percutaneous coronary intervention results and completeness of revascularization in a real-world registry investigating elderly > 75 years. Successful chronic total occlusion-percutaneous coronary intervention (CTO-PCI) group was associated with a long-term survival benefit when compared to failed CTO-PCI group at Kaplan–Meier survival analysis. Survival benefit was even greater in the complete coronary revascularization group and preserved up to 5 years. CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; CR: Complete revascularization; IR: Incomplete revascularization. Citation: Valenti R, Migliorini A, De Gregorio MG, Martone R, Berteotti M, Bernardini A, Carrabba N, Vergara R, Marchionni N, Antoniucci D. Impact of complete percutaneous revascularization in elderly patients with chronic total occlusion. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2020; 95: 145–153. Copyright ©The Author(s) 2019. Published by John Wiley & Sons, Inc[5].

lead to a survival benefit. Data showed how three-year survival was significantly higher in patients with adequate responsiveness to antiplatelet drugs: the optimal platelet reactivity group compared with high platelet reactivity patients showed a lower MACE rate (95.3% ± 0.8% *vs* 86.2% ± 2.8%; $P < 0.001$). Furthermore, in high platelet reactivity cohort of patients, escalation to a more potent antiplatelet agent allowed similar survival rates to the patients with optimal platelet responsiveness. Conversely, a prolonged clopidogrel therapy in non-responders patients (when more potent antiplatelet agents were not available) was associated with a high cardiac mortality (HR: 2.37; $P = 0.003$)[29].

Combining the evidence from randomized trials and registries, it appears clear that, although the real benefits on prognosis have yet to be fully demonstrated, it is undeniable that the revascularization of CTO leads to an improvement in patients' quality of life and more specifically to a reduction of angina. This evidence, in turn, raises further questions and in particular which strategy should be adopted in patients presenting CTO with a previous failed revascularization attempt or judged not amenable for CTO-PCI or in patient whose procedure would be at extremely high-risk to perform. Very interesting are the results of the retrospective multicenter study by Zivelonghi *et al*[30], conducted on patients with refractory angina symptoms, unsuitable for revascularization procedure or with previous revascularization failure, undergoing coronary sinus reducer (Neovasc Inc., Richmond B.C., Canada) implantation (24). In the group of patients with at least one CTO lesion, at a median follow up of 570 ± 370 d, patients experienced a statistically significant reduction in CCS class, with a significantly higher improvement respecting to the non-CTO patients' group. One of the possible explanations of these results, according to the authors, consists in the presence of collateral coronary circulation in CTO patients; this could be the key for the device mechanism of action associated with the potential clinical benefit; nevertheless, these results need to be confirmed in perspective randomized controlled trials.

ACUTE MYOCARDIAL INFARCTION WITH CONCOMITANT CHRONIC OCCLUSION

An additional complex clinical scenario is represented by acute coronary syndrome and multivessel coronary disease with the presence of a CTO.

About 50% of patients presenting with STEMI have a concomitant multivessel coronary artery disease, and about 13%-20% have a coexisting concurrent CTO; of these, only 5%-22% of cases receive an attempt percutaneous recanalization of the chronically occluded vessel, despite the current high success rate[2,31-34].

It is now recognized, from observational studies and sub-analyses of randomized trials, that the prognosis, in terms of short- and long-term survival after ST-elevation myocardial infarction (STEMI), is worse in patients with multivessel coronary artery disease and concomitant CTO. These findings have also been confirmed in a recent meta-analysis[35]. From a pathophysiological perspective, the presence of a CTO limits the possibility of providing collateral circulations to the acutely occluded vessel and, at the same time, the sudden deterioration of collaterals supplying the territory underlying the CTO may endanger a large area of myocardium.

If this intuitively explains the prognostic benefit of recanalization, which data are currently available to support this statement?

An observational study from the Florence CTO registry published in 2014[36], including patients with STEMI and concomitant CTO of the non-culprit vessel, showed a clear benefit in terms of 1- and 3-year cardiac survival in patients treated with successful CTO-PCI (performed between 7 and 30 d after primary PCI) when compared with patients with failed or non-attempted CTO-PCI; a favorable prognosis related to completeness of coronary revascularization was maintained even in very high-risk patients, such as those with cardiogenic shock, three-vessel and/or left main disease, severe LV dysfunction, and also in those patient with left anterior descending coronary artery involvement, either as culprit vessel or site of CTO (81%). In the group of patients with successful CTO-PCI, complete revascularization was achieved in 88% of cases, but even in the comparison group, extensive revascularization (non-CTO, non-infarct-related artery) was achieved in 85% of patients[36].

In 2016, the results of the randomized EXPLORE trial were published, which tested the impact of early PCI of CTO (< 7 d after the primary PCI procedure) on LV function and telediastolic ventricular volume at 4-mo follow-up[33]. Recanalization of CTO was not found to be associated with a significant improvement in LV function and telediastolic volume as assessed by magnetic resonance imaging. However, a sub-analysis of the study suggested a clinical benefit in patients undergoing PCI of the left anterior descending artery CTO[33]. Long-term follow-up (up to 5 years) showed that MACE were not significantly different in the two arms. Furthermore, no differences about the LV function were found in the two groups at 1 year[37].

The CREDO-Kyoto AMI registry analyzed 2045 patients with STEMI with or without CTO in the non-culprit vessel (18.7%). Although the presence of a CTO was independently associated with increased risk of mortality, mainly after the first 30 d after the acute event, there were no statistically significant differences in 5-year mortality between patients undergoing successful CTO-PCI and those with a failed procedure. It should be noted, however, that only 32% of cases underwent a CTO PCI, with a success rate of 64% and a low percentage of DES implantation[38].

Some evidence of MACE reduction in STEMI patients undergoing a staged CTO revascularization, compared with primary PCI and subsequent medical therapy comes from small retrospective single-center trials[39].

Although there is no clear evidence about the clinical benefit of revascularization of concurrent CTO in AMI patients, the available data are in favor of a complete coronary revascularization[40,41]. A possible explanation for the conflicting results in this setting, could be that the timing of the revascularization procedure following primary PCI must be individualized on the basis of the clinical characteristics of each patient; the application of a standardized timing in this complex clinical and procedural setting cannot be generalized.

PLANNING A TREATMENT STRATEGY: THE APPROACH TO PERCUTANEOUS REVASCULARIZATION OF CHRONIC CORONARY OCCLUSION

The first reports of CTO-PCI date back to 1985, thanks to the pioneering attempts of Japanese operators who have transferred the techniques developed in the field of

percutaneous revascularization of chronic femoro-popliteal occlusions to the coronary field. The first approach was antegrade, with procedural success in about 60% of attempts[42].

The observation that the distal cap of the occlusion is often less ambiguous and easier to penetrate than the proximal one, has soon created interest in a retrograde approach, first performed through vein grafts and then through septal collateral branches, leading to an increased procedural success, reaching 85%. Another technique borrowed again from the endovascular experience on the peripheral system is the "subintimal tracking and re-entry" (STAR), consisting in the recanalization of the occluded segment *via* a controlled subintimal dissection performed with a J-tipped wire ("knuckle"), adding a bailout strategy when failure of the "true-lumen" techniques occurs. Due to the difficulty in both navigating the guidewire and controlling the re-entry point in the true lumen, with potential loss of collateral branches, the STAR technique initially did not improve procedural success. Later, thanks to procedural refinements and devices advancements, the STAR technique has officially entered the CTO treatment option.

All these new techniques, in combination with the development of dedicated devices (among the latest the CrossBoss and Stingray system; Boston Scientific, Marlborough, MA, USA) and the use of second and third generation DES, with their improved long-term patency, have permitted a more articulated and flexible vision of CTO recanalization[22].

The indication for revascularization is conditioned by the clinical evaluation, which must take into account the patient's symptoms, LV function, comorbidities, and vitality/ischemia tests, in order to assess the expected therapeutic benefit in terms of "quality of life" and prognosis. Angiographic evaluation, on the other hand, is necessary to clarify not only the complexity of the CTO lesion, but also the probability of success and the expected risk of complications.

Indeed, only a comprehensive and integrated assessment of clinical, imaging and angiographic characteristics may define the appropriate revascularization strategy.

The goal of CTO PCI is to restore continuity between the upstream and downstream vessel segments of the occluded artery. For this purpose, two basic approaches can be used: the first one consists in penetrating the areas of loose tissue or microchannels physiologically present in part of chronic occlusions, trying to cross the thickness of the occluding plaque and proceed in the "intralesional" or "intimal" segment of the vessel; the second one aims to "bypass" the lesion, exploiting more extensively the vessel architecture and the subintimal space, proceeding within the adventitia of the vessel that, thanks to its elasticity and resistance, will constitute an operative channel.

Of note, some recently published data obtained from intracoronary imaging assessment after CTO recanalization seems to show a higher rate of all-cause mortality, post procedural myocardial infarction and target vessel revascularization in subintimal tracking techniques[43]. Subintimal recanalization was also associated with a higher prevalence of malapposed stent struts at OCT evaluation[44].

Summarizing we have two technique, intimal/intralesional and subintimal, that can be both used in antegrade and retrograde approach.

For the intimal/intralesional strategy, it's possible to adopt a wire escalation technique according to the type of guidewires used to cross the plaque, which differ in terms of stiffness, hydrophilicity, and penetrating power; mostly with two variants: (1) "Step-up" escalation (stiff-stiff-stiffest); and (2) "Step-up-step-down" escalation (stiff-soft-stiff). Conversely, it is possible to obtain recanalization through subintimal crossing with dissection and re-entry technique by surfing in the subintimal space until the patent vessel segment is reached, bypassing the occlusion.

As mentioned above, there is also the possibility of two different approaches: (1) The antegrade approach: when the lesion is tackled by advancing guidewires along the native vessel in a proximal-distal fashion, following the bloodstream; and (2) The retrograde approach: when the lesion is tackled from the distal cap, by advancing guidewires from the donor vessel through the so called "interventional" collateral.

In some cases, different approaches can coexist in the same technique, as in the controlled antegrade and retrograde subintimal tracking (CART) or reverse CART method, where a simultaneous antegrade and retrograde approach is required.

In order to select the most appropriate approach and technique, an accurate analysis of the angiogram is a key step of the procedural strategy. The angiogram for a CTO study should preferably be performed by dual, simultaneous injection of contrast medium for better definition of vessel anatomy, effective lesion length, distal segment anatomy, and characteristics of collateral circulation, combining typical and atypical projections in order to optimize the visualization of elements of interest. "Ad hoc" CTO-PCI procedures are generally discouraged in favor of careful planning. The

increased expertise in the field has allowed to identify some features of the lesions that the operator must evaluate for the choice of proper interventional strategy: morphology and localization of the proximal and distal cap, lesion length, presence of calcifications, landing zone and, finally, characteristics and quality of donor and collateral vessels.

SCORES FOR THE EVALUATION OF CHRONIC CORONARY OCCLUSIONS

Multiple scores have been developed over the years in order to stratify the procedures in various levels of difficulty. The effort was intended to provide a synthetic tool capable of predicting and expressing the procedural complexity of a CTO-PCI and to support the management of the procedural strategy. We will review below the main scores reported in the literature (Table 2)[45-48].

The Japan-CTO (J-CTO) score[45], the progenitor of the series, was developed as a model to predict the probability of success of an antegrade wiring of the lesion within the first 30 min of the procedure. It takes into account several variables, the presence of which adds one point (+ 1) to the total score. These variables are the morphology of the proximal cap, the presence of calcifications within the occluded segment, the tortuosity of the segment, the length of the lesion (cut off > 20 mm), and the failure of a previous attempt to bridge the lesion. A score of ≥ 2 identifies a lesion that is particularly difficult to overcome.

The clinical and lesion related score was then developed[46] including some angiographic parameters already used in the J-CTO score (lesion length > 20 mm, proximal cap morphology, presence of calcifications), plus the presence of a CTO in a vessel other than the left anterior descending artery and combining them with clinical variables, such as a previous myocardial infarction and/or CABG. The score obtained identifies 4 different classes, correlated with decreasing probability of successful revascularization and increasing probability of MACCE (death, myocardial infarction, need for new revascularization with PCI or CABG, tamponade, and stroke).

The ORA (ostial location, Rentrop grade < 2, age ≥ 75) includes only 3 variables, of which one clinical (age ≥ 75 years) and two angiographic (ostial location and Rentrop collateral circulation ≥ 2)[48]. In the prospective global registry for the study of chronic total occlusion score four variables are taken into account: difficult proximal cap localization, absence of collaterals, severe tortuosity, and circumflex artery CTO[47]. These last two scores, unlike the previous ones, contemplate some variables that condition the choices in the hybrid algorithm, allowing the expansion of the field of application from only antegrade crossing techniques to retrograde and combined approaches.

The RECHARGE score was a tool developed to predict technical outcomes of CTO-PCI from patients treated by "hybrid" operators with different experience levels[49]. One point is given for a long lesion length (20 mm), visible calcification on angiography, tortuosity within the CTO segment or at CTO entry, a blunt proximal cap, a diseased distal landing zone, and the presence of a bypass graft on the CTO target vessel, respectively[49].

The more recent one the Euro-CTO CASTLE score is similar to RECHARGE score but includes among the variables, the age of the patients and previous CABG (irrespective of graft location) and discard the evaluation of the distal landing zone [50]. CASTLE Score showed similar overall discriminatory capacity compared with J-CTO score, but, for more complex procedures (J-CTO > 3 or Euro-CTO CASTLE > 4), the predictive capacity of Euro-CTO CASTLE score appeared superior[51].

Scores can be a useful tool in several aspects of CTO-PCI performance. By providing a quantitative measure of the probability of success and complications, they offer useful information to be shared with the patient and in the evaluation context of a Heart Team. Furthermore, they can guide case selection, allowing less experienced operators to confidently tackle the simplest cases, while deferring more complex challenges to more experienced operators. Nevertheless, some studies show very good success rates among experienced operators, even in case of particularly unfavorable scores[52], confirming that the scores assessment should represent a moment of reflection, but not a reason to give up before the challenge of a percutaneous revascularization.

Table 2 Main scores for assessment of chronic total occlusions

	J-CTO score		CL score		ORA score		PROGRESS score		RECHARGE score		EURO-CTO CASTLE score	
Angiographic Features	Proximal cap blunt	1	Proximal cap blunt	1	Ostial location	1	Proximal cap ambiguity	1	Proximal cap blunt	1	Proximal cap blunt	1
	Tortuosity > 45°	1	Lesion lenght > 20 mm	1.5	Collateral filling Rentrop 0-1	2	Tortuosity	1	Tortuosity > 45°	1	Tortuosity > 45°	1
	Lenght > 20 mm	1	Calcification	2			Circumflex CTO	1	Lenght > 20 mm	1	Lenght > 20 mm	1
	Calcification	1	Non-LAD CTO	1			Absence of interventional collaterals	1	Calcification	1	Calcification	1
									Diseased distal landing zone	1		
Clinical features	Prior CTO PCI failure	1	Previous MI	1	Age > 75 yr	1			Previous CABG on CTO target vessel	1	Previous CABG	1
			Previous CABG	1.5							Age > 70 yr	1

Japan-chronic total occlusions (CTO) score (45): 1 point for the presence of each variable with classification into 4 categories of difficulty: Easy (0), intermediate (1), difficult (2), and very difficult (≥ 3). Clinical and lesion-CTO score (46): Non-anterior interventricular artery, previous MI, blunt stump (+ 1); previous coronary artery bypass graft, lesion length > 20mm (+ 1.5); severe calcification (+ 2). Four classes of probability of success are identified: High success rate (score 0-1), intermediate (score 2), low (score 3-4), and very low (score ≥ 5). PROGRESS-CTO score (47): 1 point for each variable. ORA score (48): 1 point for the variables of age and ostial location, and 2 points for the Rentrop collateral circle < 2; there are 4 degrees of difficulty: easy (0), intermediate (1), difficult (2), and very difficult (3-4). RECHARGE score (49): 1 point for each variable, grading CTO lesion complexity from 0 to 6 points. EURO-CTO CASTLE score (50): 1 point for each variable (0 to 6). At a score of 0, the mean predicted risk of failure of CTO percutaneous coronary intervention was 5.8%. At a maximum score of 6, the predicted risk of failure was 56.5%. CTO: Chronic total occlusion; CABG: Coronary artery bypass graft; LAD: Anterior interventricular artery; LCx: Circumflex artery; MI: Myocardial infarction.

DIFFERENT PHILOSOPHIES LEADING TO DIVERGING APPROACH FOR CTO REVASCULARIZATION

Taking into account and keeping in mind the characteristics listed, the operator will be able to select the best interventional strategy. Historically, it is possible to identify different philosophies, or experiences to approach CTO revascularization. Currently, there are two main strategic approaches followed by practitioners: the Japanese Eastern school and the American and European Western school, evolved in the so-called "hybrid approach".

Eastern-Japanese approach

The Japanese interventional philosophy is reflected in a dedicated and thoughtful approach to CTO: extreme importance is given to the coronary study, the analysis of the angiographic picture, the availability of dedicated hemodynamic rooms. Pre-procedural tomographic techniques (to assess the anatomy of the occlusion) and intra-procedural intravascular ultrasound (to resolve ambiguities of the proximal cap and guide the return of the guides in dissection techniques) play a paramount role. The choice of the technique, obviously based on coronary anatomy, is maintained even in spite of initial procedural difficulties, favoring a careful intra-procedural choice of instrumentation and a “great mastery” in handling the available material. The use of antegrade dissection/reentry techniques, considered suboptimal for CTO recanalization, is generally discouraged, in favor of a meticulous intraluminal advancement technique or "switch" to retrograde approach. Overall, the results of the Japanese experience are extremely valid and a "driver" for international performance, with a low prevalence of clinically relevant procedural complications[52]. A potential limitation of this approach is, however, linked to the difficulty in standardizing choices and the impossibility, in different economic contexts, to use facilities and resources with the same liberality.

In an attempt to respond to this need for efficiency and uniformity, the hybrid approach of the North American school was born.

Hybrid approach of the Western school

The philosophy of the hybrid approach[53] is to achieve recanalization of the occluded vessel by using all available techniques in the most effective, safe, and efficient way. It combines a limited number of anatomical information in a decision algorithm, which allows to establish the initial technique (the one with the highest probability of success in relation to the characteristics of the lesion) and the most effective bailout techniques in case of procedural failure. However, the peculiar aspect of this approach (that justifies its "hybrid" attribute) is the dynamic nature of the transition from one technique to another (Figure 2). It is recognized that excessive insistence on a single technique, in addition to being time-consuming, can even be detrimental in terms of success. Therefore, a quick "switch" is encouraged, with possible "re-cycling" among several techniques, whenever significant progress cannot be achieved within a reasonable time frame of 5-10 min. Practical benefits include shorter procedure duration, reduced radiation exposure, and potentially less use of contrast agents. Data from RECHARGE registry study evaluated the effectiveness of this approach in a "real-world" setting of European centers, finding a procedural success rate of 89%[49]. Similar results were confirmed in the recently published data from OPEN-CTO Registry: the application of hybrid approach led to a technical success rate of 86% in the index CTO-PCI[14].

A particular interesting finding was the actual application of the strategy predicted on the basis of the algorithm: in case of concordance, the success rate was higher[49]. Thanks to the algorithm, the hybrid approach leads to dissemination of learning and teaching of CTO revascularization, offering an easy guide for practitioners, particularly those with lower skills and experience level. It is worth noting that the algorithm does, however, some generalizations/limitations that are susceptible to interpretation and adaptation to individual needs.

In specialized centers, regardless of the approach strategy, safety outcomes have been shown to be very satisfactory. A meta-analysis of 65 studies, on a total of 18061 patients undergoing CTO-PCI, found an incidence of MACE (death, myocardial infarction, stroke, and CABG in emergency) of 3.1%, with a mortality of 0.2% and an incidence of cardiac tamponade of 0.3%[54]. Great care is also recommended in monitoring the amount of contrast medium used and fluoroscopy. All currently available strategies should be implemented to reduce the incidence of contrast-induced nephropathy.

Over the last years, new algorithms were developed with the aim of extending original "hybrid" approach: the Asia Pacific CTO Club algorithm[55] and the algorithm from the European CTO Club[56]. All these algorithms, the original one and his updates, are very similar. Indeed, all of them are focused on initial anatomy evaluation to guide the initial strategy choice, use of intravascular imaging is encouraged to avoid ambiguity, and criteria for failed procedure are listed. Tanaka *et al*[57] developed a revised algorithm, proposing a wider use of the retrograde approach, mainly in lesions with a higher J-CTO Score, highlighting how, in selected cases a primarily retrograde approach allows excellent procedural success rate with a shorter wire manipulation time.

Recently, a new revised version of "hybrid" approach was implemented, the minimalistic "hybrid" algorithm[58]. The two major points of the minimalistic "hybrid" algorithm are limiting the routine use of dual injection and encouraging the use of trans-radial access and smaller (6-7 French) guiding catheters. First results reported showed lower peri-procedural complications in the group treated according to the minimalistic approach, with similar procedural results and non-statistically significance differences in MACE[59].

Unfortunately, the multiplication of algorithms for CTO-PCI may lead to confusion rather than clarity, as also stated in a recent published editorial[60].

CTO: A CHALLENGE WITHIN A CHALLENGE

The ultimate challenge of coronary interventional cardiology, now fully shared by the scientific community, is to achieve a complete coronary revascularization. It has been widely demonstrated that complete coronary revascularization, achieved by either CABG or PCI, is associated with prognostic improvement, in terms of increased survival and reduction of MACE. In this scenario, the successful CTO revascularization plays a key role over the broad panorama of percutaneous coronary interventions. In this perspective, percutaneous revascularization can compete convincingly with the surgical revascularization that, to date, is the easiest way to achieve a

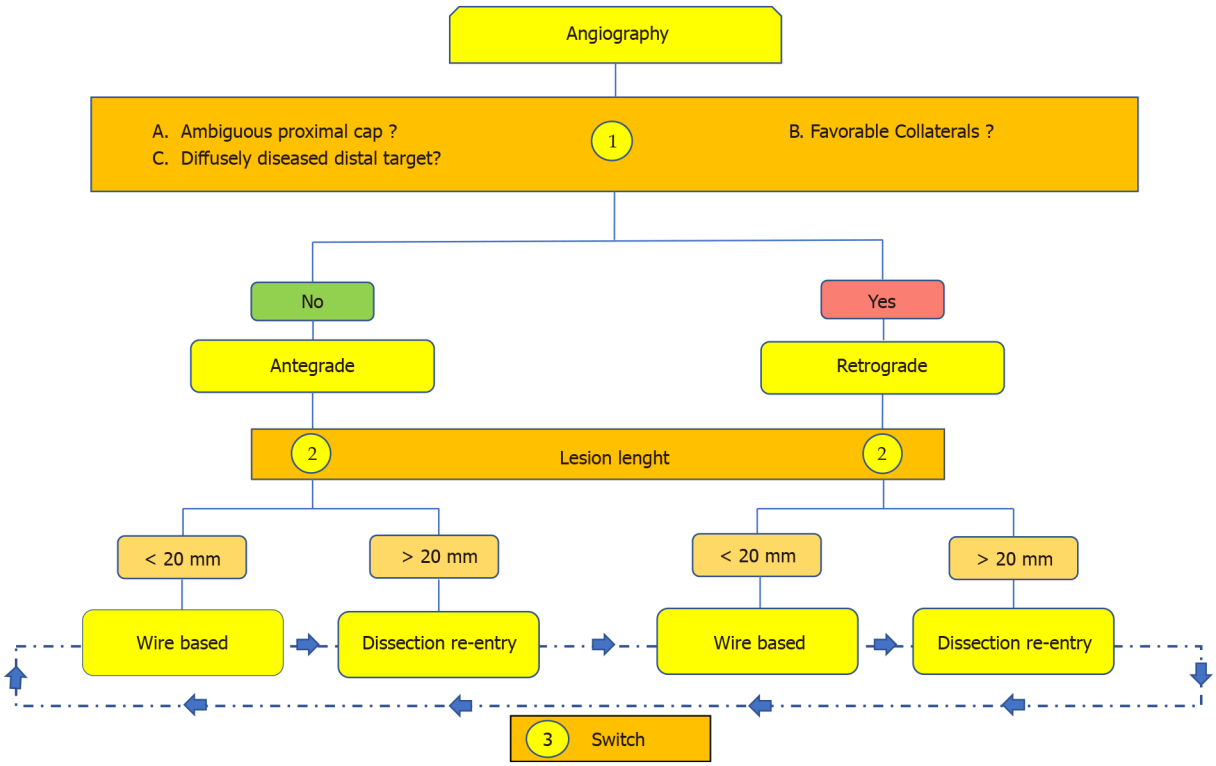


Figure 2 Hybrid algorithm for approaching strategy decision to chronic total occlusion.

high rate of complete revascularization in patients with multivessel coronary artery disease with associated CTO. When the equivalence in term of completeness between PCI and CABG will be definitively granted, we could be able to offer our patients a percutaneous revascularization associated with a long-term clinical benefit and, above all, we will be able to provide the better revascularization strategy for each patient, inspired by an "individualized medicine". Furthermore, we could finally leave behind the results of the comparison, now obsolete, between surgical and percutaneous revascularization in patients with multivessel disease of the SYNTAX trial, which still guides the revascularization modalities in the guidelines of the major cardiology scientific societies.

CONCLUSION

In conclusion, the application of "contemporary" strategies aimed to obtain a state-of-the-art revascularization by PCI allows achieving long-term clinical benefit, even in high-risk patients or complex coronary anatomy with CTO. The increasing success of CTO-PCI, allowing a complete or reasonable incomplete coronary revascularization, is enabling to overcome the last great challenge of interventional cardiology, adding a "complex" piece to "complete" the puzzle.

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MINIREVIEWS

Role of genetic testing in cardiomyopathies: A primer for cardiologists

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Abstract

Recent advances in cardiovascular genetics have transformed genetic testing into a valuable part of management of families with inherited cardiomyopathies. As novel mutations have been identified, understanding when to consider genetic testing has emerged as an important consideration in the management of these cases. Specific genetic testing has a paramount importance in the risk stratification of family members, in the prognosis of probands at higher risk of a serious phenotype expression, and finally in the identification of new mutations, all of which are discussed in this review. The indications for each type of cardiomyopathy are described, along with the limitations of genetic testing. Finally, the importance of public sharing of variants in large data sets is emphasized. The ultimate aim of this review is to present key messages about the genetic testing process in order to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team in order to offer the best care to families with inherited cardiomyopathies.

Key Words: Cardiomyopathy; Genetic counselling; Genetic testing; Variant; Hereditary

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Core Tip: In a considerable percentage of patients with cardiomyopathies, there is a

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genetic component. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies. The genetic testing process is also helpful to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team, with the objective of offering the best care to families with inherited cardiomyopathies.

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INTRODUCTION

Cardiomyopathies represent a group of disorders of the myocardium associated with cardiac dysfunction, aggravated by arrhythmias, heart failure, and sudden cardiac death (SCD). They can be classified according to their morphological and functional phenotypes, specifically as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular (ARVC)/arrhythmogenic cardiomyopathy (ACM), and as unclassified forms[1]. In a considerable percentage of patients with cardiomyopathies, there is a genetic component, even for cases in which interaction with environmental factors cannot be excluded[2-5]. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies.

The continual rapid progress of molecular techniques over the past 2 decades and the related increased choices of different genetic testing options have led to a dramatic increase in our understanding of the genetic architecture of these diseases[6,7]. For better understanding of the terms used in the genetic testing process, relevant definitions are provided in Table 1. The aim of this review is to discuss the benefits of genetic testing in cardiomyopathies and the current indications in diagnosis and prognostication of probands and risk stratification for family members, in order to promote provision of optimal care for patients and their families.

GENETIC TESTING TECHNIQUES

The type and the available technologies for gene-based sequencing have been in constant evolution; turnaround times are shorter, while their cost has been dramatically decreasing. Whole blood, dried blood spots, or tissue specimens regarding post-mortem examination could serve as acceptable specimens for genetic testing. Conventionally, genetic testing by Sanger sequencing, for individual genes has been performed[8]. Due to the genetically heterogeneous nature of cardiomyopathies and the development and availability of next-generation sequencing (NGS) technique in the clinical setting, a multi-gene panel instead of individual gene-testing is now desirable practice for these diseases. Therefore, Sanger sequencing and targeted analysis is only preferable for cascade testing, when a pathogenic or likely variant has been identified in the proband. The composition of gene panels varies and some laboratories propose larger gene panels. However, increasing the number of genes in the panel also possibly increases the likelihood of identifying variants of uncertain significance. It is therefore evident that the ordering cardiologist should be aware of the benefits and limitations of specific test types in order to select the most appropriate technique[9]. Currently, testing a small specific panel of genes is usually recom-mended for each well-defined phenotype. Together, these techniques provide excellent precision and accuracy to detect single nucleotide substitutions that produce missense, nonsense, and splice site mutations and small insertion/deletions. A subset of cases with large insertion or deletion variants or other structural DNA changes, whereas the above analyses turn out negative, might benefit from copy number assays using microarray or multiplex ligation-dependent probe amplification[8,9].

Table 1 Terminology of commonly used genetics vocabulary

Term	Definition
Allele	One of several alternative versions of a particular gene
Heterozygote	An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation)
Mutation	Any alteration in the inherited nucleic acid sequence of the genotype of an organism; a mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease
Penetrance	Proportion of individuals carrying a mutation who also express a cardiomyopathy phenotype
Genome sequencing	Sequencing of entire genome (coding and non-coding regions)
Exome sequencing	Sequencing of the coding regions (exons)
Proband or index case	Index case in the family, usually the one with the most severe phonotype
Variant	A change in the DNA sequence which may or may not be disease-causing
Pathogenicity	Process of determining whether a variant is causative or not

CURRENT RECOMMENDATIONS FOR EACH CARDIOMYOPATHY

The prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies are summarized in Table 2.

HCM

HCM, a disease of the sarcomere, is the most common inherited cardiomyopathy, with an autosomal-dominant type of transmission, leading to left ventricular (LV) hypertrophy and diastolic dysfunction. It is most often caused by variants in genes encoding cardiac sarcomere proteins[10]. The phenotype ranges from asymptomatic forms to SCD as the first and only manifestation, as seen especially in young athletes, all depending on the penetrance of the disease-causing mutations. Genetic testing should include not only the most common sarcomere genes [β-myosin heavy chain (MYH7); myosin-binding protein C3 (MYBPC3); troponin T2; troponin I3; tropo-myosin; actin alpha cardiac muscle 1; myosin light chain 2; myosin light protein] but also genes causing rare syndromic diseases with a HCM-phenotype [α-galactosidase (Fabry disease); protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2) (PRKAG2-glycogen storage disease); lysosomal-associated membrane protein 2 (Danon disease)][11,12]. In some of these diseases, such as Fabry or Danon disease, the positive genetic test result may change the clinical care of the proband, such as to involve enzyme replacement therapy or a more aggressive clinical management, respectively[12]. The diagnostic yield for the proband with a definite clinical diagnosis of HCM is approximately 30%-60%, and even higher in individuals who have severe LV hypertrophy, a known family history of HCM, or who were diagnosed at a younger age. MYBPC3 and MYH7 account for approximately 80% of all cases with positive genetic test.

DCM

About 30% of DCM cases appear to be familial in origin, isolated, or as a part of a syndrome[13-15]. The mode of inheritance is mostly autosomal dominant (AD). However, sporadic forms of DCM could be caused by non-genetic factors (*i.e.*, drugs, alcohol, viruses). Similar to HCM, the clinical severity of DCM is heterogeneous, so genetic testing is important for the surveillance of the asymptomatic genotype-positive carriers. Clinical screening combined with a three-generation pedigree of the proband are warranted in order to establish the need for genetic testing in DCM[5].

Over 100 genes have been implicated in DCM, all encoding sarcomeric and cytoskeleton proteins[16]. After the addition of titin (TTN) variants in genetic testing, the diagnoses of familial DCM increased by about 10%[17]. However, interpretation of the TTN mutations is challenging, due to the large size of the gene and the high frequency of benign variants in healthy populations. Mutations in the lamin A/C (LMNA) gene are also detected in approximately 4%-6% of familial DCM cases, causing a distinct phenotype characterized by systolic impairment together with progressive conduction disturbances and malignant arrhythmias[15]. DCM may also

Table 2 Prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies

Inherited CMP	Prevalence	Pattern of inheritance	Key genes	Diagnostic yield of genetic testing	Recommendation for genetic testing
HCM	1 in 500	AD	MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3, GLA, PRKAG2, LAMP2	30%-60%	For any patient with clinical diagnosis of HCM; Familial screening with a mutation after identified in the index case
DCM	1 in 2500	AD, X-linked	DES, DMD, DSP, FLNC, LMNA, MYH7, PLN, RBM20, TNNI3, TNNT2, TTN, TPM1	20%-30%	For patients with DCM and conduction disease and/or family history of SCD; Familial screening with a mutation after identified in the index case
ARVC	1 in 2000-5000	AD, AR	DSC2, DSG2, DSP, JUP, PLN, TMEM43	50%	Familial screening with a mutation after identified in the index case
RCM	Rare	AD, AR X-linked or mitochondrial	Troponin; MYBPC3, MYL3	Unknown	Familial screening with a mutation after identified in the index case

ARVC: Arrhythmogenic right ventricular cardiomyopathy; DCM: Dilative cardiomyopathy; HCM: Hypertrophic cardiomyopathy; RCM: Restrictive cardiomyopathy; AD: Autosomal dominant; AR: Autosomal recessive; MYH7: β-myosin heavy chain; MYBPC3: Myosin-binding protein C3; TNNI3: Troponin I3; TNNT2: Troponin T2; TPM1: Tropomyosin; ACTC1: Actin alpha cardiac muscle 1; MYL2: Myosin light chain 2; MYL3: Myosin light protein; GLA: Alpha-galactosidase; PRKAG2: Protein kinase AMP-activated non-catalytic subunit gamma 2; LAMP2: Lysosomal-associated membrane protein; DES: Desmin; DMD: Dystrophin; DSP: Desmoplakin; FLNC: Filamin C; LMNA: Lamin A/C; PLN: Phospholamban; DSC2: Desmocollin 2; DSG2: Desmoglein 2; JUP: Junction plakoglobin; RBM20: RNA-binding protein 20; SCD: Sudden cardiac death; TMEM43: Transmembrane protein 43; 2; TTN: Titin.

appear as a complication of neuromuscular diseases (*e.g.*, Duchenne and Becker muscular dystrophy). As the mode of inheritance is X-linked recessive, genetic testing should be provided in mothers of probands with Duchenne or Becker, because carrier females may develop later on[18]. At this point, we should also emphasize that due to phenotype overlapping among cardiomyopathies, HCM and ACM genes are included in DCM panels.

ACM, including right ventricular

ARVC is currently considered as a subtype of the broader group of ACM, with fibro-fatty replacement of the ventricular myocytes[19]. Clinical manifestations may vary with age and stage of disease, from asymptomatic but at-risk for SCD to end-stage heart failure with symptomatic arrhythmias. It is considered familial, with AD inheritance; although, there are recessive forms (*e.g.*, Naxos disease, Carvajal syndrome)[20]. Initially, it was identified as a disease caused by mutations in genes encoding desmosomal proteins. A pathogenic variant has been detected in up to 50% of cases referred for genetic testing who meet the 2010 Task Force criteria[3]. Mutations in the plakophilin-2 gene account for 20%-30% of cases, while variants in four other desmosomal genes (desmocollin 2; desmoglein 2; desmoplakin; junction plakoglobin) have also been detected. Changes in DNA sequence of the abovementioned genes should be cautiously approached, since different benign variants may present frequently in unaffected control populations[20].

Further genetic subtypes have been described recently; so, under the broad term of arrhythmogenic cardiomyopathies, additional genes should be included in the genetic testing, such as transmembrane protein 43, LMNA, filamin C, desmin, RNA-binding protein 20, phospholamban (PLN) and TTN genes. According to the revised Task Force criteria for the diagnosis of ARVC/ACM, for a definite diagnosis, two major criteria or one major and two minor criteria, or four minor criteria from different categories are needed. The presence of a disease-causing mutation is considered as a major criterion. However, in order to avoid confusing results, if the patient shows only one minor criterion from the revised Task Force Criteria, then genetic testing should not be recommended[3]. It is noteworthy that desmosome gene mutations have also been identified in patients diagnosed with DCM.

RCM

RCM is a rare form of cardiomyopathy, with a heterogeneous phenotype. Multiple causes have been identified, including infiltrative storage, non-infiltrative and endomyocardial diseases, many of which are associated with specific genes[21]. The

most frequent variants that have been found in RCM cases are in genes known to cause HCM. Therefore, genetic testing for RCM should include HCM genes[22].

IMPORTANCE OF FAMILY HISTORY IN THE PROCESS OF GENETIC TESTING

Irrespective of the type of cardiomyopathy, thorough comprehension of the proband's family history with an at least three-generation family pedigree and counselling should precede genetic testing[23]. Therefore, the family history is of paramount importance and should not be overlooked in clinical practice. Specifically, it reveals the phenotype of each member, the pattern of inheritance (AD, autosomal recessive, X-linked and maternal mitochondrial conditions) and enables the clinicians to provide preliminary recommendations for clinical surveillance[6,24]. Importantly, it also helps genetic counsellors to discuss the process of genetic testing with the proband and the family members, including providing realistic expectations of the findings and to develop a relationship of trust. Effective communication and psychological support are key points. Pre-genetic counselling constitutes an important clinical part of the medical management of such cases[4,25].

VARIANT INTERPRETATION AND RECLASSIFICATION

The most challenging aspect of the genetic testing process is the interpretation of results. According to the Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, each variant should be classified according to specific criteria in one of the following categories: Benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic (Table 3)[26]. Causality is based on various criteria, such as population frequency and type of identified variant (*i.e.*, missense, nonsense, *de novo*, truncating splice site); information of segregation in a pedigree and *in silico* tools are also used. It is important to bear in mind that in order to avoid the vast amount of uncertainty, rather than choosing a binary 'yes' or 'no' outcome, it is preferable to gather and weigh-up sufficient lines of evidence. A key step in this direction is the public sharing of important variant information among laboratories, such as through scientific repositories (*e.g.*, ClinVar) and the creation of large reference datasets[27]. Another important issue is the periodic reclassification of variants; although, guidelines on how this can be performed feasibly are lacking[28]. Certainly, the latest technologic advancements of NGS, together with bioinformatics software, allow accurate and rapid high-output sequencing of the human genome[29]. And, in the real world, the ability to efficiently sequence coding and non-coding regions has led to the production of multigene panels used in clinical practice currently.

At this point, we should also note that the complexity of cardiomyopathies and the difficulties in defining a specific phenotype according to genetic causes present new challenges for cardiologists who manage these patients singlehandedly. Therefore, a multidisciplinary team is required for genetic counselling and testing, as well as psychological support. This can be achieved through trained healthcare providers, in order to help individuals deal with the psychological, social, professional, ethical and legal implications of a genetic disease[30].

SPECIFIC BENEFITS OF GENETIC TESTING

Identification of undiagnosed family members

The principal advantage of the process of genetic testing is the detection of family members of the proband who have inherited the causal variant of the gene and are at-risk of developing the clinical phenotype of each cardiomyopathy. The importance of this procedure is huge, considering that life-threatening arrhythmias or SCD can be the first manifestation of a cardiomyopathy. Thereafter, only genotype-positive individuals need periodic monitoring instead of all first-degree relatives[5]. The importance of familial screening is better established in HCM and ARVC, where the yield of genetic testing is higher, and gives the opportunity for better planning to assess and address the need for implantable cardioverter-defibrillator (ICD) devices in genotype-

Table 3 Definitions of the variant classifications

Variant	Definition
Pathogenic	Variant is disease-causing with > 99% confidence; Cascade genetic testing should be offered to family members
Likely pathogenic	Variant is disease-causing with > 90%-95% confidence; Cascade genetic testing should be offered to family members
VUS	Variant is considered uncertain with an unknown effect on clinical phenotype, as there is insufficient or conflicting evidence for pathogenicity; Cascade genetic testing cannot be offered to family members
Likely benign	Variant is probably not disease-causing; Cascade genetic testing should not be offered to family members
Benign	Variant is not disease-causing; Cascade genetic testing should be offered to family members

VUS: Variant of uncertain significance.

positive carriers.

Regarding SCD in young people, almost 30% of cases are caused by a non-diagnosed type of cardiomyopathy[31]. Genetic testing in post-mortem samples could enhance the likelihood of finding a disease-causing variant and performing subsequent genetic screening of family members. Indeed, in a clinical screening in 198 cases of unexplained SCD in people below 35 years of age, five families suffering from inherited cardiomyopathies were detected; whereas, 27% of the cases had a definite or likely disease-causing mutation[32]. Therefore, according to European Society of Cardiology (ESC) guidelines, targeted post-mortem genetic analysis of potentially disease-causing genes should be considered for victims in whom a specific inheritable or cardiomyopathy is suspected[33].

Prognostic role

Several studies have proven that genotype status itself is associated with worse outcomes in HCM[34,35]. Sarcomere protein mutations in HCM have been found to be associated with increased rates of cardiovascular and SCD-related mortality[34]. In 628 HCM patients with a 12-year follow-up, positive genetic test result was identified as an independent prognostic factor for mortality in SCD and heart failure as well as all-cause mortality for the carrier, after adjustment for established risk factors[36]. In DCM, the approximately 5%-10% of probands with mutations in the LMNA gene are the best characterized, as LMNA variants manifest early-onset atrial arrhythmias and early development of conduction disturbances, coupled with a higher risk of SCD, often with only LV systolic impairment[37]. According to ESC guidelines, an ICD implantation should be considered in patients with DCM along with a confirmed disease-causing LMNA mutation and clinical risk factors, such as a non-sustained ventricular tachycardia, LV ejection fraction below 45% at first evaluation, male sex, and non-missense mutations[33].

Regarding ARVC, the prognostic role of genetic testing is not fully realized. Although probands with ARVC and known causal variants have been reported to develop ventricular arrhythmias approximately 4 years earlier than patients without a known mutation, no difference in mortality was detected in that study[38]. In another study of 105 probands with known ARVC-causal variants, the identification of a variant was found to be less important for predicting risk of life-threating arrhythmia or SCD than other factors, like sex and repolarization abnormalities in electrocardiogram or LV dysfunction[39]. Mutations in the PLN gene are also related to a poorer prognosis[40].

NGS analysis has allowed widespread identification of novel disease-causing genetic mutations[41]. Open availability of the ClinVar and ExAC databases in recent years has helped laboratories and clinicians to determine the possible pathogenicity of new detected variants. As a result, previously characterized genetic variants have been reclassified[42]. Genetic testing may identify predisposition for cardiomyopathies with unclear pathophysiological mechanisms; for example, risk of peripartum cardiomyopathy or anthracycline-induced cardiomyopathy may be identifiable by genetic testing. In patients with peripartum cardiomyopathy, in particular, and carrying mutations in the TTN gene, LV ejection fraction remains significantly lower compared to patients without this mutation[43]. Similarly, there is emerging evidence that a genetic predisposition may also be involved in anthracycline-induced cardiomyopathy [44,45]. Unfortunately, the current evidence is not sufficient to alter management decisions about the use of anthracycline but could lead to a personalized medicine

approach in patients carrying specific mutations[46].

Prenatal genetic counselling

Prenatal genetic counselling is helpful in couples at risk of transmitting a genetic condition to their offspring. Through this process, a certified genetic counsellor explains the risk of transmission of disease, the impact of the disease on an affected child, as well as the benefits and limitations of all the available reproductive options. These options include *in vitro* fertilization with preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision[12].

BARRIERS IN GENETIC TESTING

Despite the novelties in genetic techniques, there are still limitations in performing genetic testing for every diagnosed cardiomyopathy. Genetic testing seems to be of little to no value in low-yield cases with unclear inheritance pattern[36-38,47]; for this reason, the guidelines discourage genetic testing in isolated cases of idiopathic DCM where no evidence of inheritance exists[4,5]. In a study of 102 patients with idiopathic DCM, a disease-causing mutation was identified in only 10, whereas the clinical management was changed for only 1 patient, who received an ICD[47]. Unfortunately, even in disease where the yield of genetic testing is high, such as in HCM, when more possible genes were added, few additional causal variants were identified[48]. Another limitation in performing genetic testing when there is no clear clinical indication is the finding of a VUS. VUS may mislead clinicians, as it can neither confirm a genetic diagnosis nor exclude the need for familial surveillance[12]. The best practice in order to avoid an uncertain result is the performance of genetic testing after a thorough evaluation of the clinical case and a multidisciplinary management in pre-genetic counselling. Hence, any result from a genetic test can be further investigated at the research level[6,12].

CONCLUSION

At present, the mainstay of genetic testing in inherited cardiomyopathies is the identification of family members who have inherited the same causal mutation with the proband, which is important in terms of clinical decision-making. On the other hand, when the mutation is not detected in family members, anxiety and unnecessary clinical screening are avoided. This procedure is more helpful in cardiomyopathies where the yield of a positive genetic result is higher, such as HCM and ARVC. However, recent studies have provided more evidence on the genetic predisposition in specific cardiomyopathies and suggested a prognostic component when pathogenic variants are found.

Despite the progress in genetic techniques, there are currently well-documented limitations of cardiac genetic testing. Therefore, the role of family history should not be downgraded when the utility of genetic testing is questioned. A specialized multidisciplinary clinic incorporating cardiologists and genetic counsellors along with a move to a more precision-based approach seems to be the ideal model of management. Last but not least, focus should be given to teamwork of worldwide research groups in order to develop large databases that may elucidate the complexity of underlying genetics in inherited cardiomyopathies.

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MINIREVIEWS

Fondaparinux: A cornerstone drug in acute coronary syndromes

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Abstract

In acute coronary syndrome (ACS), the use of anticoagulants in conjunction with antiplatelet agents in the acute phase has resulted in reduced ischemic events and is more effective than either class of drug used alone. Though parenteral anticoagulation is essential at the time of diagnosis, a balance must be made between ischemic benefit and the increased risk of bleeding when prescribing anticoagulants. Adverse events associated with anticoagulants, such as heparin-induced thrombocytopenia, bleeding problems, and the need for close monitoring of anticoagulant activity, have contributed to finding agents that reduce these limitations. Studies like the Organization to Assess Strategies in Ischemic Syndromes 5 and 6 and their meta-analysis have proven the efficacy of Fondaparinux over the entire ACS spectrum. The convenience of administration (once daily), lack of monitoring, reduction in mortality, and better safety profile make Fondaparinux a simple and effective anti-coagulant for the management of ACS.

Key Words: Acute coronary syndrome; Anti-coagulant therapy; Antiplatelet therapy; Fondaparinux; Unfractionated heparin; Enoxaparin

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Core Tip: The simultaneous use of antithrombotic therapy and anti-platelet therapy in the acute coronary syndrome acute phase is associated with reduced ischemic events and is more effective than either class of drug used alone. The physicians must maintain a balance while prescribing these drugs to maintain an overall benefit-risk ratio. Fondaparinux is one of the simple and effective anti-coagulant for the management of acute coronary syndrome.

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INTRODUCTION

Acute coronary syndrome

Acute coronary syndrome (ACS) is one of the main causes of fatality worldwide. When compared to other countries, South Asians have a higher rate of myocardial infarction (MI) at a younger age (average age 53 years *vs* average age 58.8 years)[1-4]. In the Indian population as well, ACS presents a decade earlier in comparison to the West. Furthermore, India has the greatest ACS load in the world, with a burden 3 to 4 times that of White Americans, 6 times that of Chinese, and 20 times that of Japanese people. ACS is responsible for 3 million fatalities each year in India, accounting for 25% of all deaths[5]. Anti-coagulant therapies form the cornerstone in the management of ACS.

Anti-coagulant therapy in ACS

The mechanism of action of various anti-coagulant therapies is described in Figure 1. Anticoagulant medication is an important part of the treatment of ACS[6], while being only one step of the treatment pathway. In the past, unfractionated heparin was the most commonly used parenteral anticoagulant. However, as compared to other treatments, unfractionated heparin (UFH) has a variable dose-response and a small therapeutic window that necessitates frequent monitoring and is linked with a higher risk of side effects [*e.g.*, heparin-induced thrombocytopenia (HIT), hemorrhage, and osteoporosis]. Other systemic anticoagulants that do not require frequent monitoring or dose adjustment are more commonly used these days than UFH[7]. Maintaining a fine balance between reducing cardiovascular mortality and increased risk of bleeding is the main concern for the available treatments for ACS. The main objective of this review is to identify the current gaps of using anti-coagulant therapies in ACS and thus to bring in the evaluated clinical benefits of Fondaparinux in ACS patients.

CLINICAL PHARMACOLOGY OF FONDAPARINUX

Pharmacology

Fondaparinux, a synthetic anticoagulant, consists of a highly sulfated penta saccharide derived from the minimal antithrombin (AT)-binding region of heparin. It works as an indirect factor Xa inhibitor by binding to AT and producing a conformational change in AT that improves AT's ability to inactivate factor Xa (Figure 1)[8].

Anticoagulant effects

Unfractionated heparin and low molecular weight heparins (LMWHs) such as Enoxaparin act by inhibiting both factor Xa and thrombin. LMWHs have a lower effect on thrombin than the effect of unfractionated heparin. Fondaparinux specifically inhibits factor Xa coagulation factors[8].

Fondaparinux can be administered through subcutaneous (s.c.) or intravenous (i.v.) routes. The bioavailability is 100% after s.c. administration of fondaparinux in healthy volunteers and mean maximum plasma concentration is achieved at 1.7 h. The mean maximum plasma concentration with i.v. dose is achieved at an even faster rate without affecting half-life[9].

When compared to LMWHs like Enoxaparin and UFHs, fondaparinux sodium had no effect on fibrinolytic activity or bleeding time at the prescribed dose, promoting hemostasis and a favorable bleeding risk profile. Fondaparinux does not bind to or interact with other plasma proteins or cellular elements such as platelets or platelet factor 4, and thus, unlike Enoxaparin and UFH, it does not cause heparin-induced thrombocytopenia-like syndrome[10].

Metabolism

Fondaparinux is 100% bioavailable after s.c. injection. The half-life of fondaparinux is

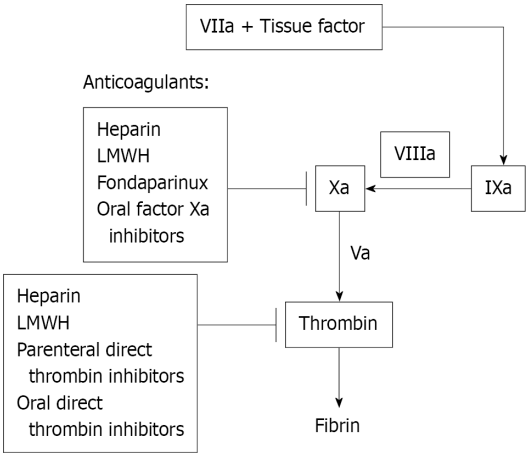


Figure 1 Mechanism of action of various anticoagulants. LMWH: Low molecular weight heparin.

17.2 h, which is quite long and allows once-daily dosing[11].

Monitoring

Fondaparinux does not require monitoring in routine clinical use. The anticoagulant effect of fondaparinux can be assessed with dedicated anti-Xa assays in high-risk patient populations (renal insufficiency, bodyweight less than 50 kg)[6].

Fondaparinux is mainly cleared through the kidney and is excreted unchanged in the urine. Clearance of this drug is reduced in individuals with reduced creatinine clearance and is therefore not recommended for use in individuals with creatinine clearance < 30 mL/min[10]. Table 1 compares pharmacokinetics, dosage frequency, and indications between UFH, LMWHs (Enoxaparin), and Fondaparinux.

FONDAPARINUX IN ACS

The effectiveness and safety profile of fondaparinux has been studied in ACS. An enormous reduction in bleeding complications in ACS has been seen in various studies where fondaparinux is utilized as an anticoagulant in ACS. Here, we present evidence on the clinical efficacy and safety of fondaparinux in patients with ACS.

OASIS 5

Organization to Assess Strategies in Ischemic Syndromes (OASIS) 5 was a randomized, double-dummy, randomized, parallel-group, controlled trial to see if Fondaparinux, when used as an anticoagulant in unstable angina and non-ST elevation ACS (NSTE-ACS), would preserve the anti-ischemic benefits of Enoxaparin while reducing bleeding. Following randomization, the study medication was administered subcutaneously. Enoxaparin 1 mg/kg twice daily s.c. for 2 to 8 d or until clinically stable, or fondaparinux 2.5 mg once daily s.c. for 8 d or until discharge, whichever came first. In patients with a creatinine clearance of 20 mL/min to 30 mL/min, Enoxaparin was given once daily at a dose of 1 mg/kg. Subjects received regular medical care, including interventions, in addition to the study medicine [percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery] [12].

Summary

Primary efficacy outcome: In terms of the primary efficacy outcome, Fondaparinux was shown to be non-inferior to Enoxaparin [Fondaparinux 5.8% *vs* Enoxaparin EX 5.7%, hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.90 to 1.13] (Table 2)[12].

Primary safety outcome: When compared to Enoxaparin, Fondaparinux reduced serious bleeding rates by nearly half (2.2% *vs* 4.1%; HR, 0.52; 95%CI, 0.44 to 0.61; P = 0.001) (Table 2)[12].

Secondary outcomes: At the end of 30 d, the Fondaparinux group showed 17% lower mortality (P < 0.02) and 23% lower stroke rate *vs* the Enoxaparin group. Bleeding rates were significantly reduced too. The effect on death, stroke, and major bleeding was

Table 1 Comparison of unfractionated heparin, low molecular weight heparins (Enoxaparin), and Fondaparinux

	UFH	Enoxaparin	Fondaparinux
Source	**Biological**	**Biological**	**Synthetic**
Bioavailability	30%	90%	100%
Mechanism	Augments AT effects on Factor Xa and thrombin. Binds to plasma proteins not specifically → unpredictable dose-response	Augments AT effects more on Factor Xa than on thrombin. Low binding to plasma proteins → more predictable dose-response, low inter-patient variability	Augments anti-Xa activity of AT, no direct effect on thrombin. Specific for AT → no binding to other plasma proteins, predictable dose-response
Plasma half-life	1-2 h	4.5-7 h	17-21 h
Reversal agents	Protamine sulfate	Protamine sulfate	Irreversible by protamine factor VII- limited data
Routine monitoring	Yes	No	No
Dosing frequency in ACS	Treatment - Continuous i.v. infusion	BID	Once daily
Clearance	Hepatic & Reticuloendothelial clearance. No renal adjustments	Renal	Renal
		Adjustment needed for CrCl < 30 mL/min	Contraindication: CrCl < 30 mL/min
Ability to cause HIT	Yes	Yes	No cases in major trials
Bleeding risk	Increased	Increased	Lesser

UFH: Unfractionated heparin; HIT: Heparin-induced thrombocytopenia; AT: Antithrombin; ACS: Acute coronary syndrome; LMWH: Low molecular weight heparin.

Table 2 Organization to Assess Strategies in Ischemic Syndromes 5: Primary efficacy and safety outcomes at 9 d

Outcomes	Fondaparinux	Enoxaparin	HR (95%CI)	*P* value
Primary efficacy outcome: Cumulative event rate-Death, MI, refractory ischemia at 9 d				
Cumulative event rate	5.80%	5.70%	1.01 (0.90-1.13)	0.007
Primary safety outcome: Major bleeding at 9 d				
Major bleeding	2.20%	4.10%	0.52 (0.44-0.61)	$P < 0.001$

CI: Confidence interval; HR: Hazard ratio.

maintained till the end of the study (Figure 2). Fondaparinux also resulted in significant reductions in the combined endpoints of death/MI/stroke at 30 d (-11%) and 180 d (-11%). There was also a significant reduction in fatal and severe bleeding rates for Fondaparinux as compared to Enoxaparin both at 30 d and 180 d. The difference in mortality favoring Fondaparinux in this study was almost completely attributed to the reduced bleeding rates[12].

Subgroup analysis

Balance of benefit and risk: The major effectiveness and safety outcomes were combined to determine the balance of benefit and risk. At 9 d, patients in the Fondaparinux group had a considerably reduced rate of death, MI, refractory ischemia, and severe bleeding than those in the Enoxaparin group. This disparity continued until the study's conclusion. The benefits and risk were consistent across subgroups, including age and gender, renal function spectrum, whether unfractionated heparin was provided before randomization, and whether revascularization was conducted within 9 d[12].

The safety of Fondaparinux over Enoxaparin was also validated in three key subgroups: Those with a wide range of renal impairment in the OASIS 5 trial, those who underwent PCI within 24 h, and those who took glycoprotein (GP) IIb/IIIa inhibitors.

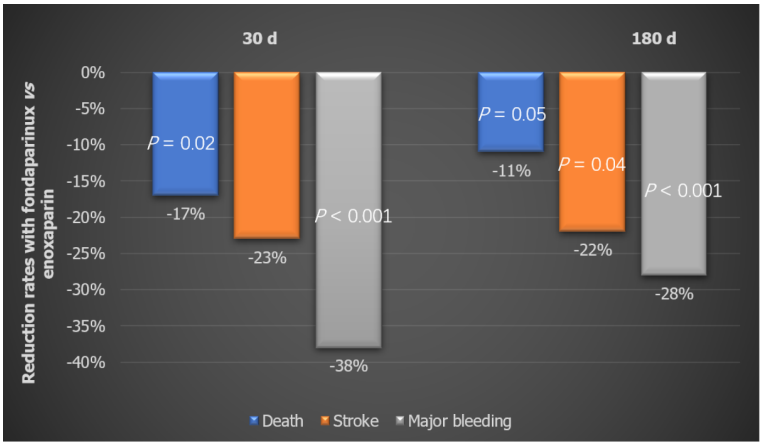


Figure 2 Secondary efficacy and safety outcomes. Outcomes-based at 30 d and 180 d.

Renal function and efficacy and safety of Fondaparinux vs Enoxaparin in NSTE-ACS

This subgroup analysis assessed if the enhanced bleeding risk with Enoxaparin was related to the level of kidney function in study participants. Efficacy and safety data have been grouped into quartiles according to estimated glomerular filtration rate [(eGFR): < 58 (n = 5141); 58 to 71 (n = 4845); 71 to 86 (n = 5012); and ≥ 86 mL/min/1.73 m^2 (n = 4996), respectively][13].

When compared to Enoxaparin, Fondaparinux was associated with significantly fewer bleeding episodes. Across all eGFR quartiles, Fondaparinux treatment was linked with decreased severe bleeding on day 9 (Figure 3). This pattern maintained for the next 30 d and 180 d. Those with an eGFR of less than 58 mL/min/1.73 m^2 had the most noticeable bleeding disparities[13].

Only individuals with an eGFR of less than 58 mL/min/1.73 m^2 saw a substantial reduction in the composite outcome of mortality, MI, and refractory ischemia at day 30. In comparison to Enoxaparin, the other eGFR groups had similar endpoint rates [13]. Therefore, the benefits of Fondaparinux over Enoxaparin in NSTE- ACS are most marked among patients with renal dysfunction and are largely due to a better safety profile of Fondaparinux due to lower rates of major bleeding with Fondaparinux.

Comparative efficacy and safety of Fondaparinux and Enoxaparin in ACS patients who went through PCI in the OASIS 5 trial

More than 60% of patients had catheterization and more than 30% had PCI In OASIS 5. When the last dose of Enoxaparin was more than 6 h before the procedure, patients were given weight adjusted UFH during PCI. An additional dosage of i.v. Fondaparinux was given to individuals who had received a s.c. dose of Fondaparinux before undergoing PCI. Following sporadic reports of catheter thrombosis, an adjustment to the protocol was made to allow investigators to use open-label UFH in patients receiving Fondaparinux[14].

When Fondaparinux was used instead of Enoxaparin on day 9, serious bleeding was considerably reduced (2.4% *vs* 5.1%, HR 0.46; P < 0.00001). When compared to Enoxaparin, Fondaparinux was associated with a slight increase in the rate of catheter-related thrombi (in patients having PCI) (0.9% *vs* 0.4%) (Table 3). The findings show that upstream Fondaparinux therapy in NSTE-ACS patients undergoing early PCI was superior to Enoxaparin in lowering severe bleeding by 50% while maintaining the same effectiveness, resulting in a superior net therapeutic benefit[14]. Patients who received open-label UFH before the treatment had a considerably lower rate of catheter-related thrombi in both groups. The Fondaparinux with Unfractionated Heparin (FUTURA) trial, which is addressed later in this article, looked at this evidence further.

In patients with ACS treated with GP IIb/IIIa inhibitors or thienopyridines, the efficacy and safety of Fondaparinux were compared to Enoxaparin. Patients with ACS (n = 20078) were randomized to either Fondaparinux or Enoxaparin as part of the OASIS 5 study. The treating physician selected whether or not to utilize GP IIb/IIIa inhibitors or thienopyridines. Fondaparinux reduced significant bleeding and improved net clinical outcome in individuals using GP IIb/IIIa inhibitors or thienopyridines when compared to Enoxaparin.

Table 3 Organization to Assess Strategies in Ischemic Syndromes 5: Fondaparinux *vs* Enoxaparin in non-ST elevation acute coronary syndrome patients undergoing percutaneous coronary intervention

Outcome day 9	Enoxaparin (*n* = 3072)	Fondaparinux (*n* = 3106)	Hazard ratio	*P* value
Death, MI, or stroke	6.2	6.3	1.03	0.79
Major bleeding	5.1	2.4	0.46	< 0.00001
Catheter thrombosis	0.4	0.9	3.59	0.001

MI: Myocardial infarction.

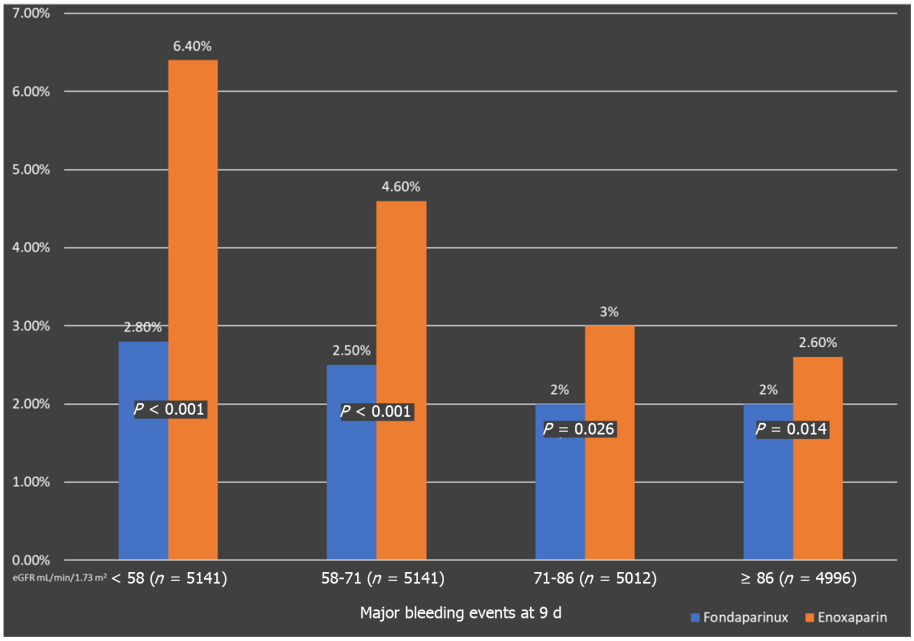


Figure 3 The figure shows comparative major bleeding events with Fondaparinux and Enoxaparin. The major bleeding events were noticed significantly lower as compared to Enoxaparin and thus its use was kindred with less major bleeding across all estimated glomerular filtration rate quartiles. eGFR: Estimated glomerular filtration rate.

Overall results from the OASIS 5 trial and subgroup analyses

While Fondaparinux and Enoxaparin both reduce the risk of ischemic events, the rate of serious bleeding with Fondaparinux was much lower than with Enoxaparin. In addition, Fondaparinux has a lower rate of combined mortality, MI, refractory ischemia, and severe bleeding than Enoxaparin. As a result, Fondaparinux at a daily dose of 2.5 mg is an appealing option for preventing ischemic events in patients with acute coronary syndromes without ST-segment elevation in the short term, and because it is associated with significantly less bleeding–this effect translates to lower long-term mortality and morbidity compared to Enoxaparin[12-14].

FUTURA/OASIS 8

FUTURA during revascularization in ACS (FUTURA/OASIS 8): The trial compared the safety of two UFH treatment regimens during PCI in high-risk patients with NSTE initially treated with Fondaparinux in a double-blind, randomized, parallel-group, multicenter trial with 2026 NSTE-ACS patients undergoing PCI within 72 h treated with Fondaparinux[15].

UFH regimens: The regimens were divided into low dose group and standard-dose group. All patients received 50 IU/kg UFH irrespective of the use of GP IIb IIIa in the low dose group. In the standard UFH group, the mean dose was 85 IU/kg to maintain activated clotting time (ACT) between 300-350 s and was reduced to 60 IU/g in those receiving GP IIb IIIa. The primary goal of the FUTURA trial was to see if low fixed-

dose unfractionated heparin *vs* standard ACT guided unfractionated heparin during PCI reduces the composite of peri-PCI major, minor bleeding, and vascular access site complications in ACS patients treated with Fondaparinux. The secondary goal was to see if major bleeding rates in FUTURA were higher than in OASIS 5 PCI (with Fondaparinux used alone)[15].

Summary

Primary outcome: There were no significant differences between low fixed-dose and standard-dose unfractionated heparin in the primary outcomes of peri-PCI major bleeding or major vascular access site problems (P = 0.27) (See Table 4).

Key secondary outcome: The primary secondary outcomes of Peri-PCI major bleeding, mortality, MI, and target vessel revascularization had a nominally significant difference. The low-dose UFH group had a rate of 5.8% at 30 d compared to 3.9% in the standard-dose UFH group (odds ratio, 1.51; 95%CI, 1.00-2.28; P = 0.05). There were very little catheter thrombus rates (0.5% in the low-dose UFH group and 0.1% in the standard-dose UFH group, P = 0.15). The low-dose regimen was linked to a numerically higher rate of definite stent thrombosis (n = 12 *vs* 5) but no reduction in severe bleeding (Table 5)[15].

Comparison with OASIS 5 PCI

The risk of major bleeding within 48 h was 1.1% in the standard-dose unfractionated heparin arm and 1.2% with low-dose heparin in FUTURA/OASIS 8, compared with 3.6% with Enoxaparin in OASIS 5. As a result, UFH + Fondaparinux has no effect on peri-PCI severe bleeding, and rates appear to be lower than when Enoxaparin is administered (Table 6)[15].

Overall Summary of FUTURA trial

When UFH was used for PCI on a Fondaparinux background, severe bleeding was not increased when compared to Fondaparinux alone, and it was lower than when Enoxaparin was used for PCI prior. Adding UFH to Fondaparinux during PCI preserves Fondaparinux's advantages and safety (*e.g.*, reduced bleeding) while reducing catheter thrombus. The finding that augmenting ACT-guided conventional UFH to Fondaparinux during PCI does not increase severe bleeding in patients with non-ST segment elevation MI (NSTEMI) is significant for interventional cardiologists. As a result, NSTE-ACS patients who have been treated with Fondaparinux can safely undergo PCI with UFH. There is no need to deviate from the UFH regular dose regimen advised by the guidelines[15].

OASIS 6

Overall Summary of FUTURA trial

Fondaparinux *vs* control in patients with ST-elevated MI (STEMI) was randomized within 24 h after the start of symptoms in a randomized, double-blind, controlled, parallel-group, multi-center, global trial. For the use of UFH, patients with confirmed STEMI were randomized to one of two strata based on the indication[16].

Summary

Primary efficacy outcomes: At 30 d, the Fondaparinux group had a significantly reduced risk of death or reinfarction than the control group (9.7% *vs* 11.2%, HR, 0.86; P = 0.008), and the results were similar at 9 d (HR, 0.83, P = 0.003) and at the end of the study (HR, 0.88; P = 0.008) (Figure 4). At 9 d, the relative risk reduction was 17%, 14% at 30 d, and 12% at the end of the study. This difference remained throughout the study, showing that treatment benefits accrue quickly and are sustained over time (Table 7).

Primary safety outcomes: At 9 d, the risk of significant bleeding in patients receiving Fondaparinux was 1.8% (107/6036), compared to 2.1% (130/6056) in patients given placebo or UFH. At 9 d, Fondaparinux was associated with significantly fewer serious bleeds (79 for placebo/UFH *vs* 61 for Fondaparinux) as well as significantly fewer cardiac tamponade episodes (48 *vs* 28; P = 0.02)[16].

Table 4 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Primary outcomes at 48 h

Primary outcomes at 48 h	Standard dose UFH (*n* = 1002)	Low dose UFH (*n* = 1024)	Odds ratio	95%CI	*P* value
Peri-PCI major, minor, bleeds and vascular access complications	5.80%	4.70%	0.80	0.54-1.19	0.27
Components					
Major bleeds	1.20%	1.40%	1.14	0.53-2.49	0.73
Minor bleeds	1.70%	0.70%	0.40	0.16-0.97	0.04
Major vascular access site complications	4.30%	3.20%	0.74	0.47-1.18	0.21

UFH: Unfractionated heparin; CI: Confidence interval; PCI: Percutaneous coronary intervention.

Table 5 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Secondary outcomes at 30 d

Secondary outcomes at 30 d	Standard dose UFH (*n* = 1002)	Low dose UFH (*n* = 1024)	Odds ratio	95%CI	*P* value
Peri-PCI major bleeding, Death, MI, TVR	3.90%	5.80%	1.51	1.00-2.28	0.05
Death, MI, TVR	2.90%	4.50%	1.58	0.98-2.53	0.06
Death	0.60%	0.80%	1.31	0.45-3.78	
MI	2.50%	3.00%	1.22	0.72-2.08	
TVR	0.30%	0.90%	2.95	0.80-10.9	
Stent thrombosis	0.50%	1.20%	2.36	0.83-6.73	0.11
Catheter thrombosis	0.10%	0.5%	4.91	0.57-42.1	0.15

UFH: Unfractionated heparin; CI: Confidence interval; PCI: Percutaneous coronary intervention; TVR: Target vessel revascularization.

Table 6 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Comparison to Organization to Assess Strategies in Ischemic Syndromes 5 major bleeding (< 48 h of percutaneous coronary intervention)

Adjusted major bleeding rate	OASIS 5 PCI	OASIS 5 PCI
	Fondaparinux	Enoxaparin
	Major bleeding	Major bleeding
FUTURA	1.5%	3.6%
Standard dose UFH 1.1% (0.6-2.1)		
FUTURA		
Low dose UFH 1.2% (0.6-2.2)		

PCI: Percutaneous coronary intervention; FUTURA: Fondaparinux with unfractionated heparin; OASIS: Organization to Assess Strategies in Ischemic Syndromes; UFH: Unfractionated heparin.

SUBGROUP ANALYSIS

In subgroups defined by the time from symptom onset to randomization in men and women, in those older or younger than the median age (61 years), with the use of various concurrent therapies or various types of thrombolytic medicines, the outcomes on death or MI were not statistically diverse.

A subgroup analysis of the OASIS 6 trial looked at the role of Fondaparinux as an addition to thrombolytic treatment in acute MI. The major goal of this subgroup

Table 7 Primary efficacy outcome of Fondaparinux *vs* unfractionated heparin (control) in preventing death or reinfarction at 30 d and 3 or 6 mo and relative risk reduction of fondaparinux *vs* control through study end

Measures	Fondaparinux	Control (UFH)
Primary composite outcome: Death or reinfarction		
Frequency at 30 d	9.70%	11.20%
P value	*P* = 0.008	
Relative risk reduction	14%	
Frequency at 9 d	7.40%	8.90%
P value	*P* = 0.003	
Relative risk reduction	17%	
Frequency at 3-6 mo	13.40%	14.80%
P value	*P* = 0.008	
Relative risk reduction	12%	

UFH: Unfractionated heparin.

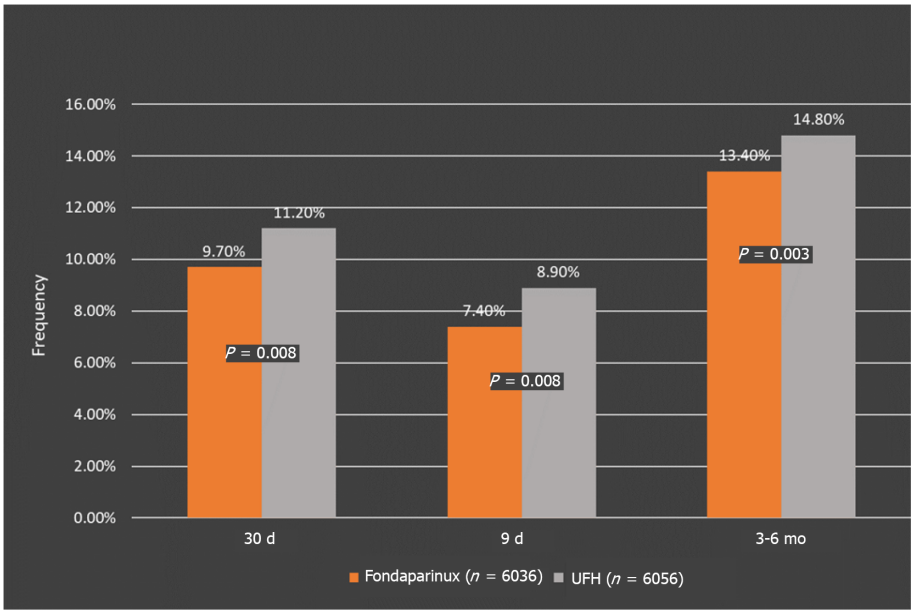


Figure 4 Primary composite outcome. Death or reinfarction was significantly lower in the Fondaparinux group compared with the control group at 30 d and at 3 or 6 mo.

analysis was to compare the efficacy and safety of Fondaparinux to a control (placebo or UFH) in thrombolytic treatment patients. Streptokinase was the most used thrombolytic agent (73%). Streptokinase and urokinase were non-fibrin specific thrombolytic medicines. Tissue plasminogen activator, reteplase, and tenecteplase were fibrin-specific thrombolytic drugs (See Table 8). In this study, stratum 1 included 4415 patients who did not have an indication for unfractionated heparin, and stratum 2 included 1021 patients who did have such an indication.

The main trial's major outcomes were employed, namely the 30-d rates of mortality, MI, and serious bleeding. Fondaparinux dramatically reduced the risk of death, re-MI, and serious bleeding in STEMI patients treated with thrombolytic drugs (mostly streptokinase). The results were consistent in both strata, over varied time periods from symptom start to treatment, and across different types of thrombolytics[16].

Table 8 Subgroup analysis Organization to Assess Strategies in Ischemic Syndromes 6, *n*

OASIS 6	Stratum I		Stratum II		Total
	Placebo	Fondaparinux	UFH	Fondaparinux	
	2835	2823	3221	3213	12092
Non-fibrin specific thrombolytic	2216	2179	83	83	4561
Fibrin specific thrombolytic	9	11	436	419	875
Any thrombolytic	2225	2190	519	502	5436

The number of patients who received thrombolytic therapy. OASIS: Organization to Assess Strategies for Ischemic Syndromes; UFH: Unfractionated heparin.

Fondaparinux's effects in individuals with ST-segment elevation acute myocardial infarction who aren't getting reperfusion therapy.

In the OASIS 6 trial, this sub-study assessed the efficacy and safety of Fondaparinux to placebo or UF heparin in a pre-specified subset of 2867 patients who were not undergoing any sort of reperfusion therapy. When compared to conventional care (UF heparin infusion or placebo), a treatment plan with Fondaparinux 2.5 mg s.c. once daily reduced the composite of mortality or cardiac re-infarction without increasing severe bleeding or strokes in STEMI patients who were not getting reperfusion therapy[16].

Overall results from the OASIS 6 trial and subgroup analyses.

In patients with STEMI, Fondaparinux significantly reduced death and reinfarction *vs* UFH/placebo at 30 d. There is a trend to a lower rate of severe bleeding with Fondaparinux use in STEMI. Fondaparinux *vs* UFH/placebo resulted in a significant reduction in death and MI, with benefits appearing early (9 d) and being constant throughout the study. Fondaparinux had a considerably reduced rate of mortality, MI, and serious hemorrhage compared to UFH/placebo.

Fondaparinux lowers mortality and reinfarction in STEMI patients, particularly those who are not undergoing primary percutaneous coronary intervention, without increasing bleeding or strokes. Fondaparinux, on the other hand, showed no benefit in patients receiving PCI[16].

SWEDEHEART registry

The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) was a prospective, multicenter cohort study of NSTEMI patients treated with Fondaparinux or LMWH (n = 40616). The outcome measures were severe bleeding events and mortality (in-hospital), 30- and 180-d major bleeding, stroke, death, and recurrent MI. In-hospital bleeding rates and death were lowered by 46% and 25% with Fondaparinux as compared to LMWH. The positive impact on bleeding was maintained over the 30-d and 180-d periods. Similarly, the composite outcome of MI, death and bleeding, also showed a reduction over the longer time intervals (Figure 5). The decrease in mortality was significant for both the 30-d and 180-d periods.

However, treatment with Fondaparinux was associated with lower severe in-hospital bleeding rates within each renal function strata, an effect that was maintained over the long term (30 and 180 d). Similarly, in-hospital mortality rates were also reduced with Fondaparinux *vs* LMWH in almost all categories of renal function. Since the SWEDEHEART analysis was conducted in a routine clinical care setting across patient subgroups, the short and long-term benefits of Fondaparinux in NSTEMI were reinforced by this analysis[17].

BRAZILIAN REGISTRY

A retrospective analysis of Brazilian NSTE-ACS patients (n = 2282) treated with Fondaparinux or Enoxaparin with in-hospital all-cause mortality as the primary outcome and secondary outcome being combined events (cardiogenic shock, reinfarction, death, stroke, and bleeding) showed a significant impact of Fondaprinux

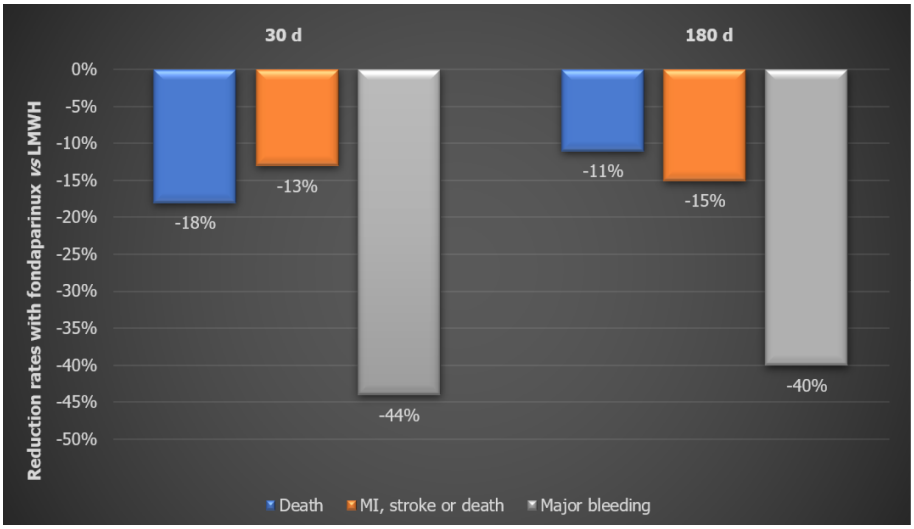


Figure 5 The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Analysis. Outcomes at 30 d and 180 d. LMWH: Low molecular weight heparin.

therapy on bleeding as well as combined events (Figure 6). This study further established the superiority of Fondaparinux over Enoxaparin in NSTE-ACS patients. Several additional studies provide clinical evidence favoring the use of Fondaparinux in ACS patients (Table 9)[17].

Position of Fondaparinux in recent guidelines and some studies

Fondaparinux is recommended by several guidelines for use in ACS. Its use is recommended in case of both invasive and conservative management strategies. The latest ESC guidelines[18] recommend Fondaparinux in NSTE-ACS as having the most favorable efficacy–safety profile with respect to anticoagulation. ACC/AHA 2014[19] and National Institute for Health and Care Excellence 2010 guidelines also recommend its use in NSTE-ACS management (Table 10). Various Studies like the OASIS 5 and 6 also showed the efficacy of Fondaparinux in ACS. The convenience of once-daily administration, lack of monitoring, reduction in mortality, and better safety profile make Fondaparinux a simple and effective anti-coagulant agent. Fondaparinux is a reasonable choice in NSTE-ACS where patients are managed with invasive approaches like angiography and possible revascularization and thus are at increased risk of the bleeding[6].

Cost-effectiveness of Fondaparinux

Compared to Fondaparinux, Enoxaparin is a twice-daily formulation with the dose tailored to the bodyweight of the patient. This increases the cost of the medication and the time invested by the clinician in calculating and administering the appropriate dose. The cost-effectiveness of Fondaparinux has been proven in economic analyses carried out in several countries such as Brazil, Thailand, United States of America (US), and Canada.

In Thailand, when compared to Enoxaparin, Fondaparinux was 99% more cost-effective [threshold of 160000 Thai Baht (THB), *i.e.* 4857.3 USD/ quality-adjusted life-year (QALY)], especially in NSTEMI patients. The benefit was 2-fold, from both the provider and societal perspectives. In another analysis, the economic benefit of Fondaparinux was observed across all the subgroups studied, with maximum impact seen in younger patients, in those at high cardiac risk, and those with the greatest risk of bleeding. Avoidance of the costs associated with managing major bleeding also makes Fondaparinux an attractive option.

Fondaparinux was also more cost-effective than Enoxaparin in the Brazilian registry for NSTE-ACS patients. In a Canadian study, data from the OASIS 5 trial were used to evaluate short-term (180 d) and life-term costs with Fondaparinux *vs* Enoxaparin. Fondaparinux was found to be more cost-effective with a saving of $439 for 180 d and a lifetime incremental cost-effectiveness ratio of $4293/QALY. This was determined by not only its lower acquisition cost but also due to the decrease in clinical event rates over 6 mo post-treatment. In a US study evaluating the OASIS 5 data, the 180-d cost saving with Fondaparinux was found to be $547 per patient. This resulted in long-term

Table 9 Comparative studies between low molecular weight heparin/enoxaparin and fondaparinux

Name of study	Type of study	No of patients	Endpoints	Results	Conclusions
Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes	Network metanalysis of 42 randomized controlled trials	117353	Death, MI, revascularization, bleeding	Death and MI rates with Fondaparinux were lower than that with 5 other anticoagulant regimens. [UFH + glycoprotein IIb/IIIa inhibitor (GPI), UFH ± GPI, Bivalirudin, LMWH, and Otamixaban (a direct Factor Xa inhibitor)].	Fondaparinux had the most balanced profile compared to other evaluated strategies, ranking high for both efficacy and safety.
Comparison between Fondaparinux and low molecular-weight heparin in patients with acute coronary syndrome	Meta-analysis	62900	MACE, mortality, major bleeding events	Fondaparinux had significantly lower rates of MACE and major bleeding events. Lower all-cause mortality (-16%) *vs* LMWH.	In this meta-analysis of head-to-head comparisons, fondaparinux-based regimens presented advantages in MACE and major bleeding, as well as a net clinical benefit, compared with LMWH.
Choosing between Enoxaparin and Fondaparinux for the management of patients with acute coronary syndrome: A systematic review and meta-analysis	Meta-analysis	9618	Mortality, MI, Stroke, Minor/Major and all bleeding	Fondaparinux resulted in significantly lower bleeding rates during short-term (10 d) and long-term (30 d or 6 mo to 1 yr) intervals.	Fondaparinux could be a better option *vs* Enoxaparin, especially in NSTEMI patients, in terms of short to mid-term bleeding risk.
Comparison of Efficacy, Safety and Hemostatic Parameters of Enoxaparin and Fondaparinux in unstable coronary artery disease	Prospective, comparative study	180	Recovery, recurrence, major and minor bleeding	Recurrent MI or angina numerically more in the Enoxaparin group. At 30 d, enoxaparin showed a higher incidence of hemorrhage than fondaparinux ($P < 0.05$).	Fondaparinux appears to be better than enoxaparin in efficacy. Fondaparinux also has a better safety profile. Therefore, Fondaparinux is an attractive option compared to Enoxaparin in NSTE-ACS patients.

MACE: Major adverse cardiac–events; NSTE-ACS: Non-ST elevation acute coronary syndrome; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; GP: Glycoprotein; GPI: GP inhibitor; NSTEMI: Non-ST segment elevation myocardial infarction.

Table 10 Guideline recommendations for fondaparinux in acute coronary syndrome patients

AHA/ACC 2014	SC Fondaparinux for the duration of hospitalization or until PCI is performed.	2.5 mg s.c. daily	IB
ESC 2015	Fondaparinux is recommended as having the most favorable efficacy – safety profile regardless of the management strategy. In patients on Fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70-85 IU/kg, or 50-60 IU/kg in the case of concomitant use of glycoprotein IIb/IIIa inhibitors) is recommended during the procedure.	2.5 mg s.c. once daily	IB
NICE 2010	Fondaparinux is offered to patients who do not have a high bleeding risk (unless coronary angiography is planned within 24 h of admission). It should not be used in patients with significant renal dysfunction (those with a serum creatinine > 265 μmol/L were excluded from the trial).	2.5 mg s.c. once daily	NA
SIGN 2016	When there are ischemic electrocardiograph changes or elevation of cardiac markers, treat immediately with Fondaparinux. Continue for 8 d, or until hospital discharge or coronary revascularization.	2.5 mg s.c. once daily	1++
CPG Malaysian guidelines 2011	Fondaparinux for 8 d or duration of hospitalization.	2.5 mg s.c. daily	IA
SBC Brazilian guidelines 2015	Fondaparinux once a day for 8 d or until hospital discharge.	2.5 mg s.c. daily	IB

PCI: Percutaneous coronary intervention; UFH: Unfractionated heparin; NICE: National Institute for Health and Care Excellence; i.v.: Intravenous; s.c.: Subcutaneous.

cost-effectiveness both in terms of cost as well as QALYs across the range of event risks observed. These analyses add yet another positive aspect to the treatment of ACS with Fondaparinux, making it one of the best options available to clinicians today.

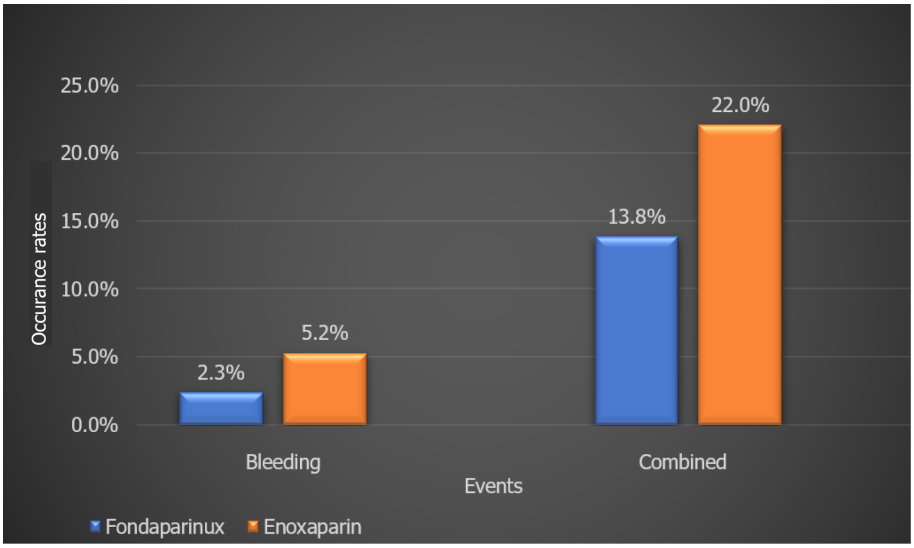


Figure 6 Brazilian registry data. Outcomes for bleeding and combined events.

CONCLUSION

In India, registry data have shown that the prevalence of ACS is quite varied, and the time taken to reach the hospital after symptom onset is more than in the western world and it is an area of concern. Hence, a patient who is presented later than 6 h (*i.e.* has been suffering for an extended period) especially needs prompt and effective treatment. Effective antithrombotic treatment in the form of antiplatelet agents and anticoagulants has been accepted as the cornerstone of therapy for ACS. However, reducing ischemic events without increasing bleeding risk with matchless anticoagulant therapy is the need of the hour. This requirement is remarkably fulfilled by the novel anticoagulant Fondaparinux, with its unique mode of action, once-daily administration, efficacy across patient groups, and consistent effectiveness in reducing bleeding risk. Moreover, several studies conducted in ACS patients have compared Fondaparinux to Enoxaparin and found it to be a safer and equally effective option. Its proven clinical efficacy has resulted in several reputed organizations recommending its use in ACS patients. Fondaparinux also scores over Enoxaparin in terms of cost-effectiveness, both by way of actual costs and QALYs. All these aspects reaffirm that Fondaparinux is one of the best choices in the treatment of ACS.

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CASE REPORT

Anesthetic management of a child with Cornelia de Lange Syndrome undergoing open heart surgery: A case report

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Abstract

BACKGROUND

Cornelia de Lange syndrome (CdLS) is a congenital multisystemic genetic disorder. The expected lifespan of children with this disorder has been prolonged in parallel with the advances in medicine in recent years. However, they still more frequently undergo cardiac surgery. There are some challenges for clinicians when faced with CdLS patients. We present the perioperative management of a child with CdLS undergoing open-heart surgery.

CASE SUMMARY

Severe pulmonic and subpulmonic valvular stenosis, enlargement of the right side of the heart, mild tricuspid regurgitation, atrial septal defect, and patent ductus arteriosus were diagnosed in a 14-month-old boy with manifested cyanosis, developmental delay, and malnutrition. Attempted balloon valvuloplasty was unsuccessful due to a severe stenotic pulmonary valve, therefore it was decided to perform an open surgical repair. Following a successful and uncomplicated intraoperative course, the patient was extubated on postoperative day 5, and adrenalin and dopamine infusions were gradually decreased and stopped on postoperative days 6 and 10, respectively. Moderate laryngomalacia and suboptimal vocal cord movements were diagnosed, and tracheotomy and percutaneous endoscopic gastrostomy were performed under general anesthesia in the same session at postoperative day 32. The patient was discharged on postoperative day 85 after a challenging postoperative period with additional

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Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

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airway and nutritional problems.

CONCLUSION
This is the first report of the perioperative anesthetic and clinical management of a CdLS patient undergoing open-heart surgery.

Key Words: Cornelia de Lange Syndrome; Brachmann de Lange Syndrome; Pulmonary valve stenosis; Valvular heart disease; Cardiac surgery; Anesthesia; Case report

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Core tip: Cornelia de Lange Syndrome (CdLS) is a congenital multisystemic genetic disorder with multiple congenital abnormalities. The expected lifespan of children with CdLS has been prolonged in parallel with the advances in medicine in recent years. Patients with CdLS undergo cardiac surgery more frequently. In any patients with multiple medical challenges, anesthesiologists, cardiovascular surgeons and pediatricians may face unexpectedly unusual perioperative courses with additional difficulties when undergoing congenital open-heart surgery. The case presented here demonstrates an example of a challenging perioperative management period of a child with multisystemic congenital disease undergoing multiple high-risk surgeries.

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INTRODUCTION

Cornelia de Lange Syndrome (CdLS), also known as Brachmann–de Lange Syndrome, is a genetic developmental disorder with a prevalence of 1.24 per 100 000 births[1]. It is characterized by congenital craniofacial, gastrointestinal, cardiac, musculoskeletal, genitourinary, behavioral and neurodevelopmental anomalies[2]. Although CdLS patients are expected to have growth retardation, intellectual disabilities and a shorter lifespan due to these multiple severe malformations, there have been no previous population-based studies on survival, and some of the patients (particularly with the milder forms) have been reported to reach adulthood[3,4]. Most patients need diagnostic and/or interventional procedures and surgical operations under general anesthesia (GA) to survive. Previous research has described anesthetic implementations in non-cardiac surgery. We present the perioperative management of a child with CdLS undergoing open-heart surgery.

CASE PRESENTATION

Chief complaints

A 14-month-old male patient presented with severe cardiac manifestations including pulmonic and subpulmonic valvular stenosis with 91 mmHg gradient, enlargement of the right side of the heart, mild tricuspid regurgitation, atrial septal defect (ASD), and patent ductus arteriosus (PDA).

History of present illness

After genetic evaluation, CdLS diagnosis was approved, and the *SMC3* gene was reported to be implicated. When the patient was aged 14 mo, the decision to undertake pulmonary valvuloplasty was taken.

History of past illness

The patient was born at 37 wk gestation after a standard spontaneous vaginal delivery,

weighing 2009 g due to intrauterine growth retardation because of ABO maternal–fetal incompatibility. The baby was admitted to the neonatal intensive care unit for 15 d (intubated in the first 2 d) due to respiratory distress and a cleft lip and palate. In the first month after delivery, severe pulmonic stenosis (PS) was diagnosed, and the patient was admitted to a cardiology follow-up program. Lip adhesion surgery was conducted for the cleft lip at age 5 mo.

Personal and family history

The patient was born in Syria, and no information was available regarding his family history.

Physical examination

The patient was a 14-month-old boy weighing 4700 g, 60 cm in height (< 3rd percentile) and 39 cm head circumference (< 3rd percentile). Mild exertional dyspnea, cyanosis, developmental delay, and malnutrition were manifest. Synophrys, brachycephaly, long and thick eyelashes, depressed nasal bridge, repaired cleft lip, micrognathia, short neck, and thickened helices in both ears were distinguishing craniofacial features (Figure 1). There was no apparent renal, musculoskeletal, gastrointestinal and neurological involvement. There was a systolic thrill at the left upper sternal border. The auscultation of the patient revealed a grade 2–3/6 midsystolic (ejection systolic) murmur, systolic ejection click, and a widely split, fixed S2 at the upper left sternal border. Also, there was widened S2 and delayed pulmonic component of S2 due to the increased duration of systole and late closing of the pulmonary valve.

Laboratory examinations

In the preoperative laboratory examination all parameters were normal except: white blood cell count 13.1 10^3/μL, hemoglobin 11.0 g/dL, hematocrit 32.7%, platelet count 504 K/μL, aspartate aminotransferase 71 U/L, and urea 58 mg/dL.

Imaging examinations

Echocardiographic evaluation revealed severe cardiac manifestations including severe PS and sub-PS with 91 mmHg gradient, enlargement on the right side of the heart, mild tricuspid regurgitation, atrial septal ASD, and PDA (Figure 2).

FINAL DIAGNOSIS

The ASA Class III patient was scheduled for percutaneous pulmonary valvuloplasty under general anesthesia.

TREATMENT

Percutaneous pulmonary valvuloplasty

The patient was transferred to the catheter laboratory with an O_2 supply without premedication. After standard monitoring with ECG, oxygen saturation (SpO_2) and noninvasive blood pressure, anesthesia was induced with 2 mg/kg intravenous (iv) 1% propofol followed by 1.5 mg/kg iv fentanyl and maintained with 2% sevoflurane in 50:50% O_2 in air. I-Gel No. 2 was used in airway management without any problems. Due to the severe stenotic pulmonary valve (Figure 3), the attempted balloon valvuloplasty was unsuccessful. Therefore, the decision to perform an open surgical repair was taken.

Correction of PS and closure of PDA and ASD

Nine days after valvuloplasty, the patient was transferred to the cardiac theater with supplemental nasal O_2 without premedication. After standard monitoring with ECG, SpO_2 and NIBP, anesthesia induction was begun with 8% sevoflurane in 100% O_2 followed by 3 mg/kg iv fentanyl, 0.75 mg/kg iv midazolam, 1 mg/kg iv rocuronium, and 1.2 mg/kg iv dexamethasone after insertion of a 20 G cannula. Intubation was easily achieved with a 4.5-mm uncuffed endotracheal tube (grade 1 Cormack–Lehane). Anesthesia was maintained with 2% sevoflurane in 50:50% O_2 in air and 0.5–1.0 mg/kg iv rocuronium, 0.5 mg/kg iv midazolam, and 2–5 mg/kg iv fentanyl intermittently as



Figure 1 Distinguishing craniofacial features of the patient.

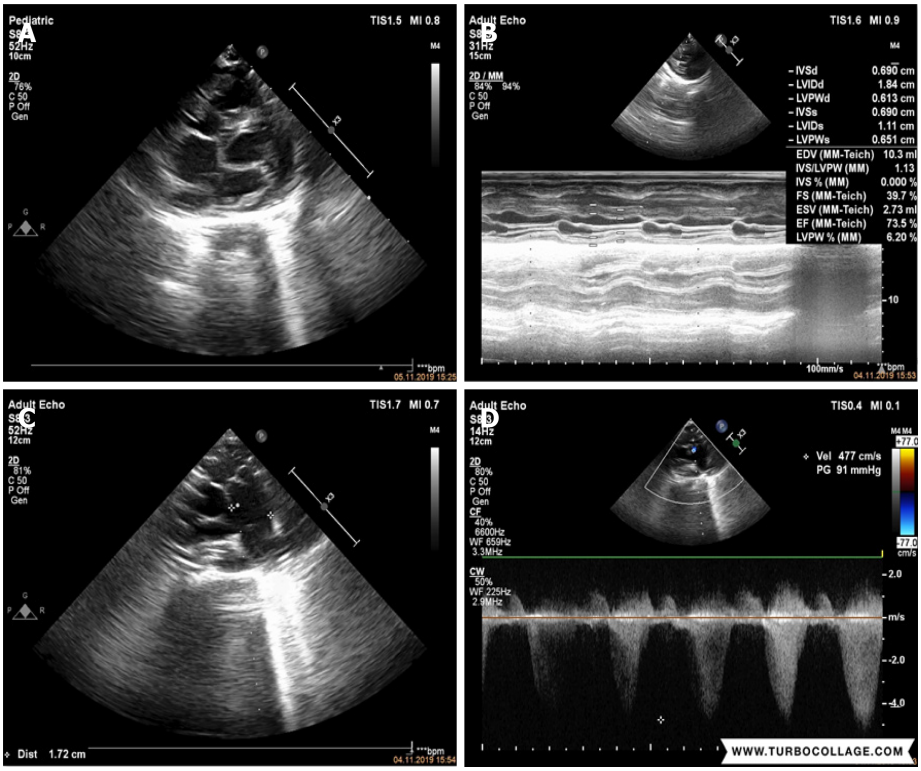


Figure 2 Echocardiographic images. A: The heart of the patient; B: Mild to moderate regurgitation in the tricuspid valve; C: Left ventricular systolic function was observed, functions were maintained (EF: 73.5 %, FS: 39.7 %); D: 91 mmHg gradient was obtained at pulmonary valve level in parasternal short axis imaging.

needed. Canulations were completed with the placement of a 20 G 5-cm arterial cannula with floswitch (BD Arterial Cannula; Becton Dickinson Infusion Therapy Systems Inc, Sandy, UT, USA) placed in the left femoral vein; a 4 F 8-cm double lumen central venous catheter (Royal Fornia Medical Equipment Co. Ltd., Guangdong, China) placed in the right femoral vein; and a 20 G 5-cm single lumen catheter (FMTO; Royal Fornia Medical Equipment Co. Ltd.) placed in the left femoral artery.

After standard anticoagulation with heparin (3 mg/kg) and ensuring activated clotting time of > 400 s, cardiopulmonary bypass (CPB) was established by aortic and bicaval cannulations. Under hypothermic (28 °C) CPB and cold crystalloid cardioplegic arrest, transatrial and transpulmonary incisions were performed. A 15 mm 25 mm ASD, subpulmonic infundibular stenosis and pulmonic valvular stenosis were present. Intracardiac repair with excision of the infundibular membrane and pulmonary valvular commissurotomy were achieved. At the pulmonic level, the outlet admitted a size 12 Hegar's dilator (normal size 11). The ASD closure was done through the right atrium using an autologous pericardial patch. After rewarming to 35 °C and

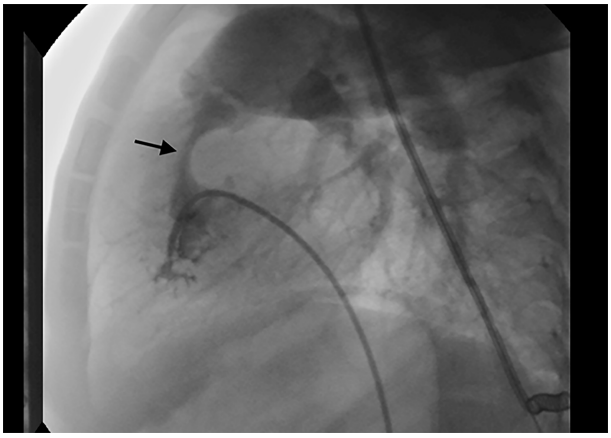


Figure 3 Appearance of the stenotic pulmonary valve in the angiography image.

ensuring normal serum electrolytes, the patient was removed from CPB. The child had a stable sinus rhythm after discontinuing heart–lung machine support. For heparin neutralization, 3 mg/kg protamine was applied. CPB was terminated with 52 min aorta cross-clamp time and 81 min of CPB. During anesthesia, iv infusions of 5 g/kg/min dopamine, 0.1 g/kg/min adrenaline, and 0.5 g/kg/min milrinone (after 50 g/kg loading for 1 h) were begun. Intravenous methylprednisolone (5 g/kg/min) and 10 mg/kg iv tranexamic acid were given in the off-pump period. Arterial blood gas analysis was conducted intermittently during surgery (Table 1). The total amount of saline and gelatin fluid (Gelofusine; B. Braun Medical AG, Crissier, Switzerland) and erythrocyte suspension given were 60 mL, 20 mL and 70 mL, respectively. Fresh frozen plasma was not used. The total urinary output was recorded as 350 mL. The hemodynamically stable patient was transported intubated to the pediatric cardiac intensive care unit (CICU).

OUTCOME AND FOLLOW-UP

The patient was extubated on postoperative day 5; adrenalin and dopamine infusions were gradually decreased and stopped on postoperative days 6 and 10, respectively. On postoperative day 14, the patient was transferred to the pediatric ICU (PICU). On the first day in the PICU, continuous positive airway pressure (CPAP) support (due to respiratory distress) and total parenteral nutrition (TPN) were started. Endoscopic evaluation by the ear, nose and throat (ENT) consultant revealed moderate laryngomalacia and suboptimal vocal cord movements. Intermittent CPAP therapy was terminated upon recovery of respiratory functions after 4 d. Enteral nutritional (EN) was begun. With the improvement of the general medical condition, a tracheotomy (based on the ENT consultant's recommendation) and a percutaneous endoscopic gastrostomy (PEG) to provide a convenient way of feeding were performed under GA in the same session on postoperative day 32.

The patient was discharged on postoperative day 85 after the parental educational discharge program. The general medical condition of the patient was good at the time of discharge. The patient was breathing spontaneously *via* tracheotomy cannula without requiring additional oxygen therapy with SpO_2 95–96%. The hemodynamics were within the normal range without inotropic support. The nutritional support was achieved with enteral nutritional products. The parental educational discharge program included content for feeding and general care of the patient at home. The patient's medical care was planned to be implemented within the home health service program of the Ministry of Health.

DISCUSSION

The present case is the first report of perioperative management of a CdLS patient undergoing open-heart surgery. CdLS is a multiple congenital anomaly and mental retardation syndrome accompanied by multiple disorders in different clinical forms, including classical and mild forms. Although the estimated prevalence of CdLS has

Table 1 Results of arterial blood gases conducted at different timings

Parameters	Beginning of surgery	Beginning of bypass	End of surgery	End of bypass
pH	7.43	7.46	7.52	7.38
PCO_2 (mmHg)	30.8	29.1	27.6	38.1
PO_2 (mmHg)	200	172	186	68.3
Hb ($g.dL^{-1}$)	9.7	11.4	12.2	13.3
Htc (%)	30	35.1	37.4	40.9
SaO_2 (%)	99.6	98.9	99.3	92.8
K^+ (mmol/L)	3.4	3.3	3.1	2.7
Na^+ (mmol/L)	149	143	146	150
Ca^{2+} (mmol/L)	1.25	1.16	1.14	0.87
Glucose (mg/dL)	77	191	196	177
Lactate (mmol/L)	1.0	1.9	1.8	1.1
Base (mmol/L)	-3.1	-2.6	0.3	-2.2
HCO_3^- (mmol/L)	22.2	22.9	25.6	22.6

been reported as 0.5–1.0 per 100 000 Live births, when the mild forms are also taken into account, the prevalence has been reported to be as high as 1 per 10 000 live births. Due to problems in the diagnosis of the syndrome, particularly for the mild forms because of the lack of objective diagnostic criteria for this subgroup, the exact prevalence is still unknown. Barisic *et al*[1] have given the overall prevalence including mild and classical forms of CdLS as 1.6–2.2 per 100 000 births.

Prior to the definitive molecular studies, CdLS was thought to be caused by defective expression of a multifunctional protein involved in chromosomal function, gene regulation, and DNA repair[5]. More recently, CdLS has been genetically found to be a cohesinopathy disorder caused by autosomal heterozygous or X-linked mutations in the cohesion core subunits of the genes of SMCA1, SMC3, RAD21, or in the cohesion-associated factors NIPBL and HDAC8[6]. The phenotype of this syndrome is a spectrum that is formed by classical forms as well as nonclassical variants that are caused by pathogenic alternatives in genes involved in cohesion functioning[7].

The characteristic phenotype of patients with CdLS includes thick eyebrows that meet in the midline, a short nose with a depressed or wide nasal ridge, anteverted nares with upturned nasal tip, a long and smooth philtrum, a thin upper lip and downturned corners of the mouth[6]. These phenotypic features may overlap with the appearance of patients with other chromatin disorders such as Wiedemann–Steiner syndrome, Rubinstein–Taybi syndrome, and Coffin–Siris syndrome[8]. Also, patients with this syndrome may present different phenotypic features that are completely dissimilar to each other. This phenotypic diversity poses a major challenge in diagnosing patients with this syndrome in clinical practice.

CdLS is characterized by multisystem involvement. Common craniofacial features of classic form are synophrys, micro-brachycephaly, long and thick eyelashes, a high and arched palate with clefts, micrognathia, short neck, and hairy ears with thickened helices[9]. The most prominent and existing comorbidity that can be seen in almost every patient, particularly in the neonatal period, is gastroesophageal reflux and related complications. Congenital cardiac abnormalities such as ventricular septal defects, ASD, PS, tetralogy of Fallot, hypoplastic left heart syndrome, and bicuspid aortic valve can be diagnosed in approximately 25% of patients[10]. Syndactyly, clinodactyly, bradydactyly, oligodactyly, clubbed feet, poikilothermia, pectus excavatum, scoliosis, and hip dislocation or dyplasia are common and diagnostic musculoskeletal findings[3,11]. Renal functions may be adversely affected by structural kidney and/or urinary tract anomalies such as vesiculoureteral reflux, pelvic dilation and renal dysplasia[12]. Peripheral neuropathy, autonomic dysfunction, and seizures are reported as possible neurodevelopmental manifestations.

Patients with CdLS with all genetic variants may have global developmental delays, intellectual disabilities, and prenatal and postnatal growth retardation. When evaluated from this point of view, prenatal diagnosis becomes even more important.

The major indications for prenatal diagnosis are a history of having an earlier child with CdLS, a recent pregnancy in a family with a known genetic problem in a *CdLS* gene, and suggestive features of CdLS on fetal ultrasonography[7]. Since our patient and his family were Syrian immigrants and only his delivery was performed in a state hospital in Turkey, there was no prenatal care according to the information we received from the parents. The diagnosis of CdLS was made after the genetic examination performed in our university hospital when our patient was aged 5 mo. The absence of prenatal care and the presence of other pathologies that may cause growth retardation can cause delays in diagnosis, as in our patient.

There are some challenges for clinicians when facing CdLS patients, and our patient underwent four different surgical operations under general anesthesia in 85 d. Airway management is of particular interest. Different authors have referred to difficult airway probabilities, and various reports have mentioned some device suggestions instead of a conventional laryngoscope such as a laryngeal mask airway, fiberoptic endoscopes, and a Pentax Airway Scope GlideScope video laryngoscope[13-15]. Uncomplicated airway management, particularly in the intraoperative period has also been reported[16,17]. In our case, micro-brachycephaly, short neck, macroglossia, micrognathia, and a cleft lip and palate were some craniofacial features that could increase the probability of difficulties in airway management. Although no airway difficulties were encountered during the intraoperative period, our patient suffered postoperative respiratory problems, failed to reach adequate extubating criterion during the weaning period, and could not be extubated until postoperative day 5. Despite intermittent CPAP treatments, the patient underwent a tracheotomy in line with ENT consultant's recommendations after diagnosing moderate tracheomalacia and suboptimal vocal cord movement.

Gastroesophageal reflux and related complications such as esophagitis, aspiration, chemical pneumonitis, and irritability can be seen in almost every CdLS patient, particularly in the neonatal period[18]. Gastroesophageal reflux and intestinal malformations may lead to regurgitation and aspiration of gastric contents, particularly in the anesthesia induction period. Although rapid sequence induction and intubation should be considered as a precaution to avoid regurgitation and aspiration of gastric contents, we did not have a chance to apply these until a secure intravenous line had been achieved.

Another possible severe risk is the presence of perioperative nutritional problems and underfeeding in the postoperative course. Malnutrition is an accepted problem in children with congenital heart disease because of unmatched energy requirements with poor feeding, and inadequate caloric intake[19]. Major surgery (mainly upper gastrointestinal surgery and cardiac surgery) and existing gastrointestinal abnormalities are additional risk factors. Although early oral feeding is the recommended mode of nutrition for surgical patients in the early postoperative period, EN is considered admissible for any surgical patient at nutritional risk[20]. We started TPN on postoperative day 1 and EN *via* a nasogastric tube on postoperative day 5 after extubation. Early extubation is particularly critical for patients with a cleft palate as prolonged intubated may impair sucking and swallowing reflexes. EN is problematic in the pediatric CICU, and satisfactory EN support is provided after performing the PEG procedure.

PS occurs in 0.6–0.8 per 1000 live births, and its prevalence is 8%–12% of all congenital heart defects[21]. It can be an isolated lesion or associated with other congenital heart defects such as ASD, ventricular septal defect, PDA, and tetralogy of Fallot[22]. There are three different morphological types of valvular PS. In the classic or dome-shaped pulmonary valve, there is a narrowed central orifice with a preserved mobile valve mechanism. In the dysplastic pulmonary valve that represents approximately 20% of all cases, there are poorly mobile and marked myxomatoses-thickened leaflets without commissural fusion. In the third type, the pulmonary valve is unicuspid or bicuspid and mostly seen in the context of tetralogy of Fallot[23]. Obstruction of the right ventricular outflow tract leads to a rise in right ventricular afterload, which also induces ventricular muscle hypertrophy producing thicker chamber walls, decreased compliance, increased ventricular stiffness, and higher right atrial filling pressures[24]. As the obstruction increases, cardiac output and the patient's physical activity is increasingly limited due to impaired compliance and worsening diastolic dysfunction. When obstruction becomes critically severe, right ventricular systolic and diastolic dysfunction and ischemia can occur. At this point, chest pain, dyspnea, arrhythmia, syncope, and even sudden cardiac death can be seen. For patients with severe PS (peak-to-peak transcatheter gradient > 50 mmHg), who have not undergone surgical correction, poor long-term outcomes have been reported. In contrast, excellent survival rates have been achieved in patients with > 80 mmHg

gradient after surgical valvotomy[25]. In our patient, the cardiac pathology was severe due to the severe PS with 91 mmHg gradient, which was combined with PDA and ASD, and the main purpose of the surgical operation was to prolong the lifespan of the patient.

The severity and characteristics of stenosis determine the clinical consequences and optimal treatment modality. An obstruction in the right ventricular outflow tract with a gradient of > 64 mmHg (peak velocity > 4 m/s) on Doppler imaging indicates repair [22]. Although balloon valvuloplasty is the first-choice treatment option, in some circumstances, such as hypoplastic and severely dysplastic valves, infundibular stenosis, and associations of other congenital lesions, surgical repair may be required. Due to the various risks associated with the surgical intervention such as procedural complications, prolonged hospitalization and recovery times, and a higher cost than nonsurgical interventions, surgical intervention is reserved only for more complex diagnoses or in cases in which intervention is not possible[26]. In our case, the guidewire could not be passed through the severe stenotic pulmonary valve, and the decision to undertake a surgical repair was made due to procedural failure.

Severe PS and pulmonary hypertension increase right ventricular work while decreasing left ventricular output, and are significant independent risk factors for mortality and morbidity in both cardiac and noncardiac surgery[27]. The essential targets of anesthetic management are the maintenance of adequate right ventricular preload and contractility and left ventricular afterload with decreasing systemic and pulmonary vascular resistance. In the intraoperative period, right ventricular filling pressure is significant in optimizing myocardial contractility and maintaining hemodynamic stability[28]. Intravascular volume status is also crucial as acute right heart failure and cardiac arrhythmias can easily be precipitated by excessive intravenous fluid. The total amount of intravenous fluids and erythrocyte suspension is limited during surgery. Although all volatile anesthetics may worsen right ventricular dysfunction by reducing preload, afterload, and contractility, desflurane and nitrous oxide, unlike others, are reported to increase pulmonary vascular resistance and should be avoided[29].

CONCLUSION

CdLS is a complex disease in which many organs and systems are affected. The existence of milder forms of CdLS has been demonstrated by advanced molecular and genetic diagnostic methods. In addition, with the medical developments in recent years, the expected lifespan of children with CdLS has been prolonged, with these patients undergoing cardiac surgery more frequently. In CdLS patients who present various anesthetic challenges, anesthesiologists, cardiovascular surgeons, and pediatricians may face unexpectedly unusual perioperative courses with additional difficulties in congenital open-heart surgeries.

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REVIEW

Exercise stress echocardiography: Where are we now?

Carlos Alberto Cotrim, Hugo Café, Isabel João, Nuno Cotrim, Jorge Guardado, Pedro Cordeiro, Hortense Cotrim, Luis Baquero

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Abstract

Exercise stress echocardiography (ESE) is a widely used diagnostic test in cardiology departments. ESE is mainly used to study patients with coronary artery disease; however, it has increasingly been used in other clinical scenarios including valve pathology, congenital heart disease, hypertrophic and dilated cardiomyopathies, athlete evaluations, diastolic function evaluation, and pulmonary circulation study. In our laboratories, we use an established methodology in which cardiac function is evaluated while exercising on a treadmill. After completing the exercise regimen, patients remain in a standing position or lie down on the left lateral decubitus, depending on the clinical questions to be answered for further evaluation. This method increases the quality and quantity of information obtained. Here, we present the various methods of exercise stress echocardiography and our experience in many clinical arenas in detail. We also present alternatives to ESE that may be used and their advantages and disadvantages. We review recent advances in ESE and future directions for this established method in the study of cardiac patients and underline the advantage of using a diagnostic tool that is radiation-free.

Key Words: Exercise stress echocardiography; Coronary artery disease; Valve disease; Athletes; Intraventricular gradients; Children

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Core Tip: The fair cost, safety, diagnostic accuracy, ability to evaluate functional capacity, and lack of radiation use associated with exercise stress echocardiography (ESE) render this method a first-line procedure for patients with suspected or confirmed coronary heart disease. The evaluation of Doppler data and the enormous amount of information obtained during and after exercise, including in a standing position if appropriate, in patients with hypertrophic cardiomyopathy, athletes, syndrome X patients and patients with valve and congenital heart disease necessitates the use of ESE.

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INTRODUCTION

Coronary artery disease is highly prevalent and has led to the development of reliable and accessible noninvasive diagnostic techniques. Stress echocardiography is accepted as a valuable method for the detection of myocardial ischemia[1,2] and overcomes the limitations imposed by the widely used treadmill stress test. In our centers, stress echocardiography is preferentially performed using a treadmill exercise protocol. We use pharmacological stress echocardiography only to evaluate aortic stenosis patients with severe compromise of left ventricular function, to determine myocardial viability or when patients cannot exercise adequately.

As a rule of thumb, any patient capable of physical exercise should be tested with an exercise modality, since the integrity of the electrocardiogram (ECG) response is preserved and valuable information regarding functional status is provided. Performing echocardiography at the time of physical stress also allows links to be drawn among symptoms, cardiovascular workload, and wall motion abnormalities. When treadmill exercise is performed, scanning during exercise is hard but possible. Consequently, the first protocols in our and other echo labs[3-5] relied solely on postexercise imaging[6]. In this case, it is imperative to complete postexercise imaging as soon as possible. As an alternative, bicycle exercise echocardiography is conducted with the patient either upright or recumbent and allows imaging during the various levels of exercise, which can be easier and more informative than postexercise imaging with a treadmill. The exercise stress echo in clinical practice is useful in many different conditions aside from coronary disease, from valvular to congenital heart disease and from heart failure to hypertrophic cardiomyopathy (HCM), to optimize risk stratification and timing of intervention.

METHODOLOGY OF EXERCISE STRESS ECHOCARDIOGRAPHY

Exercise tests on a treadmill

Patients are questioned about their symptoms, past cardiovascular medical history, and risk factors for coronary artery disease. After an explanation and preparation for the procedure by a cardiovascular technician, a classic 12-lead ECG is obtained. The Bruce protocol, by routine, is performed. The criteria for test interruption are fatigue, angina with increasing intensity, dizziness, ST-segment depression greater than 3 mm, complex ventricular arrhythmias, systolic blood pressure greater than 240 mmHg or diastolic blood pressure greater than 130 mmHg or a blood pressure drop greater than 20 mmHg during exercise. The test result is considered positive for myocardial ischemia when ST-segment depression occurs, with a horizontal or down-sloping displacement greater than 1 mm measured 0.08 s after the J point. The ECG exercise treadmill test result is considered inconclusive when there are baseline ST-T changes (left bundle branch block, the digitalis effect, or left ventricular hypertrophy) or when the patient does not reach 85% of the theoretical maximum age-adjusted heart rate. The test result is considered negative for myocardial ischemia when the patient's heart rate exceeds 85% of the theoretical maximum age-adjusted heart rate and the previously mentioned changes did not occur.

Exercise stress echocardiography on a treadmill

We started performing exercise stress echocardiography (ESE) with an evaluation of cardiac function during exercise more than 20 years ago. The method was published and is also used by other groups[4, 5].

Patients undergo symptom-limited treadmill exercise tests following the standard Bruce protocol. A modified Bruce protocol can be used for the assessment of non-coronary artery disease, allowing an easier evaluation of Doppler parameters than that offered by the classical Bruce protocol. Standard 12-channel electrocardiographic monitoring is performed. Blood pressure, heart rate, and 12-lead electrocardiography are performed at baseline and at each stage of the exercise protocol. Before starting an exercise test, a baseline echocardiogram is performed in the left lateral decubitus position for an initial assessment, with 2D and M-mode image acquisition in at least four planes, *i.e.*, parasternal long axis, parasternal short axis, apical four-chamber, and apical two-chamber, with Doppler parameters being evaluated and stored based on the patient's condition. Two-dimensional echocardiographic images are obtained from the parasternal (long axis and short axis) and apical (four-chamber and two-chamber) views, in the standing position at rest, during exercise (Figure 1) and at peak exercise, in the immediate postexercise period, and during the recovery period. Peak and immediately postexercise imaging acquisition is obtained using a continuous image-capturing system. After the test, those frames with the best image quality in each view are selected. The acquired digitized images are reviewed and compared in digital side-by-side quad-screen format within the echocardiographic equipment. After the exercise test is stopped, when appropriate, the patient is quickly placed in the left lateral decubitus position, and images are reacquired in the same plane. When relevant, for example, for the detection and evaluation of intraventricular gradients (IVGs) in HCM or in symptomatic athletes, the patient remains standing after finishing the stress test, and echocardiography is carried out in this position. For the evaluation of left ventricular regional wall motion abnormalities, we use the model that divides the left ventricle into 17 segments[7]. Ischemic changes are considered when the segments develop hypokinesia, akinesia or dyskinesia. However, when an akinetic segment becomes dyskinetic, it is not considered to be ischemic. Most groups that use exercise echocardiography in treadmill exercise acquire echocardiographic images only before and after exercise[6].

APPLICATIONS OF ESE

Ischemia detection

Stress echocardiography has demonstrated substantial clinical relevancy in ischemia detection because of its high sensitivity and specificity[8,9] both in patients without antecedents of prior intervention and in those previously submitted to percutaneous coronary intervention[10] or coronary artery bypass graft surgery[11]. Women have a higher rate of false-positive results with exercise electrocardiographic testing. In this group, stress echocardiography has been shown to be an accurate method for ischemia detection[12]. In patients with left ventricular hypertrophy, stress echocardiography has a sensitivity of 84% and a specificity of 75% for the detection of ischemia[13], substantiating its use in clinical practice. Detection of ischemia with exercise electrocardiographic testing is not possible in patients with left bundle bunch block. ESE may also be limited in these patients because of the paradoxical motion of the interventricular septum. In a series of 30 patients with left bundle branch block, Pellika and colleagues showed that ESE had 60% sensitivity for ischemia detection, compared to 88% sensitivity with dobutamine stress echocardiography (DSE)[14]. The prognostic accuracy of myocardial perfusion and stress echocardiography appeared similar. Although these conclusions are based on a small sample study, DSE was preferred to ESE for this subgroup of patients in our center. Detection of ischemia, as well as its magnitude, has obvious prognostic implications. In a study with more than 500 patients, Marwick *et al*[15] demonstrated that the use of stress echocardiography to detect ischemia provides additional prognostic information. The comparative advantage of exercise echocardiography with image acquisition during treadmill exercise was clearly demonstrated by the Peteiro *et al*[16,17], who showed an increased diagnostic accuracy with this methodology compared with evaluation only before and after exercise. Those results confirm our preliminary results from a previous small study. In comparison with other widely available imaging techniques, ESE has some advantages, including greater safety, with only one adverse event in every 7000 exams compared to one adverse event in every 700 dobutamine stress echocardiograms[18]. This issue was addressed by the international practice guidelines[19], reserving drug-induced stress echocardiography for those unable to perform an exercise stress test. Another important advantage of ESE is that the procedure does not involve radiation[20,21].

Evaluation of patients with suspected or confirmed pulmonary hypertension, including patients with mitral stenosis.

The evaluation of pulmonary artery systolic pressure at rest using echocardiography is common and of great clinical importance. A diagnosis of pulmonary arterial hypertension is based on a mean pulmonary artery pressure > 25 mmHg at rest[22]. Although usual assessment is generally carried out at rest, the clinical utility of determining pulmonary artery systolic pressure during exercise has been demonstrated in various clinical situations, such as heart failure, rheumatologic disease, mitral stenosis and mitral regurgitation[23-27].



Figure 1 Echocardiographic data acquisition with the patient in the orthostatic position during exercise on a treadmil. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26 [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

In one study using our methodology[23], we included 56 patients with mitral stenosis and determined the gradient between the right ventricle and right atrium using continuous wave Doppler in left lateral decubitus (LLD) before exercise testing, in the orthostatic position at peak workload before termination of the test, and in LLD in the first 60 s of the recovery period. The mean gradient between the left atrium and left ventricle was also determined at different stages of the test in patients with mitral stenosis. In patients with mitral stenosis, the effect of access to gradient values obtained at peak workload on clinical management was compared to the effect if this parameter had been evaluated only in the immediate recovery period. In this group of patients, basing the decision to treat on pulmonary artery systolic pressure > 60 mmHg at peak workload resulted in 10 patients (18% of those with this pathology) being referred for valvuloplasty or valve replacement. These patients would have continued with medical therapy if the decision had been based on the values obtained during the recovery period.

In the same study's 42 patients with scleroderma, basing the decision for right heart catheterization in patients with systemic sclerosis on the gradient between the right ventricle and right atrium at peak exercise resulted in 13 more patients (30% of those with this pathology) being referred for this procedure than if it had been based on the values obtained only during the recovery period, *i.e.*, as ESE is usually performed in most centers.

In patients with a previous history of thromboembolic pulmonary disease, with mild or moderate pulmonary hypertension or with unclear cause for symptoms, we have used ESE to help in clinical evaluations and decision-making. In one published case[28], right ventricular dilatation occurred that was not seen before exercise and that was detected only during exercise. The right ventricle after exercise was also normal.

It is often difficult to obtain adequate tricuspid regurgitation signals for the measurement of the gradient between the right ventricle and right atrium, potentially leading to its underestimation. Therefore, air-blood-saline contrast during exercise has been utilized to improve the Doppler signal in several clinical situations. We have concluded that the utilization of contrast should probably be limited to patients with a poor tricuspid regurgitation jet signal, to obviate the high number of false positives results that occur. Therefore, contrast should be an aid to obtain a measurable gradient but should not be used routinely in patients submitted to this type of study.

Intraventricular obstruction induced by exercise in athletes with "positive screening" in medical evaluations for participation in sports

The development of IVGs during exercise is a rare finding and occurs usually in association with left ventricular hypertrophy[29,30]. The development of IVGs during exercise has been described in athletes [31]. The clinical meaning of this observation and the most suitable exercise technique (upright exercise *vs* semisupine exercise *vs* lying supine after exercise) to trigger IVGs remain unknown. Supine exercise and lying supine after exercise are less technically demanding but also less physiological than upright exercise.

Importantly, in usual daily life, after exercise, individuals generally do not lay supine, as practiced in postexercise treadmill stress echocardiography in most cardiology departments. Therefore, we have conducted other studies in which we searched for IVGs during ESE, in a standing position after exercise, in athletes who screened positive according to the Guidelines of the European Society of Cardiology[32] and who also had an echocardiogram considered normal at rest. In that investigation[33], 139 athletes (135 were amateur, and four were professional; 30 were female), with a mean age of 22 ± 9.9 years (age

range from 9 to 56 years old), were included. The athletes participated in the following sports: athletics (58), soccer (51), tennis (7), basketball (5), handball (5), swimming (5) and other (8).

As stated, all athletes screened positive: 112 had symptoms (chest pain, dizziness, or syncope) or a positive exercise ECG treadmill test (11 athletes). Of the 27 asymptomatic athletes, four had a history of sudden death in the family, three had slight mitral valve prolapse without mitral regurgitation, 18 had alterations in their ECG, and three had ventricular premature beats on ECG. All the athletes had a normal resting echocardiogram, *i.e.*, no left ventricular hypertrophy or significant valve pathology.

Of all 139 athletes, 52 (37.4%) developed IVGs (group 1), and 87 (62.6%) did not develop IVGs (group 2) (we considered only IVGs greater than 50 mmHg).

Of the 52 athletes in group 1, 23 (63%) developed systolic anterior motion (SAM) of the mitral valve associated with significant IVG during exercise (Figure 2).

In group 1, IVGs were present in all athletes after exercise in the standing position. In seven of these athletes, IVGs were detected only at this timepoint.

Small IVGs are a common phenomenon. Three mechanisms have been proposed by Yotti[34] regarding their significant increase during exercise: (1) Increase in nonobstructive physiological gradients; (2) End-systolic obstruction secondary to ventricular cavity obliteration; and (3) Midsystolic obstruction caused by SAM of the mitral valve with restriction of ejection. However, for SAM to occur, there must be some alteration in the geometry of the ventricular chamber or in the mitral valve apparatus. This was not the case in our athletes, although it has been demonstrated that IVGs can be caused by maneuvers that change loading conditions in structurally normal hearts[35] that participating in sports can bring about such changes. In a study with children[36], IVGs induced by exercise were considered normal; however, the clinical data for the population were not contextually clear[37], and further studies are needed to better clarify the clinical meaning of these gradients.

In our study, the athletes had normal echocardiograms, indicating that a morphological study of their hearts would probably reveal no abnormalities[38,39]. The phenomenon that we detected before, during and after exercise testing, in the standing position – IVG associated with mitral valve SAM at the end of and after exercise – could well have been responsible for the positive screening in the athletes in group 1. Medical examinations of these athletes were carried out mostly because of symptoms arising from intense effort; for most of the athletes, we did not reproduce the symptoms during exercise, but we detected an anomaly in cardiac function[31] that, in our opinion, may explain the symptoms. The abnormality, however, was only detectable before (two athletes), during (41 athletes), and after exercise in the orthostatic position (52 athletes). These phenomena are not among the diagnoses that contraindicate participation in competitive sports according to the recommendations of the 36th Bethesda conference[40] and the European Society of Cardiology[32]. It is possible that the phenomena observed in these athletes could be among the causes of sudden death in cases where anatomopathological examination reveals no abnormalities, and we accordingly advised the athletes to suspend their participation in sports and referred them to a sports medicine center for further assessments. In our opinion, the cases described in which significant abnormalities in cardiac function were found before, during, and more clearly after exercise (Figures 3 and 4) in the standing position suggests that this methodology should be applied to the athletes who have symptoms related to exercise and no structural abnormalities. We emphasize that this phenomenon has almost been excluded as a normal response to exercise in healthy adults[41]. The results of this study underscore the importance that the literature attributes to searching for IVGs as a possible cause of symptoms related to exercise in athletes and in pediatric populations[42,43].

The athletes in whom these findings were detected should also undergo long-term follow-up to accurately assess the clinical significance of the findings.

To the best of our knowledge, our group provided the first report on the importance of the standing position before and after exercise to detect IVGs in symptomatic athletes without left ventricular hypertrophy. Our study of the evaluation of IVGs with continuous wave Doppler also constitutes a new step in the use of stress echo as a diagnostic tool beyond is initial use for coronary heart disease[44] and in the use of a new stressor: the standing position[33,45].

Considering our experience, ESE, with evaluation in an upright position before, during, and after exercise, should possibly be part of a new diagnostic algorithm whenever athletes have a positive screening on a medical evaluation. This is especially true if the athletes have symptoms.

Monitoring beta-blocker use

Because most of the athletes evaluated in the previous study were treated with beta-blockers, we conducted an open-label, prospective, nonrandomized study to provide proof-of-concept that ESE can guide tailored treatment in athletes with positive screenings[46] on medical evaluations for participation in sports and who develop IVG and mitral valve SAM on exertion. Of the 52 athletes who developed IVGs, 35 repeated ESE while taking beta-blockers. Thirty-three had exercise-related symptoms or a positive exercise ECG. Thirty athletes (85%) showed improvement on the follow-up ESE, with a significant reduction in gradients (Figure 5) and SAM.

We concluded that for athletes with positive screening - mostly by symptoms - on medical evaluations for participation in sports and IVG on exertion, treatment with beta-blockers prevented the occurrence of IVGs and SAM or significantly reduced their magnitude. These changes were associated

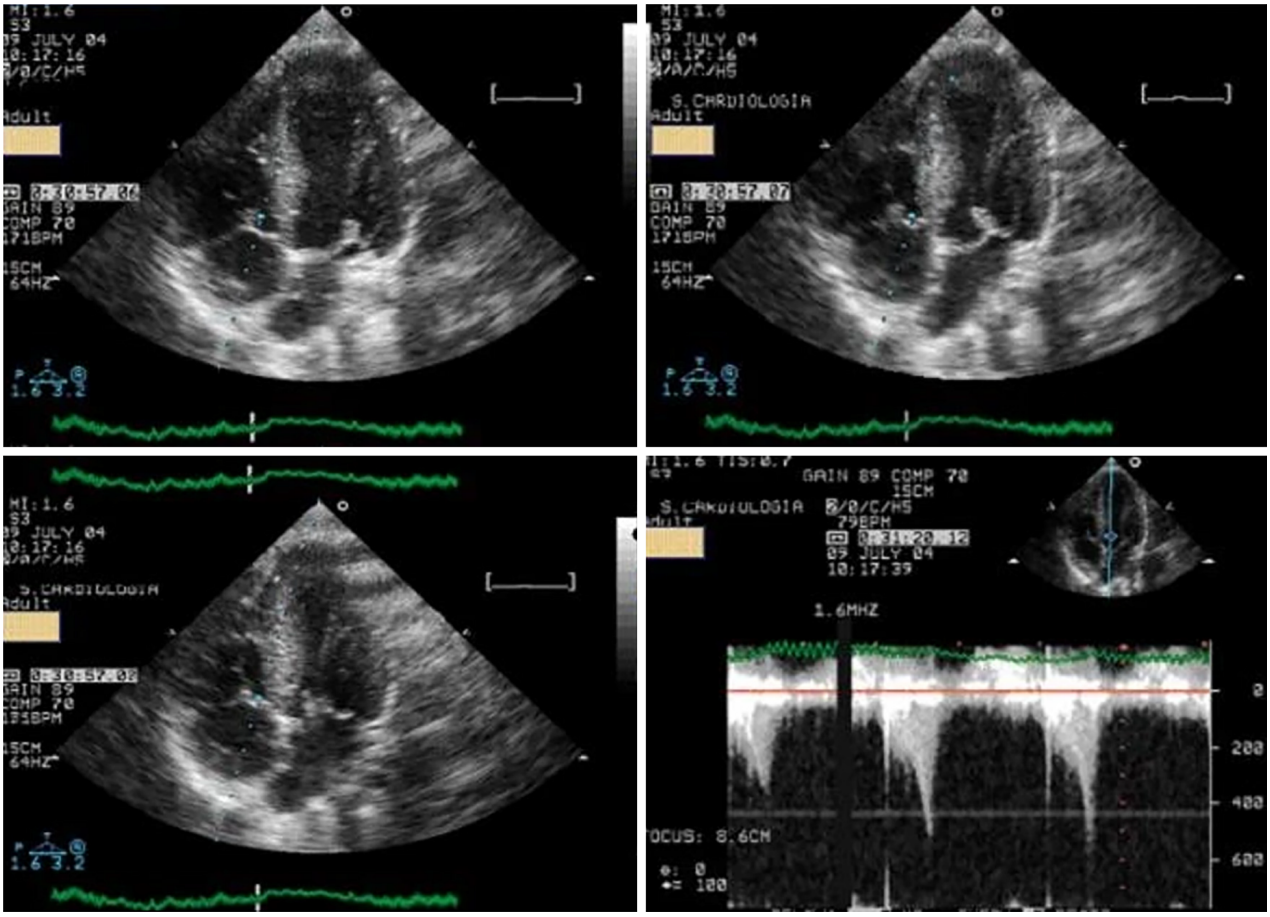


Figure 2 Systolic anterior movement of the mitral valve and significant intraventricular gradient detected at peak exercise. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26 [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

with a significant reduction in heart rate at peak exercise and reflect clinical improvement, which occurred in 85% of the study population.

Exercise echocardiography represents a useful tool to evaluate athletes who screen positive and have a normal rest echocardiogram, allowing identification for beta-blocker therapy. The findings of this study represented a proof-of-concept of tailored beta-blocker therapy, driven by exercise Doppler echocardiography results, in symptomatic athletes and were also observed by other authors[47].

Intraventricular gradients in patients with cardiac X syndrome

The development of IVGs during DSE has been reported and is commonly associated with symptoms during the study[48,49]. The occurrence of IVGs during ESE is rare[29,30]. In a group of 10 patients who developed IVGs during DSE, we performed ESE and found a small IVG in only one patient. A 23-year-old male with angina and a positive treadmill test, a structurally normal heart, and normal coronary angiography underwent an ESE, and during the study, we unexpectedly detected a 102 mmHg IVG[31] and SAM of the mitral valve. A similar case was reported by Lau *et al*[30] and was treated successfully with beta-blockers. After this first case, we conducted a study for IVG detection during ESE in patients with angina, positive stress electrocardiography, normal coronary arteries, and a normal echocardiogram (cardiac X syndrome)[50]. This study included 91 patients, 44 of whom were women. All patients had angina, positive exercise ECG treadmill tests (four patients had only ischemia in a myocardial perfusion study), normal resting echocardiogram - no left ventricular hypertrophy - and no coronary artery disease on coronary angiography.

Of the whole group, 33 patients (36%) developed IVGs, and 58 patients (64%) did not develop IVGs as defined previously by the authors. In the first group, the IVG at peak exercise was 86±34 mmHg (ranging from 30 to 165 mmHg), and 23 patients (70%) developed SAM during exercise, associated with IVGs. No patients developed segmental wall abnormalities. The results of our study, in which 36% of the patients with normal coronary angiograms and positive treadmill exercise tests developed IVGs, suggest that ST-segment depression may be related with the development of IVGs during exercise, which is possibly involved in the genesis of electrocardiographic changes. The possible association between cardiac X syndrome and IVG development during exercise has previously been described[51,

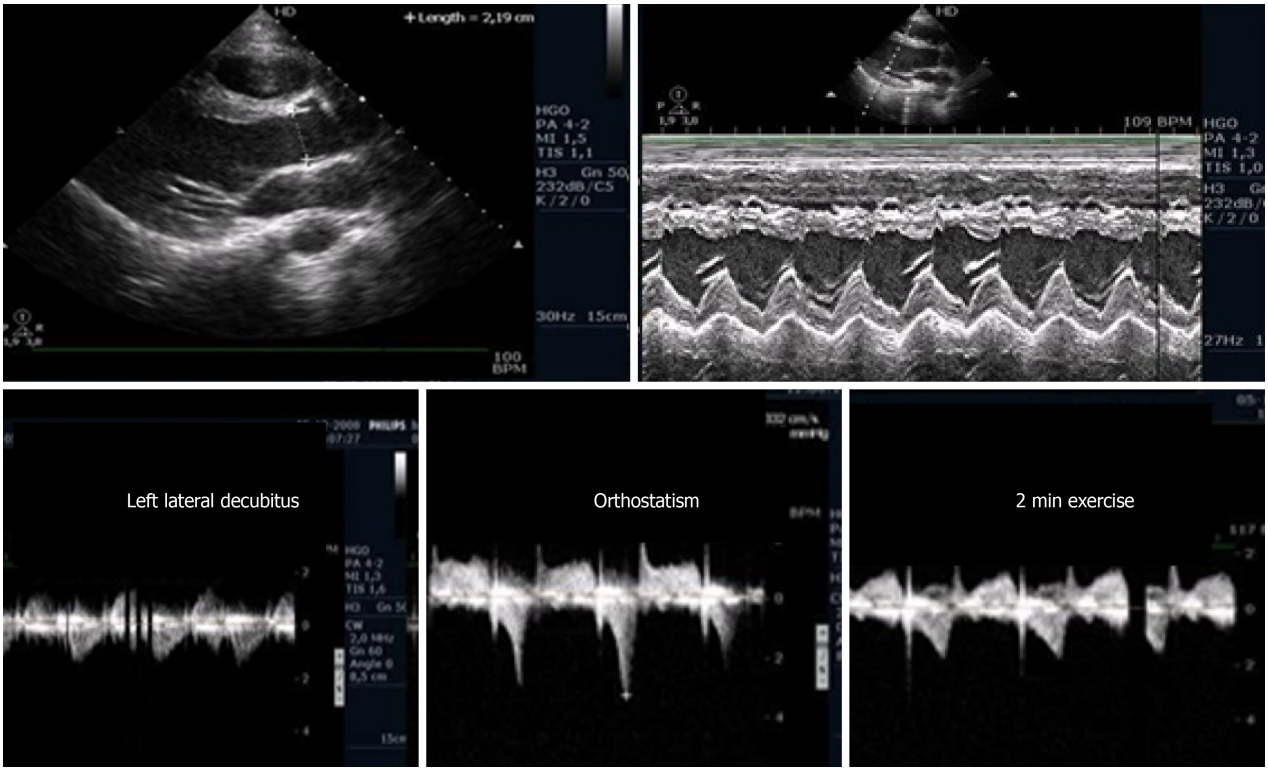


Figure 3 Intraventricular gradient present in the orthostatic position before exercise in an athlete, decreased during the initial phase of exercise testing. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

52], however, some of the patients from these studies had arterial hypertension and left ventricular hypertrophy, more frequently developed IVGs[29] and were therefore excluded based on the definition of cardiac X syndrome[53].

In our study population, we found a great number of patients who developed SAM of the mitral valve in association with IVGs, in contrast to the findings of other authors. We hypothesize that we can detect SAM in a greater number of patients because we use echo throughout the entire treadmill exercise protocol and in the standing position after exercise[45]. The magnitude of the IVGs that we have detected in our patients is also greater for the same reason.

We conclude that a relevant number of patients with cardiac X syndrome develop significant IVGs during exercise. The authors believe that this phenomenon may constitute a new entity that should be included as a factor in the heterogeneous group of patients with angina, ST-depression during treadmill exercise tests and normal coronary arteriography. Because of these results, we believe that ESE should be part of a new diagnostic algorithm whenever patients with angina are suspected of having cardiac X syndrome.

Evaluation of patients with HCM

In our centers, ESE with image acquisition during treadmill exercise (a representation of regular exercise) is also commonly used for the evaluation of patients with HCM, enabling assessment of the outflow gradient during physiologic exercise and in recovery period in LLD[5]. In patients with obstructive HCM under resting conditions, it has been demonstrated that obstruction may increase after the change in position from supine to standing. The LVOT gradient increases in the orthostatic position and continues to increase at peak exercise, but after exercise, the gradient decreases rapidly when measured in LLD, indicating that the assessment of IVGs during the recovery period in the supine position does not reflect changes during effort. The LVOT gradient measured during the recovery period in the supine position does not reflect patients' daily activities (in their daily lives, patients simply do not assume a supine position after an effort) nor the pathophysiology of this condition[54-58]. We unexpectedly found, in one patient, that after exercise, the IVG continued to increase if the patient remained in the standing position. Based on this observation, a new study was conducted[45] in 17 patients diagnosed with HCM based on echocardiographic findings of a nondilated hypertrophic left ventricle in the absence of diseases known to cause ventricular hypertrophy, including 11 patients with obstructive HCM due to an LVOT gradient greater than 30 mmHg under resting conditions and six patients with nonobstructive HCM. Three patients without resting obstruction developed IVGs during

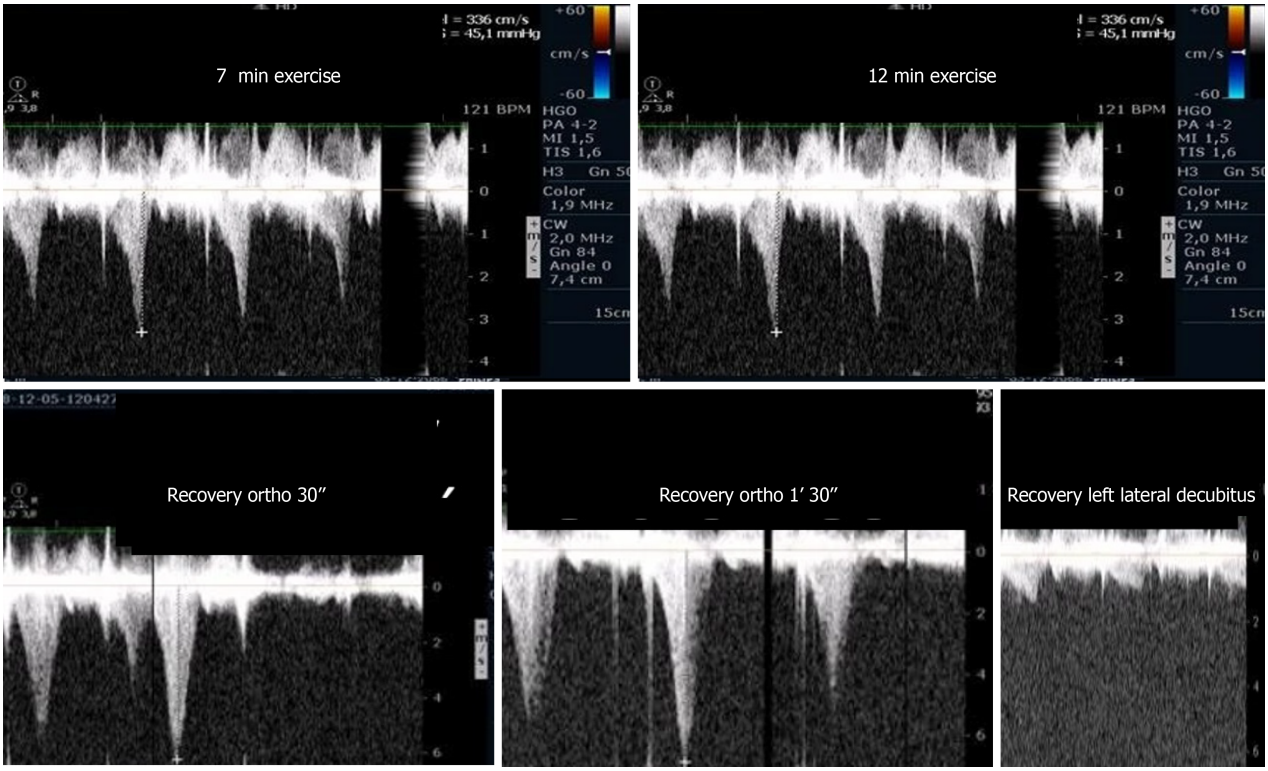


Figure 4 Intraventricular gradient increased during the last portion of the exercise test and after exercise in the orthostatic position. Obstruction suddenly disappeared after placing the athlete in decubitus. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

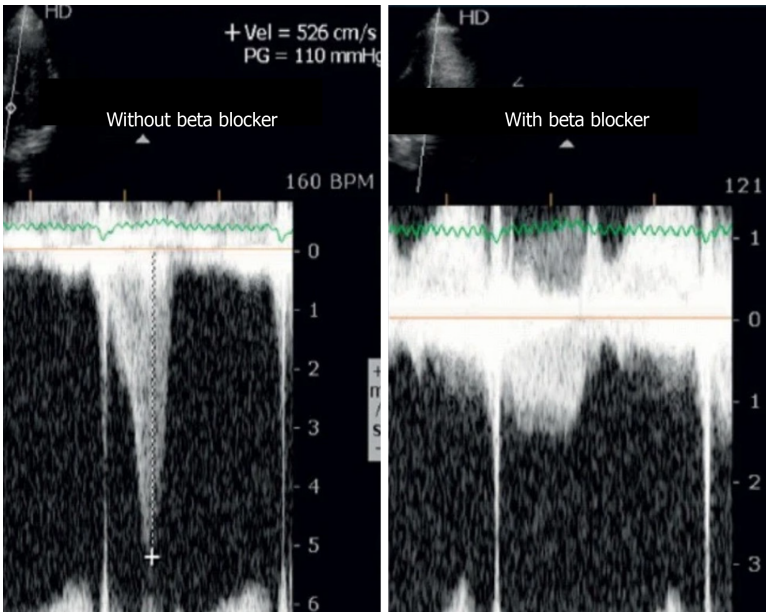


Figure 5 Intraventricular gradient in an athlete assessed before and on beta-blocker therapy. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

exercise; one patient developed a gradient only during the recovery period in the orthostatic position ; two patients had neither resting nor exercise-induced obstruction. All patients with obstructions exhibited increased IVGs in orthostatic recovery. These findings differ from those reported in other studies in which the participants assume the supine position immediately after exercise[59,60]. The importance of the standing position in this group of patients and in patients with other conditions as an

additional and new stressor with important clinical application has been underscored by our group[61] and by other investigators[62-65]. Reflecting on our experience and referencing the literature, we believe that the standing position is the only way these patients can be correctly evaluated, and the mechanisms of their symptoms understood. The clinical importance of upright evaluation during and particularly after exercise was recently underscored by Dimitrow *et al*[66] and Petkow Dimitrow *et al*[67], and we think that laying patients in a supine position after any type of exercise is meaningless from the clinical point of view because this does not usually happen in real life. We recommend[67] that future guideline of scientific societies should clearly state one uniform methodology to be employed by all groups that study and treat these types of patients, with the aim of having a common language that can be used in the future.

OTHER USES OF EXERCISE STRESS ECHOCARDIOGRAPHY WITH ECHOCARDIOGRAPHIC EVALUATION ALSO DURING EXERCISE IN TREADMILL

Aortic stenosis

Most of the recommendations in the guidelines do not have an extensive evidence base, underscoring the need for more clinical investigations in this area. In valvular heart disease, exercise testing is preferred over pharmacological stress testing because it provides insights regarding exertional symptoms and blood pressure variations[27]. Supine bicycle exercise is recommended because Doppler information can be obtained during the different stages of exercise[19] rather than during post-treadmill imaging when substantial and rapid changes in heart rate and loading conditions occur. We and the Peteiro group[4,68,69] disagree with those recommendations, and we conduct echocardiography during treadmill exercise. Additionally, supine exercise is not as physiologic as is treadmill exercise, the equipment is not nearly as widely available as is a treadmill, and the maximum VO_2 attained is at least 10% lower with a bicycle[70]. We routinely use ESE for the evaluation of patients with asymptomatic aortic stenosis. With the literature as support[24,71-73], we utilize ESE to better understand patients, adding information regarding exercise testing[74] and consider surgery accordingly with recommendations.

About one third[71-74] of asymptomatic patients with severe aortic stenosis submitted to exercise tests are in fact symptomatic, but complications do not usually occur in this group of patients. In selected symptomatic patients with aortic stenosis, we employ ESE to better clarify the mechanism of symptoms. As an example, we have published the case of a symptomatic patient in whom symptoms were due to the development of a significant IVG[75] due to SAM of the mitral valve and were treated with beta-blockers. Patients with severe aortic stenosis in whom there is proof that the symptoms have another cause should be considered, more aptly, symptomatic aortic stenosis patients, with symptoms due to other causes (false symptomatic aortic stenosis).

Mitral regurgitation and aortic regurgitation

The assessment of regurgitant mitral flow, with ESE, is mandatory in valvular heart disease in patients with symptoms and mild-moderate mitral regurgitation at rest and in patients with severe mitral regurgitation who have no symptoms[76]. Mitral regurgitation should also be evaluated when studying patients with HCM or heart failure with preserved ejection fraction or pulmonary edema with unknown etiology. Finally, but importantly, mitral regurgitation should also be evaluated in patients with coronary disease to determine if there is an increase in severity or a new appearance of mitral regurgitation[77]. In all these conditions, the presence of mitral regurgitation may contribute to risk stratification and may provide a potential explanation for clinical data susceptible to specific interventions. In aortic regurgitation, as in mitral regurgitation, the evaluation of the inotropic reserve (increase of 5% in the ejection fraction with exercise) can be used to indicate valve surgery in patients with compromised left ventricular function.

Prosthetic heart valves

A significant percentage of patients with aortic valve disease and mitral valve disease who undergo surgery are given a prosthesis[24]. Most prosthetic valves are inherently stenotic, as the effective orifice area is often too small in relation to the body surface, a phenomenon classified as valve prosthesis-patient mismatch[78]. In clinical practice, it is common for normal and abnormal prostheses to produce similar gradients at rest, and therefore, ESE may be valuable for confirming or excluding the presence of prosthetic valve dysfunction or mismatch. This is particularly true for disagreements between symptoms and the hemodynamic profile evaluated by Doppler echocardiography at rest[79-81]. According to Picano *et al*[27], a disproportionate increase in the transvalvular gradient (greater than 20 mmHg for an aortic prosthesis or greater than 12 mmHg for a mitral prosthesis) generally indicates severe prosthesis dysfunction or mismatch.

We use ESE for patients with valve prostheses whenever there exists a discrepancy[82] between the gradients evaluated *via* echocardiography and the presence of the symptoms (Figure 6). Evidence-based

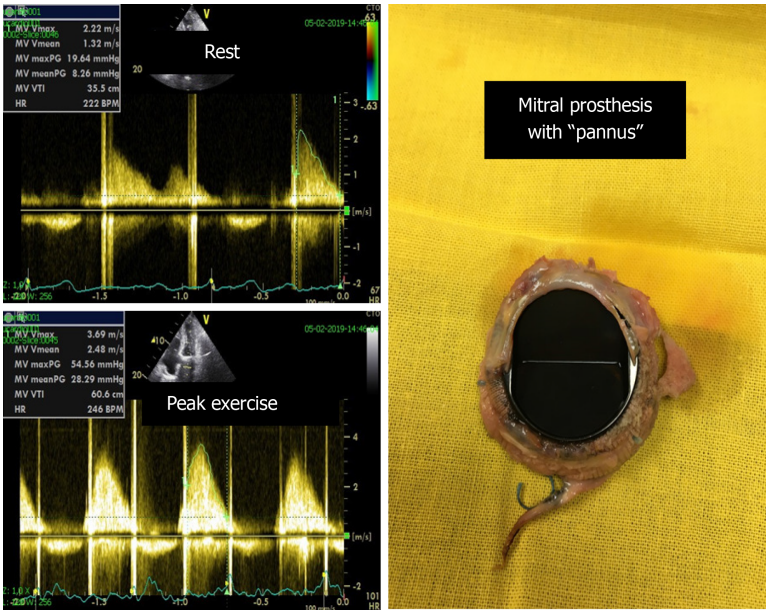


Figure 6 Significant increase in the mean gradient (from 8 mmHg to 28 mmHg) and appearance of severe symptoms with exercise in one patient with a mechanical mitral prosthesis with "pannus".

gradient cut-offs are needed for clinical decision-making. Until such cut-offs are established, we associate exercise Doppler parameters with clinical and exercise test data.

Congenital heart disease and children

ESE is an imaging technique that has been almost exclusively used to evaluate and elucidate cardiac abnormalities in adult patients. Though it may have the potential to offer the same benefit in the pediatric population, it remains an underexplored field, perhaps due to concerns about its safety and applicability in younger children. Given its diagnostic accuracy, ability to assess cardiac reserve and lack of radiation, ESE is increasing in importance as a helpful tool in the clinical assessment of pediatric patients[83].

The usage of ESE in patients with congenital heart disease has been limited despite its potential for broader applications in different clinical scenarios[84]. In patients with congenital heart disease, measuring pulmonary systolic pressure and ventricular function both at rest and during exercise by echocardiography may be essential for determining the etiology of exercise intolerance in these individuals and for better treatment timing.

The presence of any stenotic lesion evaluated by echocardiography can also be studied during exercise, and the data obtained can be used for better clinical decision-making. We performed ESE in one patient with congenital mitral stenosis[3] and evaluated the mean mitral gradient before and at peak exercise and verified the absence of pulmonary hypertension. The exercise Doppler data in conjunction with the exercise data and clinical data led us to keep the patient in close clinical follow-up. The same result was obtained for a young 14-year-old boy, a soccer player, with cor triatriatum sinister who had only a small increase in the mean gradient with exercise (Figure 7).

ESE can also be used to screen for residual narrowing in patients after repair of the coarctation of the aorta by detecting a significant diastolic gradient in the descending aorta during exercise provocation (Figure 8). This evaluation is also feasible with the method that we use to evaluate aortic flow during exercise. A significant increase in the diastolic gradient[85] was used as a guide for patient treatment decisions.

Our group is increasingly using ESE to investigate intraventricular gradients in symptomatic children with normal hearts[33,42,43] or with HCM[86].

We believe that ESE can and should influence clinical decision-making for congenital heart disease patients if pediatric and adult cardiologists with experience in ESE start collaborating.

ESE and diastolic heart failure

We employ ESE in the treadmill evaluation of E/e' as a measure of left ventricular filling pressure. This method has been validated against invasively measured LV filling pressure using simultaneous exercise echocardiography-catheterization[87]. The addition of E/e' during exercise echocardiography improved the sensitivity of the diagnosis of heart failure with preserved heart function compared with that for a resting assessment alone, and the specificity can be improved if the gradient between the right ventricle and right atrium increases above the normal range with exercise. The independent prognostic value of

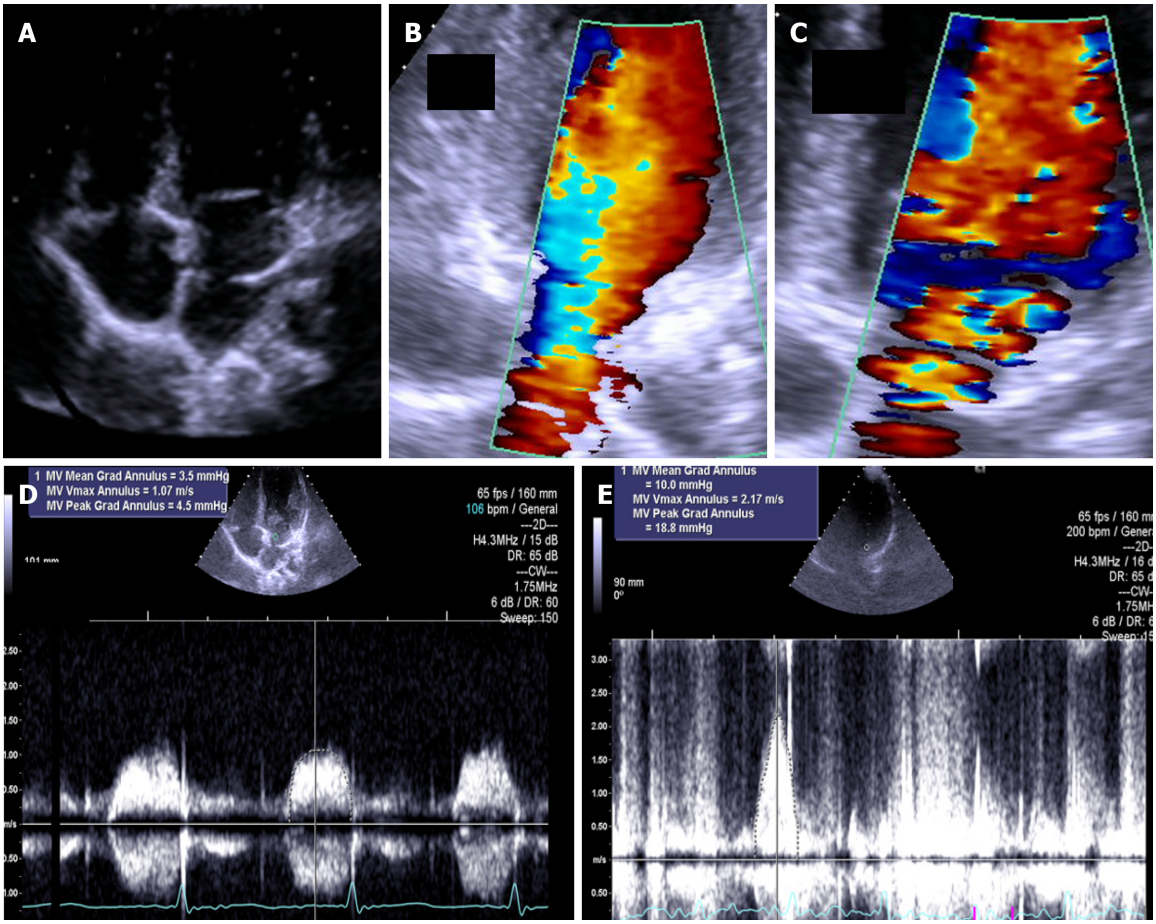


Figure 7 The exercise Doppler data in conjunction with the exercise data and clinical data led us to keep the patient in close clinical follow-up. A: Intraauricular septum in "cor triatriatrium"; B: Color flow before exercise; C: Color flow at peak exercise; D: CW flow before exercise; E: CW flow at peak exercise.

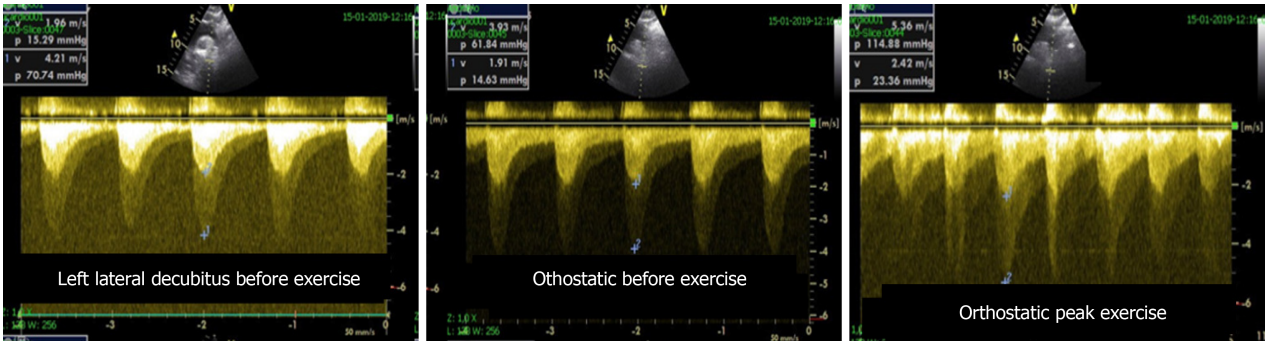


Figure 8 Aortic gradient evaluated in a patient previously treated with a stent. Based on the exercise stress echocardiography results, the patient was treated again.

exercise E/e' has also been documented. We recommend that diastolic stress exercise echocardiography should be considered for patients with unexplained exertional dyspnea and normal diastolic filling pressure on resting echocardiography. The addition of a diastolic assessment to exercise echocardiography improves test sensitivity in patients with dyspnea, and there have been sufficient data that have led us to integrate diastolic exercise testing into our clinical practice.

THE LATEST ADVANCES IN ESE AND THE FUTURE

The exercise stress echo protocol has remained unchanged for more than 40 years[1] and focuses primarily on imaging regional wall motion abnormalities. In recent years, a significant evolution has

occurred, and the technique was further exploited through the inclusion of four variables with recognized clinical, diagnostic, and prognostic importance with ESE, representing the new standard method. The variables are summarized in the ABCD protocol[88]. The four parameters converge conceptually, logistically, and methodologically: (1) Regional wall motion abnormalities[89]; (2) Comets or B-lines measured by lung ultrasound[90]; (3) Left ventricular contractile reserve assessed as the stress/rest ratio of elastance, also called force (systolic arterial pressure by cuff sphygmomanometer/end-systolic volume from 2D)[91]; and (4) Coronary flow velocity reserve in the left anterior descending coronary artery (with color-Doppler-guided pulsed wave Doppler)[92]. This new way to conduct stress echo allows a functional assessment of epicardial coronary artery stenosis (wall motion), lung water (lung comets), myocardial function (left ventricular contractile reserve) and coronary small vessels (coronary flow velocity reserve in the mid or distal left anterior descending artery). In this new "ABCD" protocol, A stands for asynergy (ischemic *vs* nonischemic heart), B stands for B-lines/lung comets (wet *vs* dry lung), C stands for contractile reserve (weak *vs* strong heart), and D stands for Doppler flow evaluation (warm *vs* cold heart because the increase in blood flow increases the local temperature of the myocardium). From the technical and training points of view, B-lines/lung comets are the easiest to evaluate; on the other hand, the acquisition and analysis of left ventricular contractile reserve requires a higher level of competency. Wall motion evaluation is an even more challenging skill to obtain, and coronary flow velocity reserve is the hardest to evaluate. More recently[93], the protocol was amended with E, for EKG-based heart rate reserve (HRR, defined as peak/rest HR < 1.62), which also provides prognostic information, and ABCDE was born. This protocol has been used in the last 5 years in the SE2020 study[94-96], demonstrating utility in defining diagnosis and prognosis criteria with the new data acquired and evaluated with this methodology. This protocol will be now expanded in the new SE2030 study[97], with selected patients by further evaluating flows (mitral regurgitation flow) gradients (intraventricular or valvular gradient), left atrium volume , pulmonary circulation , and right ventricular function . These new steps should be viewed as diagnostic tools that can be used for each patient, according to the clinical condition and question to be answered, to obtain essential information for helping cardiologists design the most appropriate tests for each patient.

ETHICAL AND SAFETY ISSUES RELATED TO CARDIAC IMAGING: THE INSURMOUNTABLE ARGUMENT FOR THE PREFERENTIAL USE OF ESE IN CARDIOVASCULAR PATIENTS

Cardiac imaging methods

When addressing the ethical implications of the diagnostic options for heart disease, the main options include scintigraphy, CT angiography and catheterization, in which the individual is exposed to radiation; magnetic resonance imaging, which may require general anesthesia and intravenous administration of contrast and/or vasodilators; and stress echocardiography, which can be performed using exercise or pharmacological administration.

Regarding pharmacological stress echocardiography, it presents an increased risk of side effects, such as arrhythmias and anaphylactic reactions of greater or lesser severity, related to the administration of dobutamine or dipyridamole and thus requires an ethical review regarding the information to be made available to patients and obtaining informed consent. Regarding stress echocardiography, the European Association of Cardiovascular Imaging and the American Society of Echocardiography emphasize that this is the test of choice for most indications, reinforcing that any patient able to exercise should be tested with an exercise modality because doing so preserves the integrity of the electromechanical response and provides valuable information about functional status. The performance of echocardiography at the time of exercise also allows establishing links between symptoms, cardiovascular workload, wall motion abnormalities and hemodynamic responses, such as pulmonary pressure and transvalvular flows and gradients[98].

In addition to these advantages of exercise echocardiography, it is a radiation-free procedure, significantly reducing the associated ethical implications. Conversely, diagnostic options using radiation present a set of ethical implications that should be considered, namely, patients' right to adequate and complete information, including risks, benefits and alternatives, on the diagnostic procedures available [99].

One of the main risks clearly associated with radiation exposure is the possibility of developing cancer.

According to Brody *et al*[100], there is clear evidence, observed in fundamental cellular processes, that even at in low-dose range of a few tens of mSv, it is scientifically plausible to assume that the risk of cancer will increase in direct proportion to the dose absorbed in organs and tissues. This may explain why cancer rates remain stubbornly high despite the great advances in its prevention and treatment and may, in the United States and soon, surpass heart disease as the main cause of death. One of the explanatory reasons points to the use of radiation in clinical practice, with exposure to medical radiation increasing sixfold between 1980 and 2006, largely due to the use of computed tomography because the

radiation dose from this diagnostic technique is 100 to 1000 times higher than the radiation dose from a conventional radiograph[101].

Informed consent and communication quality

Considering the risks associated with radiation, information and informed consent are some of the ethical aspects to be highlighted. However, the information to be made available to patients involves some challenges, such as defining the exposure dose above which radiation is considered to pose an increased risk of developing radiation exposure-related diseases and determining what type of information should be given; although it is clear that this information should include the type and nature of the procedure, the risks, benefits and possible alternatives, as well as the risks of refusing a certain diagnostic test, it is not easy to define this information because these data vary according to a set of factors, such as patient age and sex[102].

As Picano[103] underscored, these difficulties seem to lead health professionals to develop strategies for risk communication to obtain informed consent to perform diagnostic tests with radiation exposure; such strategies include (1) Not mentioning the risk; (2) Underestimating the risk; and (3) Specifying the risk in detail. Regarding the first strategy, even for interventions with fluoroscopic control, there is no explicit or implicit mention of long-term risks. The risk exists and can be substantial, but it is still not heard by patients or spoken by doctors. Thus, patients' right to information is eclipsed by two forces: efficiency and paternalism. In the second strategy, underestimating risk, obtaining informed consent is part of the "standard" practice of the team, and patients are not exposed to radiation without a consent form being signed. However, information on the actual effects and dose of radiation to be administered is not made available. Finally, the third strategy, full disclosure of risks, addresses the radiation dose to which patients will be exposed as well as the incidence of cancer and/or genetic diseases associated with it, especially if the test is performed for inclusion in a research study.

Regarding the pediatric population, children with congenital or acquired heart disease may be exposed to relatively high cumulative doses of ionizing radiation, resulting from imaging procedures requested, including radiographs, fluoroscopic procedures, such as diagnostic or interventional cardiac catheterizations, electrophysiology tests, CT angiography and nuclear cardiology tests, which in total and because the radiation dose is cumulative, represent an increased risk of cancer throughout life[104].

These children represent a vulnerable population group, considering the continuing need for medical care, and this requires greater ethical and professional responsibility, which underlies the fact that children do not have full decision-making ability nor adequate information about the various available care-related options they consider most suitable for themselves. Thus, health professionals ultimately have the obligation to make decisions that protect the well-being and life of this population and included among these is the decision regarding the diagnostic and therapeutic methods selected, considering the immediate and long-term effects on quality of life[105].

In addition to the previously mentioned ethical implications, such as the right to reliable and complete information and informed consent, which includes the risk of radiation, another ethical aspect is now being recognized, namely, the impact of medical radiation on the planet. This adds a new dimension to the ethical discussion about the best diagnostic approach, namely, the environmental impact, in addition to the medical benefits, costs, and long-term risks of radiation[20,21].

In conclusion, although we are aware of the life-long risks associated with exposure to ionizing radiation and although we recognize the vital role – both diagnostic and therapeutic – of medical imaging procedures, it is only prudent to perform such procedures using the lowest possible radiation doses while also ensuring their diagnostic value[106].

CONCLUSION

Exercise is the most physiologic stressor of all and should thus be preferable in patients who are able to exercise. In coronary artery disease diagnosis, exercise echocardiography is the appropriate first-line test for patients who are asymptomatic or with chest pain or dyspnea as the chief complaint. A major advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and versatile evaluation of valve function and pulmonary hemodynamics and of special subsets of patients, such as patients with heart failure, pulmonary hypertension, valve disease, congenital heart disease, or athletes with symptoms of unknown etiology in search of intraventricular gradients. In all these patients, the physiologic nature of exercise stress and the versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the stress echocardiography laboratory. More importantly, the option of ESE is advantageous over techniques with higher cost and radiation burden for effective primary prevention of cancer, which should begin in the cardiac imaging laboratory.

FOOTNOTES

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ORIGINAL ARTICLE

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Barriers and facilitators to participating in cardiac rehabilitation and physical activity: A cross-sectional survey

Matthew James Fraser, Stephen J Leslie, Trish Gorely, Emma Foster, Ronie Walters

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Abstract

BACKGROUND

Cardiovascular diseases (CVD) have been shown to be the greatest cause of death worldwide and rates continue to increase. It is recommended that CVD patients attend cardiac rehabilitation (CR) following a cardiac event to reduce mortality, improve recovery and positively influence behaviour around CVD risk factors. Despite the recognised benefits and international recommendations for exercise-based CR, uptake and attendance remain suboptimal. A greater understanding of CR barriers and facilitators is required, not least to inform service development. Through understanding current cardiac patients' attitudes and opinions around CR and physical activity (PA) could inform patient-led improvements. Moreover, through understanding aspects of CR and PA that participants like/dislike could provide healthcare providers and policy makers with information around what elements to target in the future.

AIM

To investigate participants' attitudes and opinions around CR and PA.

METHODS

This study employed a cross-sectional survey design on 567 cardiac patients. Cardiac patients who were referred for standard CR classes at a hospital in the Scottish Highlands, from May 2016 to May 2017 were sampled. As part of a larger survey, the current study analysed the free-text responses to 5 open-ended

questions included within the wider survey. Questions were related to the participants' experience of CR, reasons for non-attendance, ideas to increase attendance and their opinions on PA. Qualitative data were analysed using a 6-step, reflexive thematic analysis.

RESULTS

Two main topic areas were explored: "Cardiac rehabilitation experience" and "physical activity". Self-efficacy was increased as a result of attending CR due to exercising with similar individuals and the safe environment offered. Barriers ranged from age and health to distance and starting times of the classes which increased travel time and costs. Moreover, responses demonstrated a lack of information and communication around the classes. Respondents highlighted that the provision of more classes and classes being held out with working hours, in addition to a greater variety would increase attendance. In terms of PA, respondents viewed this as different to the CR experience. Responses demonstrated increased freedom when conducting PA with regards to the location, time and type of exercise conducted.

CONCLUSION

Changes to the structure of CR may prove important in creating long term behaviour change after completing the rehabilitation programme.

Key Words: Cardiovascular disease; Cardiac rehabilitation; Physical activity; Barriers; Facilitators; Patient experience

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Core Tip: The exercise component of cardiac rehabilitation (CR) is considered key to the success of the programme. However, attendance of CR is sub-optimal. The current study examines cardiac patients' opinions and attitudes around several key elements of CR. Participants provided several ideas going forward to get more patients taking part in CR, which at the moment is a real issue. Experiences around physical activity were also explored, and it was found that patients viewed this as contrasting to CR.

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INTRODUCTION

Cardiovascular diseases (CVDs) are now the greatest cause of death worldwide[1]. In the United Kingdom there are currently 7.4 million people living with a specific heart or circulatory disease, accounting for 27% of all United Kingdom annual deaths[2]. Cardiac rehabilitation (CR) can aid recovery and help manage the long-term impact of CVD[3]. The exercise component of CR (exCR) is considered a priority and key to the success of the programme[4]. In the United Kingdom it is estimated that 100000 patients attend exCR, approximately 50% of eligible participants[2]. Developing new methods to increase attendance at exCR is deemed paramount[5]. Such methods could include telehealth, remote monitoring, or a hybrid approach, to increase accessibility and participation[6].

Research has explored factors that prevent and promote patient attendance. Previous systematic reviews have shown that women, older patients, the unemployed and those with comorbidities and depression are less likely to take up the opportunity to conduct exCR[7,8]. In contrast patients who are more affluent, have higher levels of education and who do not smoke are more likely to attend[7,8]. There is also evidence that geographical location may influence uptake but not drop out[8]. Castellanos *et al*[9] found that rural participants or those who live further from CR classes attended fewer sessions in comparison to those in urban areas. This was due to transport, distance and cost related factors. It appears that those with most to gain are the least likely to attend the sessions. Medical staff referral is also a key factor in CR participation and therefore barriers can exist based on general practitioners' (GP) or cardiologists' preconceptions of CR[10].

Reasons that prevent patients regularly attending exCR interventions are not fully understood, however, a large percentage that start do not finish[9,11,12]. The National Audit of Cardiac Rehabilitation[13] found that 77% of patients complete the full CR programme in the United States. However, Ritchey *et al*[14] found only 26.9% of patients above 65 years old in America completed the full

programme. The low rates of uptake and completion are a concern given the known benefits of CR. There is a need to better understand patients' experiences of CR and the influences on attendance and completion.

This study reports on the experiences of CR patients living in the Scottish Highlands. The aim of the present study was to explore participants' experience of CR and their attitudes, opinions, and perceptions of physical activity (PA) by answering the following research questions.

What are the barriers and facilitators to PA and CR attendance and programme completion?

What are the patients' views around deliverable service modifications with a view to improving attendance and completion?

MATERIALS AND METHODS

Design

The data employed in this study was from a larger cross-sectional survey[15]. Cardiac patients who were referred for standard CR classes at a hospital in the North of Scotland from May 2016 to May 2017 were sampled. Participants were excluded from taking part in the study if they had been previously referred, did not live in the catchment area, were < 18 years old, had a non-cardiac or unclear diagnosis or if CR, PA or completing the questionnaire was considered inappropriate for the specific patient. The full methods for this study are reported in Foster *et al*[15].

Procedures

Ethical approval was obtained from the Bromley Research Ethics Committee (study reference number 17/LO/1389, project number 231385). Identified participants were sent a "study pack" consisting of a cover letter, participant information sheet, consent form and questionnaire. A reminder was sent to the participants 2-3 wk later for those that had not responded. The current study analysed the free-text responses to 5 open-ended questions included within the wider survey. Participants were invited to respond to the following open-ended questions on their experience of CR and PA: (1) Did you find the CR classes useful? Please tell us why? (2) We would like to improve attendance at the CR classes- is there anything you think we could do to help you, or others attend? (3) If you did not attend any CR classes could you please tell us your reasons for not attending? (4) How important do you think being physically active is to your health and recovery? And (5) If there is anything else you would like to tell us then please use the space below to do so (*e.g.*, what do you think the local govern-ment/community or NHS could do to help improve the amount of activity you do or make it easier for you to be active?).

Analysis

A thematic analysis following the 6-step method of Braun and Clarke[16] was used to analyse the data. The themes are provided below in the results section, along with quotations from the respondents. The respondents' gender, age and attendance of classes is also provided.

RESULTS

Overall characteristics of patients

A total of 567 participants were invited to take part in the study, 293 (52%) returned a response. 76.7% of respondents were male, and the average age of the participants was 68.4 ± 10.4 years (range 33-90)[15]. In total 279 participants responded to at least one open-ended question of these 70 (25.1%) responded to 1 question, 88 (31.5%) responded to 2 questions, 104 (37.3%) responded to 3 questions and 17 (6.1%) responded to all 4 questions). Participants had a range of heart conditions (NSTEMI, STEMI, stable/unstable angina, heart failure, valve stenosis/regurg, arrhythmia, aortic aneurysm/dissection, type 2 myocardial infarction and valve/angina coronary artery disease) and had on average 2.59 comorbidities. In terms of smoking status, 139 participants were ex-smokers, 112 had never smoked, 24 currently smoked, 4 did not answer. PA levels were wide-ranging, 132 participants conducted "high" levels, 81 conducted "moderate" levels, 58 conducted "low" levels of PA and 8 did not respond. The table below breaks down the responses to the different questions (Table 1).

Responses were explored under two broad topic areas: "Cardiac rehabilitation experience" and "Physical activity". The two topic areas were made up of several sub-themes and codes, and a hierarchy tree diagram was created to display these (Figure 1)[17].

Main topic: CR experience

A wide range of themes were explored within the main topic of "cardiac rehabilitation experience". These were grouped in-to three sub-themes: "Barriers and reasons for non-attendance", "benefits" and "solutions and ideas to increase attendance". Table 2 displays the topic along with the sub-themes, elements, and exemplar quotes. For a detailed explanation of each element see the codebook (Appendix

Table 1 Response rate to questions

Question	Response rate
1	162 (55.2%)
2	130 (44.3%)
3	98 (33.4%)
4	236 (80.5%)

1).

Barriers and reasons for non-attendance

This sub-theme was related to barriers to attending CR classes. These included the type of activity conducted at the classes and physical limitations of respondents due to health conditions. Moreover, the location of the classes was highlighted as an issue especially for those in rural areas where this increases travel time considerably. With regards to timing, the duration and the time the classes were held at, meant those who work during the day could not attend. Whilst some responses reflect the desire to take responsibility for their own rehabilitation, for some it appears that the group exercise environment is not appealing. With respondents citing barriers such as not feeling comfortable in the group environment and in some cases feeling embarrassed. Finally, many respondents noted that poor communication in terms of a lack of advertising or information being available to patients around where or when the classes were to take place was a barrier. Within barriers around communication, respondents also highlighted on several occasions that the follow-up time was lengthy and deemed unacceptable.

Striving for independence

Several respondents highlighted that they chose not to attend CR and felt that they wanted to take responsibility for their own rehabilitation. Reasons included already being active enough, personal preference, feelings that they should take responsibility for their own wellbeing and living in a remote area.

Health benefits

On the whole responses were positive in relation to the outcomes of exCR. Respondents cited both physical and mental health benefits. Physical health benefits included improved fitness and weight loss. Mental health benefits included being able to learn coping strategies and relaxing. Additionally, with reference to the sub-theme of "peer support" respondents noted that being monitored and being able to ask staff questions improved psychological aspects of health. Respondents also noted that following the education element of CR they now knew significantly more about their condition and the best ways to manage it. There were some respondents however that noted they felt no benefits from attending the exCR classes to their health.

Peer support

Respondents highlighted that the social element of CR was important to them. A frequently cited area was in relation to exercising and meeting people with a similar condition. The ability to interact and communicate with like-minded/bodied people came across as one of the most important aspects of attending the group-based CR programme.

Healthcare provider support

Within the element of “benefits” there were several links with reference to the environment and atmosphere created by staff and other attendees. Moreover, being able to gain knowledge and understanding around PA and their condition was important, in addition to feeling free to ask questions helped regain confidence and understanding around their condition. However, it should be noted though that not all respondents felt this way, with some reporting in some instances that they felt out of place. Respondents indicated that staff play a significant role in the exCR experience and in some instances are crucial in promoting uptake, attendance, and completion of these programmes. Generally, most participant responses highlighted that they deemed the support offered from the staff as essential, encouraging, and supportive. Specific types of staff mentioned were physiotherapists, nurses, cardiologists, and gym instructors.

Being in safe hands

Responses consistently referred to increased levels of confidence within a range of contexts but primarily the increased belief that the respondents could exercise without fear. This code was related to

Table 2 Topic: Cardiac rehabilitation experience

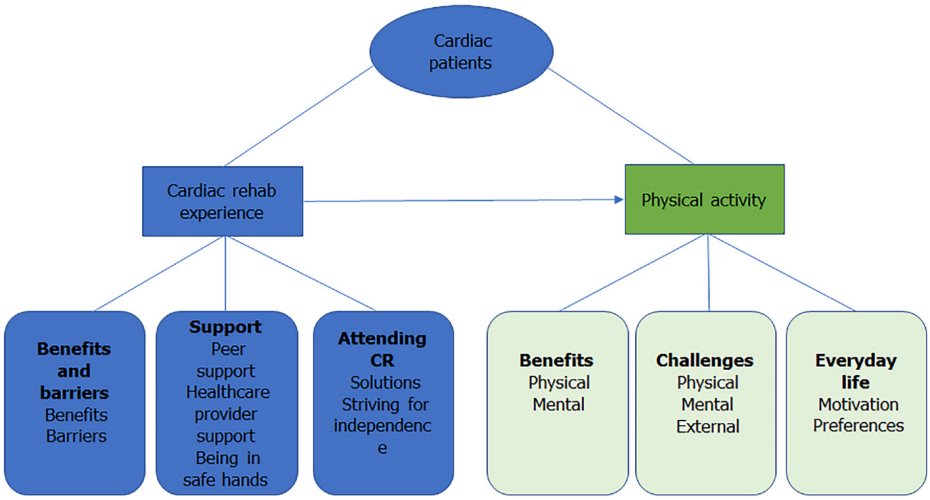
Sub-theme	Element	Description	Example quotes
Barriers and reasons for non-attendance	Barriers to attending regular cardiac rehabilitation	Barriers to attending class. Includes aspects such as the type of activity, distance and timing of the classes as well as lack of information on when the classes are or failure to be referred.	Participant 74: "*Inconvenience, chest pains, shortness of breath when doing physical work*." (Male, 60-79, no classes). Participant 318: "*I found the traveling, 1 hour each way too much*." (Male, 80+, some classes). Participant 135: "*No classes out with working hours*." (Male, 60-79, 9 classes). Participant 259: "*It was difficult to get information as to where and when these classes were*." (Male, 60-79, some classes). Participant 354: "*6 months wait to be contacted regarding rehab is not good enough. We don't all live in large towns or cities*." (Male, 40-59, no classes). P243: "*It is difficult in rural areas to travel to venue far away*." (Male, 60-79, all classes)
	Striving for independence	Wanting to take responsibility for own health, feeling the need to figure it out independently.	Participant 360: "*Living in a relatively remote place I feel it is particularly incumbent on me to take responsibility for my own rehabilitation - and I feel that this should be an underlying principle. This would mean that resources could then be focussed on those who, for whatever reasons, cannot do this themselves*." (Male, 60-79, no classes). Participant 542: "*I had already started my own rehabilitation exercises at local gym.*" (Male, 60-79, some classes).
Benefits	Peer support	Being amongst other people who have shared experiences. This is not always perceived as a good thing.	Participant 575: "*Good to be able to talk to people with similar problems as me. Made me realise I was getting better and helped me regain some confidence.*" (Female, 60-79, some classes). Participant 282: "*Mixed with others and talked about how others coped*." (Male, 40-59, all classes). Participant 441: "*Just felt embarrassed and out of place*." (Male, 40-59, some classes). Participant 48: "*Assumed it would involve group activity. I'm not very good with group activity*." (Male, 60-79, no classes).
	Healthcare provider support	Being supported by knowledgeable staff.	Participant 33: "*They were carried out locally with excellent physiotherapist who carefully provided and monitored exercise which suited each individual member of small group. Relaxed atmosphere, advice and encouragement. Benefit felt*." (Female, 60-79, all classes) Participant 52: "*The pace and programme were tailored to my needs. The physios were superb - always supportive and encouraging. Meeting with and talking to, others in a similar situation was reassuring. It was great to see my heart-rate recovery time improving as the weeks went by. The post-exercise discussions and presentations were very helpful*." (Male, 60-79, all classes).
	Being in safe hands	Being cradled gently in safe hands. Being supported and encouraged to take the steps necessary to return to physical activity. This leads to increasing confidence and motivation.	Participant 430: "*To be able to exercise in an Hospital where I can feel safe. If anything happens to me I know that I have the full benefits to immediate health care that isn't available in the local communities*." (Male, 40-59, all classes). Participant 473: "*I could exercise under supervision which took away anxiety about how much to do, how much to push myself. I could ask questions, no questions too small or silly, provided reassurance and enabled me to do exercise at home without having to worry*." (Female, 40-59, some classes). Participant 327: "*After my cardiac event I felt some apprehension to participating in physical activity, but after attending a session, I felt more confident.*" (Male, 60-79, all classes). Participant: 367: "I felt motivated and encouraged to carry on with exercises at home." (Female, 60-79, all classes).
	Health benefits	Benefits and outcomes gained through attending classes. Includes both physical and mental benefits as well as increased knowledge of their condition.	Participant 146: "*They restored my fitness following surgery. They were convenient and well run*." (Male, 60-79, all classes). Participant 449: "*Controlled and supervised exercise giving much benefit to wellbeing and fitness*." (Male, 60-79, all classes). Participant 599: "*They helped me to understand that exercise helps not hinders recovery*." (Male, 60-79, all classes).

		Participant 149: "*Understanding of illness explained well and why the exercises and diet helped recovery taking into account my Parkinson's disease.*" (Male, 60-79, all classes). P49: "*Did not feel any significant difference to my condition - but I'm sure they are beneficial.*" (Male, 60-79, all classes). P50: "*I only attended one session, because I was getting reasonable exercise at home and thought there would be others who would benefit more than me .*" (Male, 60-79, some classes).
Solutions and ideas to increase attendance	Time and duration	Participant 599: "*The classes I attended were on the afternoon, which was not a problem for me, but could be for those still in employment. It may help to hold some classes in the evening.*" (Male, 60-79, all classes). Participant 5: "*Would have liked a class every day or every other day instead of once a week.*" (Male, 40-59, all classes). Participant 466: "*Would have liked longer than 8 weeks cardiac rehab.*" (Female, 60-79, all classes). P67: "*Make it sooner after the OP/procedure.*" (Male, 60-79, all classes).
	Class Structure	Participant 116: "*Not really, I would like to have been worked harder; however, as the classes have to satisfy different age groups and conditions, it would be difficult.*" (Male, 60-79, some classes). Participant 325: "*Give more interest, doing the same exercises every week is boring - virtually no equipment is used.*" (Male, 60-79, some classes). P6: "*As far as I know I attended all my classes, there was talk of more advanced classes, but I haven't heard any more news. I would like to attend more classes if there are any.*" (Male, 40-59, all classes). P101: "*I do find any gym based exercise very boring, perhaps any walking activities could be explored? A booklet on country walks suitable for people with heart problems, local community green gyms etc. Any outdoor activity organised in the Summer months to bring local communities together.*" (Male, 60-79). P44: "*Have more experts to give talks on cardiac problems and how to avoid another event. This may include food, exercise, medical advice etc.*" (Male, 60-79, all classes).
	Location	P141: "*Make them more reliable in my part of the world (Highlands - Caithness).*" (Male, 60-79, some classes). P133: "*Include them at the local gym so that people could attend whenever the wanted to. (Cost may be prohibitive though).*" (Male, 60-79, all classes). P227: "*Make the classes available in all medical centres.*" (Female, 60-79, some classes) P430: "*Help with travel arrangements and travel expenses out with Inverness for people not on benefits. Possible age-related groups and group buddies.*" (Male, 40-59, all classes). P41: "*Information on local support groups that are available. Discounted fees on joining local sports centres.*" (Male, 60-79, some classes).

safety and reassurance, in that feeling safe to exercise increased feelings of confidence and motivation. Respondents believed that the environment the classes were conducted in allowed them to work harder than they typically would. The role staff play in monitoring, encouraging, and supporting was deemed vital in creating feelings of safety. By monitoring the type of exercise and intensity, respondents noted that they could 'push themselves harder' with the confidence that if an adverse event occurred, the correct procedures were in place. Moreover, many respondents expressed increased confidence in their ability to do everyday tasks again, regaining their independence and thus increasing their motivation to keep exercising.

Solutions and ideas to increase attendance

Participants were asked to describe methods to increase attendance of exCR. There were a range of ideas suggested, three main elements were seen within respondents' responses, and these were related to time, structure, and location around CR. Within the element of time, frequent responses were seen around what time classes were held, a want for more classes across the week and an increase to the duration of the overall programme. In terms of structure, respondents highlighted a want for varying intensities, more variety of exercises which can be advanced and more elements to the classes such as education or teaching. Location frequently came up within responses and these were related to



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Figure 1 Hierarchy of the topics, themes, and sub-themes from the qualitative analysis.

reliability of classes and a desire to have the programme conducted at local gyms and more medical centres in the future.

With the primary goal of CR to create long-term health behaviour change particularly with respect to PA the following section outlines participant responses related to PA. The two modes can be considered different due to patients having to take responsibility for planning and conducting their own PA and the locations in which it is conducted unlike exCR. The two main themes are also interconnected in that following completion of the exCR programme it is anticipated that participants will continue with regular PA.

Main topic: Physical activity

Within the main topic of "physical activity" there were similar and contrasting themes to those for "cardiac rehabilitation experience". The theme of "physical activity" was comprised of three sub-themes: "Benefits of being active", "challenges to being active" and "reasons for staying physically active". Table 3 shows this theme along with the sub-themes, elements, and exemplar quotes. For a detailed explanation of each element see the code book in Appendix 1.

Benefits of being active

Perceptions of PA appeared to be different to that of the exercise component of CR. Respondents recognized that they could conduct PA in a range of locations besides indoor environments, they could select when they wanted to conduct PA, there is more variety when conducting PA, and they can conduct PA whilst achieving other goals (*e.g.*, housework). Yet the range of benefits to participating in PA both in terms of psychological and physical benefits were similar to those reported for exCR.

Physical and mental benefits from PA

Respondents identified many benefits to their health from being physically active, including "maintaining weight, improving breathing, managing other diseases and ability to do things you enjoy." They also cited improvements in their mental health because of being more physically active, including "Improved confidence, wellbeing, stimulated mind, increased optimism and bringing joy and energy to their lives."

Barriers to physical activity

As within the main topic of "cardiac rehabilitation experience", barriers to PA were frequently discussed and these were grouped as physical, mental, and external barriers.

Physical

This included health – from other conditions as well as their heart. Respondents also referred to their age as a barrier.

Mental

Mental barriers included a lack of confidence and anxiety about being safe whilst exercising. Respondents also discussed that mental health issues such as anxiety and depression, which may also be linked to their cardiac issue, prevented them from taking part in regular PA.

Table 3 Topic: Physical activity

Sub-theme	Element	Description	Example quotes
Benefits	Physical	Physical benefits from being active.	Participant 33: "*Physical activity can help other/many other illnesses/diseases e.g., diabetes. It can also help you to feel better.*" (Female, 60-79, all classes). Participant 423: "*Keeping my weight at a good level is important and regular walking helps this. Walking helps me keep fit and helps with a good breathing pattern.*" (Male, 40-59, all classes). Participant 101: "*Being physically active not only improves recovery but stimulates the mind, especially when walking outdoors.*" (Male, 72, some classes). Participant 49: "*I am not PA as above - but I always endeavour to be active daily by other means i.e., gardening, walking, household etc., relevant to my age/weather conditions etc.*" (Male, 79, all classes).
	Mental	Mental benefits from being active.	Participant 358: "*Physical activity has given me a positive outlook for the future.*" (Male, 60-79, all classes). Participant 90: "*Improved confidence and mental wellbeing.*" (Male, 60-70, all classes).
Challenges	Physical challenges	Physical health barriers to being active.	Participant 28: "*At present I am troubled with retention of fluid which is affecting my breathing. If something could be done about this, I feel I would be able to get back to my golf and fishing.*" (Male, 80+, 8 classes). Participant 531: "*Because of my age and state of health I would find it very difficult to exercise.*" (Male, 80+, no classes).
	Mental challenges	Mental barriers to being active.	Participant 87: "*I don't go out by myself in case I suffer a bad turn. It's not just a physical barrier with some patients it's a mental barrier that stops them from exercise.*" (Male, 60-79, no classes). Participant 103: "*I have suffered from severe depression my whole life and lately it's been getting worse with everything that's going on so it's a bad place I'm in just now*" (Male, 40-59, no classes). Participant 450: "*To be honest I feel very anxious about strenuous or prolonged exercise: close to paranoia!*" (Male, 60-79, no classes).
	External challenges	External barriers to being active.	Participant 61: "*Normally in good weather my husband and myself are out walking about 3 d a week but with all the snow and ice we have had we have hardly been out of doors.*" (Female, 60-79, no classes). Participant 278: "*I really enjoy lifting weights and as my local gym does not have much I use a private gym. It has all health questions and if you have a health problem (heart attack etc.) you need a doctor's letter which is £30. This could put people off.*" (Female, < 39, 8 classes).
Reasons for staying physically active	Motivation	Motivation for being physically active.	Participant 160: "*Would like to keep active for my grandchildren and my great grandchildren and also for my remaining son and family.*" (Female, 60-79, 8 classes). Participant 115: "*Being physically fit, for your age, helps to be mentally fit and become able to participate in family and community events.*" (Male, 60-79, 8 classes).
	Preferences	Preferences of types of activity.	Participant 318: "*Most of my activity is concerned with work around the home e.g., cutting trees for wood burner, splitting logs for wood burner, digging garden, looking after chicken, mowing grass etc.*" (Male, 80+, some classes). Participant 258: "*I've been involved with physical activity in my work environment all my working life. Most of my hobbies focus around exercise skiing, biking, golf, swimming and walking. Don't like to be unfit.*" (Female, 40-59, no classes).

External

External barriers included factors such as where they lived, distance from leisure facilities, the cost of leisure facilities, the need for medical notes to gain access to gyms which cost money and the weather.

Reasons for staying physically active

This sub-theme includes two elements: "Motivation" and "preferences" and discusses instances where respondents suggested why PA is important for their lives and what activities they like to do.

Motivation

This sub-theme related to motives and reasons for being active or becoming more active. When noting elements around their condition and PA, many responses were related to aspirations, plans and goals for their future after overcoming the event and attending CR. Respondents highlighted a want to be able to conduct more regular forms of PA and regain their independence, they had prior to having their cardiac issue. Other responses were in relation to behaviour change and living a more active lifestyle with the aim of prolonging life and living better mentally and physically. Finally, respondents also noted improving their lifestyle so that they can continue to see their family and friends.

Preferences

Respondents described types of activities that they now preferred to participate in. In some instances, as outlined within the 'solutions and ideas to increase attendance' sub-theme, some of these types of PA could be considered within future rehabilitation programmes. Specifically, most participants noted that they prefer to participate in PA outdoors.

DISCUSSION

This study, conducted in cardiac patients in the North of Scotland, demonstrates a range of opinions and attitudes around CR. The two main topics from the data were termed "cardiac rehabilitation experience" and "physical activity". Each topic was made up of several sub-themes and codes. Whilst the two main topics are different, they are connected in that once attending CR programmes, individuals should progress to conducting levels of PA that meet the national guidelines.

Respondents outlined benefits to taking part in exCR, including improved fitness, mood, and mindset. Respondents also noted that following the education element of CR they knew significantly more about managing their condition which may be important in creating long-term behaviour change. Conversely, respondents frequently cited distance and travel as reasons for non-attendance. Other barriers were related to age, health/injury status, accessibility, and timings (classes during working hours). These barriers were similar to those found in previous CR research[18,19]. External barriers included communication around the referral process, specifically a lack of advertising or information availability. Respondents noted not being informed and unacceptable lengths of follow up. Foster *et al* [15] found "perceived need" to be the single most important factor in patient non-attendance to CR where perceived need consisted of patient and healthcare factors. Healthcare factors include lengthy referral process, a lack of contact, information, or knowledge[20]. The current findings are consistent with the quantitative phase of the larger study[15]. In terms of barriers to PA, there was little mention of time, location, or distance. However, the feeling of safety was removed when conducting PA and worry around adverse events was an issue. This, however, is a common misconception and more needs to be done to reassure patients after a cardiac event that PA is safe[21].

Consistent with previous research into CR[15,22], responses demonstrated that being monitored and shown the correct exercise form alongside enhanced understanding of managing their condition could result in increased self-efficacy for conducting PA. The social cognitive theory[23] describes how learning drives human behaviour. Self-efficacy is one of the most powerful predictors of behaviour in health environments[24]. Patient education has also been shown to increase self-efficacy[25]. Such evidence is supported by Frohmader *et al*[26] who found that following interviews, patients' confidence increased to develop lifestyle changes as a result of viewing their own success and positive reinforcement by mentors. The use of telehealth, specifically videoconferencing, may be one method for increasing accessibility to such interviews and overcoming patient barriers to attendance[27]. Thus, focusing on methods to increase patient confidence could increase adherence to CR programmes.

Responses were positive and demonstrate the role that staff play in facilitating attendance to CR through creating safe, enjoyable environments. Participants highlighted that exercising alongside others with similar conditions made them more likely to attend CR and enhanced their levels of enjoyment and support. Moreover, group dynamics such as looking out of place or embarrassment which are often cited as barriers to exercise[28] are potentially removed when exercising with people with a similar health condition. These responses show CR to be more than just an "exercise regime", individuals create friendships and socialise, creating mental and physical benefits. Contrastingly, in some cases group exercise was considered a barrier to attendance and this demonstrates the complexities of trying to increase CR attendance.

The second research question analysed patient feedback to increasing attendance of CR. Numerous studies have developed methods to increase attendance in CR programmes[29,30]. However, few have considered patient generated ideas and whether they will be relevant to patients in rural areas. Karmali *et al*[29] considered the use of structured telephone calls, visits from staff following leaving hospital, the creation of peer support groups, early appointments, motivational letters, and a gender-tailored cardiac programme. The review found that many of these methods were successful in increasing attendance, however many displayed high levels of bias which makes it challenging to generalise. A clear barrier identified within the current research to attending CR classes was related to the organisation or accessibility of the sessions. A lack of classes and no classes out with work hours were frequently cited. One clear method to overcoming these is to provide more classes, especially for rural patients where travel time and distance are typically large. Particularly in the Scottish Highlands, it is likely financial and staffing constraints will mean this is challenging to implement, but possibilities may exist with regards to increase provision through local companies such as Highlife Highland or Argyll Active.

In relation to increasing the number of CR classes, new methods away from centre-based CR have been developed[31]. Further, due to the COVID-19 pandemic changes to where CR is conducted have occurred[32]. Even before the pandemic, many CR services began to implement home-based exCR[33]. Previous research has investigated online home-based exercise and post-exercise telemonitoring.

Anderson *et al* (2017)[33] and Batalik *et al*[27] found such modes to be at least equally as effective as centre-based rehabilitation, increasing access and participation. Such methods of delivery may facilitate attendance for individuals who dislike exercising in groups, in that they attend the group classes without being viewed. However, in rural areas connectivity (Wi-Fi and 4G/5G) may be substandard and considered a barrier to such forms of CR[34].

Other methods to overcome the barriers that were identified within the current study include peer support groups, third sector partnerships and patient travel funds supporting results seen within other similar studies[30]. Currently, if a patient lives more than 30-miles from the clinic or have a co-morbidity they are entitled to travel reimbursement[35], which it appears respondents were unaware of, highlighting the need again for better communication. The distance to the classes may not be solely responsible for non-attendance and perhaps the lack of awareness around funding or alternative methods of travel are a greater issue. The healthcare team and referral staff should make sure on discharge that patients have information about these funds and even provide details of low-cost travel such as dial-a-bus services running in their area.

Many of the ideas to overcome the barriers are related to communication, providing better information and perhaps this comes down to creating more streamlined services or educating staff about their roles, responsibilities, and the importance of CR. Previous research has shown that patients pick up on doctors' perceptions and how their beliefs and values can shape behaviour[10]. Thus, if a GP or doctor does not deem CR to be necessary then it is unlikely that the patient will consider attending. Quirk *et al*[36] note that poor maintenance of PA post CR is common, and that regular attendance of CR does not guarantee regular PA following completion of the CR programme. The patients' responses highlight that greater emphasis should be placed upon strategies to increase self-efficacy and self-regulation.

Physical activity

The responses demonstrated respondents that attended CR now have a good understanding of why they should conduct regular PA, highlighting that the education element of the programme is effective. Respondents recognise exCR and PA as two separate entities, much as exercise and PA are different in definition in the literature[37]. Differences centred on the structured nature of CR. Respondents identified that PA can be conducted at any time and place, whereas exCR classes take place at a set location and time. This gives patients less freedom, restricting the time they can spend doing other activities.

As exCR is typically conducted indoors this presents another way in which the two forms of activity differ. When referring to types of PA, many responses were related to activities conducted outdoors and in natural areas. This perhaps warrants discussion with regards to the locations of where exCR is conducted. Previous research has shown decreased levels of motivation when conducting exercise indoors[38]. Whilst clearly weather is a barrier to implementation, patient responses show that exCR outdoors may increase attendance. Respondents noted that they would like to see more walking and cycling clubs included to increase participation. Specific responses were termed "reasons for staying physically active" and how respondents prefer to conduct PA such as housework or cleaning whereby they can achieve both health and day-to-day goals. Many respondents considered the future, expressing they conducted PA to maintain their health, feel better and external reasons such as to see their grandchildren grow up. There is a myriad of reasons individuals will select to adopt new behaviours. Finding ways to make the exercise element of CR more like PA is a concept that requires attention.

Future research

The current study provides ideas and directions for future research and policies. Further qualitative research in the form of interviews and focus groups should be conducted to gain more in depth understanding of factors associated with non-attendance. It should not only be patients who are sampled however, collecting more data from the referral staff may provide a greater understanding with regards to CR. An evaluation report of referral processes may allow understanding into why so many do not receive adequate communication about CR classes. Following on from this, investigating new methods of referral such as those outlined in the discussion to understand if they improve attendance is warranted. Finally, future research may look to use longitudinal or follow-up study designs to understand how the behaviours of those individuals who both attended CR and those who chose not to attend differed.

Limitations

Whilst the study displays a range of responses with regards to respondents' attitudes and perceptions of both CR and PA, there was a large amount of data brevity or responses due to the format of the questionnaire. This resulted in an inability to probe and ask follow-up questions. Moreover, not all participants replying to the questionnaire was deemed a limitation.

CONCLUSION

The current study provides several suggestions for increasing attendance of CR. Self-efficacy is a large aspect of what CR offers patients and this is built up through effective communication, socialising with similar people and the safe environment that exCR provides. However, before individuals can achieve such benefits, successful methods to get them to attend exCR need to be better investigated. Barriers to exCR range from age and health to the distance and starting times of the classes, resulting in increased travel time and costs. To overcome these barriers respondents outlined a range of ideas such as the provision of more classes held out with working hours, a greater variety of classes and classes conducted in different locations. Finally, financial incentives to help conduct PA from travel reimbursements to reductions at fitness centres were also highlighted. As a result of the findings of the current study, future studies should continue to attempt to develop, test and evaluate methods to increase the uptake and attendance of CR based on the current low statistics of eligible patients' attendance.

ARTICLE HIGHLIGHTS

Research background

Cardiovascular disease remains the largest cause of death globally and rates continue to rise. The exercise component of cardiac rehabilitation (CR) is regarded as an important element of such interventions. Recent statistics have demonstrated that attendance of CR programmes is low, despite continued calls for methods to increase attendance.

Research motivation

Such a study is warranted as low rates of uptake and completion of rehabilitation programmes are a concern. The barriers and facilitators towards CR are still somewhat unknown. Patients should continue to conduct regular exercise and physical activity after completing the rehabilitation programme. Thus, understanding patient perspectives on this area is also necessary. Exploring such topics should allow researchers and health care staff to target specific elements of service delivery to improve attendance in the future.

Research objectives

The aims of the present research study were to identify the barriers and facilitators to CR and physical activity. The study also aimed to explore cardiac patient views around service modification and ideas to increase attendance at such programmes.

Research methods

The data analysed in this study was from a larger cross-sectional survey. Cardiac patients from the North of Scotland, who were referred for standard CR classes at a hospital were sampled. The current study qualitatively analysed the free-text responses to 5 open-ended questions included within a wider survey. A 6-step thematic analysis was used to analyse the data.

Research results

Patient responses were explored under two main topic areas: "Cardiac rehabilitation experience" and "physical activity". Patients described barriers to CR including time of day, location, a lack of communication and group dynamics. Patient generated ideas to increase the uptake of such programmes included more available classes, a greater variety of intensities and types of exercise and a change to the location of classes. Patients highlighted various benefits to both mental and physical health as a result of conducting the classes and physical activity.

Research conclusions

It appears based on the findings of the current study that CR increases patients' self-efficacy through a number of mechanisms. Key barriers to attending CR in this cohort included age and physical health, distance to the classes and the cost of attendance. With regards to these barriers, participants highlighted a range of methods to overcome these including provision of more classes held out with working hours, classes conducted in different locations and the need for a greater variety of exercise classes.

Research perspectives

The study provides several ideas which future research can implement or examine. Future studies should attempt to develop, test, and evaluate methods to increase the uptake and attendance of CR based on the current low statistics of eligible patients' attendance.

FOOTNOTES

Author contributions: Foster E, Gorely T and Leslie S designed the research study; Foster E and Leslie S performed the research; Fraser M, Gorely T and Walters R analysed the data; Fraser M, Gorely T, Walters R and Leslie S wrote the manuscript; All authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Untangling the difficult interplay between ischemic and hemorrhagic risk: The role of risk scores

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Abstract

BACKGROUND

Bleedings are an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention. This represents a hazard equivalent to or greater than that for recurrent ACS. Dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events, but the benefit of such therapy is counteracted by the increased hemorrhagic complications. Therefore, an early and individualized patient risk stratification can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients.

AIM

To review existing literature and gain better understanding of the role of ischemic and hemorrhagic risk scores in patients with ischemic heart disease (IHD).

METHODS

We used a combination of terms potentially used in literature describing the most common ischemic and hemorrhagic risk scores to search in PubMed as well as references of full-length articles.

RESULTS

In this review we briefly describe the most important ischemic and bleeding scores that can be adopted in patients with IHD, focusing on GRACE, CHA2DS2-Vasc, PARIS CTE, DAPT, CRUSADE, ACUITY, HAS-BLED, PARIS MB and

PRECISE-DAPT score. In the second part of this review, we try to define a possible approach to the IHD patient, using the most suitable scores to stratify patient risk and decide the most appropriate patient treatment.

CONCLUSION

It becomes evident that risk scores by themselves can't be the solution to balance the ischemic/bleeding risk of an IHD patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD.

Key Words: Acute coronary syndrome; Ischemic heart disease; Risk score; Bleeding; Mortality; Percutaneous coronary intervention

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Core Tip: We present a review of the most relevant scores developed or adjusted for the risk stratification of patients affected by ischemic heart disease. For each score, the strengths, weaknesses, statistical pertinence and applicability are evaluated.

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INTRODUCTION

Hemorrhagic complications have emerged as an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI), representing a hazard equivalent to or greater than that for recurrent ACS[1-4]. As known, dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events in ACS[2]. However, the benefit of such therapy is counteracted by the increased hemorrhagic complications: major bleeding also considerably prolongs the hospital stay and increases resource consumption. Minimizing bleeding complications, most of which are attributable to the use of potent antiplatelet and antithrombin medications, is therefore an important objective in the management of patients with ischemic heart disease (IHD). It must be noted that, similarly to ischemic risk, risk of bleeding is not homogeneous, and various predictive models have been developed to stratify both bleeding and ischemic risk in patients affected by IHD[5]. Clinical guidelines recommend that optimal management of patients with IHD should include early, individualized patient risk stratification by the treating physician[6,7]. In addition to informing patients about their prognosis, accurate risk assessment can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients. The development of simple-to-use risk scores could standardize quality of care and patient outcomes. Risk stratification could also be employed to compare outcomes across different clinical studies.

MATERIALS AND METHODS

We screened the titles and abstracts of studies against predefined terms using PubMed, EMBASE and Cochrane databases. Key words used have been "GRACE score", "CHA2DS2-Vasc score", "PARIS CTE score", "DAPT score", "CRUSADE score", "ACUITY score", "HAS-BLED score", "PARIS MB score", "PRECISE-DAPT score", "derivation" and "validation" in order to identify relevant articles published. The title and available abstracts of all returned articles were reviewed to identify relevant articles for a full-length review. Reference lists from the articles were reviewed to identify additional relevant articles. All studies that contained material applicable to the topic were considered. Data was analyzed using descriptive statistics.

RESULTS

Ischemic risk

GRACE score: The GRACE risk prediction model was developed from an earlier cohort of GRACE (Global Registry of Acute Coronary Events) patients (a total of 11389 patients enrolled in 14 countries from April 1, 1999, to March 31, 2001)[8]. It evaluates the probability of death within 6 mo of hospital discharge in patients with ACS. The components of the GRACE score are systolic blood pressure, age, Killip class, heart rate, cardiac arrest, serum creatinine, ST-segment deviation and cardiac biomarker increase. All variables refer to data at patient presentation. GRACE score was subsequently validated in a cohort of 3972 GRACE patients and 12142 GUSTO-IIb trial patients. It has been demonstrated an important predictor of in-hospital mortality across the whole spectrum of the ACS population[9]. However, the substantial geographic variation of patient cohorts used to develop the GRACE do not confirm its applicability in all the ACS patient populations and additional assessment has been performed to validate the score. Currently, GRACE score is suggested by ESC Guidelines to stratify patients according to their estimated risk of future ischemic events in order to overcome the so called "risk-treatment paradox"[10,11]. Indeed, it is well recognized that the delivery of guideline-directed care is inversely related to the estimated risk of the patient with NSTEMI and a GRACE risk score-based risk assessment has been found to be superior to the subjective physician assessment for the occurrence of death or ACS[12,13].

Moreover, benefit with an early invasive strategy is strongly associated with the patient's risk profile. In a pre-specified subgroup analysis, patients with a GRACE risk score > 140 benefited from an early invasive strategy while those with a GRACE risk score < 140 did not (TIMACS trial: HR = N0.65, 95%CI: 0.48-0.89 *vs* HR = 1.12, 95%CI: 0.81-1.56, *P* for interaction = 0.01; VERDICT trial: HR = 0.81, 95%CI: 0.67-1.00 *vs* HR = 1.21, 95%CI: 0.92-1.60; *P* for interaction = 0.02)[14,15].

C-statistics in the derivation study: 0.81 for predicting death and 0.73 for death or myocardial infarction.

CHA2DS2-VASc score: The CHA2DS2-VASc score is a well validated risk model for predicting thromboembolic events and guiding anticoagulant therapy in patients affected by atrial fibrillation (AF). It has been developed as a refinement of the older CHADS2 score by incorporating female sex and vascular disease and by assigning two points for age ≥ 75 years[16,17]. Although being developed for thromboembolic risk prediction in AF patients, both these scores contain common cardiovascular risk factors that are associated with thromboembolic events regardless of the presence of AF and are well known predictors of both coronary atherosclerosis and major cardiac adverse events (MACE) in patients with known coronary artery disease and ACS[18,19].

C-statistics in the derivation study: 0.61.

PARIS CTE score: The PARIS CTE score has been derived from The Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients (PARIS) registry, an observational study of patients undergoing percutaneous coronary intervention (PCI) and stenting. From that registry, PARIS risk scores for major bleeding (MB) and for coronary thrombotic events (CTE) were created. The PARIS CTE risk score predicts the stent thrombosis and myocardial infarction risk for up to 2 years after PCI. It considers diabetes, ACS, smoker, creatinine clearance, prior PCI and prior CABG[20]. The score showed very good results both in the derivation and validation cohort. Once external validation studies had been performed, they showed limited to poor discrimination thus far. As the simplicity of the CTE score might be favorable for clinical use, its value compared to other ischemic scores is yet to be established.

C-statistics in the derivation study: 0.70.

DAPT score: The dual-antiplatelet therapy (DAPT) score is recommended by Guidelines as a tool to stratify ischemic and bleeding risk. However, the score can be used to distinguish patients suitable for standard term DAPT and long term DAPT, so it is our opinion that it can be considered mostly an ischemic risk score. The prediction rule assigns 1 point each for myocardial infarction at presentation, prior myocardial infarction or PCI, diabetes, stent diameter less than 3 mm, smoking, and paclitaxel-eluting stent; 2 points each for history of congestive heart failure/Low ejection fraction and vein graft intervention; −1 point for age 65 to younger than 75 years; and −2 points for age 75 years or older[21]. The DAPT score has been validated in several studies outside its derivation cohort; however, these studies have yielded conflicting results in which some have confirmed its predictive value and some have not[22]. Of note, most of the analyses were from registries and a substantial number of patients were treated with bare-metal stents or first-generation DES. Moreover, the present score considers among its items the use of paclitaxel-eluting stents, that are no more considered a standard in most catheterization laboratories. It is well known that using newer-generation DES mitigates the ischemic risk of patients treated with PCI. It becomes evident looking at C-statistics: in the derivation/validation study, the C-statistic for ischemic and bleeding outcomes were 0.64/0.70 and 0.68/0.64, respectively; among the validation studies, the C-statistics for composite outcomes ranged from 0.53 to 0.71 for ischemic outcomes and 0.49 to 0.71 for bleeding outcomes[23].

Bleeding risk

CRUSADE score: CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) score has been developed by investigators of the CRUSADE registry as a stratification tool for in-hospital major bleeding among NSTEMI patients[24]. Variables included are female sex, diabetes mellitus, peripheral artery disease, heart rate, systolic blood pressure, congestive heart failure, hematocrit, and creatinine clearance. Considering only the variables present at admission, the CRUSADE bleeding score is an easily applicable and useful tool in predicting patient risk that showed adequate calibration and excellent discriminatory powers in the whole population as well as in the different treatment subgroups, except in patients treated with ≥ 2 antithrombotics who did not undergo cardiac catheterization[24,25].

C-statistics in the derivation study: from 0.56 to 0.81 in different subgroups.

ACUITY: Mehran *et al*[26], using data from the ACUITY and the HORIZONS-AMI trials (17421 patients), developed a bleeding risk score. Six independent baseline predictors for major bleeding were identified: female sex, age, creatinine, white blood cell count, anemia and ST-segment-elevation. The risk score differentiated patients with a 30-d rate of non-CABG-related major bleeding ranging from 1% to over 40%. As a difference with the other bleeding risk scores, this one includes white blood cell count as a risk factor for major bleeding. It has been compared with CRUSADE score in subsequent observational study and shows an acceptable discriminative capacity[27].

C-statistics in the derivation study: 0.74.

HAS-BLED score: The HAS-BLED score, initially developed to assess the bleeding risk in patients with AF receiving chronic anticoagulant therapy[28], has shown to predict cardiovascular events and long-term outcomes in these patients. The observation by Pisters *et al*[28] that HAS-BLED predictive efficacy was particularly high in patients receiving antiplatelet therapy led to its evaluation in predicting bleeding events and major acute cardiovascular events (MACE) in patients receiving DAPT after PCI and stenting with or without AF[29]. Moreover, the HAS-BLED score predictive performance was tested in patients with ACS receiving DAPT or triple antithrombotic therapy, showing moderate accuracy[28].

C-statistics in the derivation study: 0.72 overall; 0.91 with antiplatelet only therapy.

PARIS MB score: The PARIS risk score for major bleeding was developed from the same previously mentioned PARIS registry, in which also patients on oral anticoagulation were included. This six-item risk score (age, BMI, smokers, anemia, creatinine clearance and triple therapy) showed reasonable discrimination for major bleeding up to 2 years post-PCI across different validation cohorts[20].

C-statistics in the derivation study: 0.72.

PRECISE-DAPT score: The PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score is a simple bedside risk assessment tool, recommended from the ESC Guidelines, which can be easily implemented in everyday clinical practice, and that might be particularly useful for its applicability at the time of treatment initiation[6,7,30]. It has been developed for prediction of bleeding risk during DAPT after PCI using pooled data of 8 randomized clinical trials. It comprises 5 variables: age, creatinine clearance, hemoglobin, white blood cell count and previous spontaneous bleeding. In patients with high bleeding risk (PRECISE-DAPT score ≥ 25), the bleeding risk of 12-mo or longer DAPT could outweigh the benefit of ischemic prevention. Patients not at high bleeding risk (score < 25) might receive a standard (*i.e.* 12 mo) or prolonged (*i.e.* > 12 mo) treatment without being exposed to significant bleeding liability.

C-statistics in the derivation study: 0.71.

DISCUSSION

Risk scores or risk factors?

We now move forward looking at the multivariate analysis from which every score has been developed, focusing on repeated items among scores belonging to ischemic or bleeding category and on the real weight of these items in the score (*i.e.* the OR or HR values). We want to specify that we do not apply this analysis to the GRACE score that is composed by items of the acute phase of ACS that are not common to other scores and that has a very strong predictive value for mortality by itself. We think that the GRACE score should be applied in every ACS patient, in order to define the patient prognosis, regardless of ischemic and bleeding risk which should be analyzed separately.

Going back to the analysis in Table 1 and Table 2, we summarized the OR or HR derived from the multivariate analysis of the derivation cohorts and the ischemic and bleeding risk scores, respectively.

At first, looking at ischemic risk scores, it becomes evident that in the CHA2DS2-Vasc score, only the female sex was really statistically significant in the logistic regression analysis, while the other items were not. This is because, in the derivation and validation study, rather than considering the single item, patients have been grouped in 3 groups according to the score, that were low risk (0 point), intermediate risk (1 point) and high risk (≥ 2 points), and the authors demonstrated a better discrimination capacity

Table 1 Ischemic risk scores items and OR/HR

Item	OR/HR (CI)
CHA2DS2-Vasc (OR)	
Congestive HF	0.72 (0.27-1.88) NS
Hypertension	1.01 (0.38-2.66) NS
Age ≥ 65	NR
Age ≥ 75	1.46 (0.63-3.35) NS
Diabetes mellitus	1.79 (0.73-4.40) NS
Stroke	2.22 (0.78-6.35) NS
Vascular disease	2.27 (0.94-5.46) NS
Female sex	2.53 (1.08-5.92)
DAPT (OR)	
Age, per 10 yr increase	1.54 (1.34-1.78) (on bleedings)
Current smoking	1.4 (1.11-1.76)
Diabetes mellitus	1.38 (1.1-1.72)
Acute coronary syndrome	1.65 (1.31-2.07)
PCI or prior ACS	1.79 (1.43-2.23)
Stent diameter < 3 mm	1.61 (1.3-1.99)
Paclitaxel stent	1.57 (1.26-1.97)
Congestive HF	1.88 (1.35-2.62)
Saphenous vein graft stenting	1.75 (1.13-2.73)
PARIS-CTE (HR)	
Current smoking	1.69 (1.14–2.52)
CrCl < 60 mL/min	2.12 (1.46–3.05)
Diabetes mellitus	
Non-insulin dependent	1.69 (1.14–2.52)
Insulin dependent	3.42 (2.32–5.04)
Acute coronary syndrome	
Troponin negative	1.47 (1.03–2.08)
Troponin positive	2.09 (1.24–3.53)
Previous revascularization	
Previous PCI	1.91 (1.38–2.66)
Previous CABG	1.80 (1.24–2.61)

CI: Confidence interval; CrCl: Creatinine clearance; HF: Heart failure; HR: Hazard ratio; NR: Not reported; NS: Not significant; OR: Odds ratio.

of the CHA2DS2-Vasc score compared to the CHADS2 score. Therefore, they still included variables not independently associated to the outcomes but that fit the prognostic model[17]. Moving on, the other 2 scores, we found a precise statistical derivation with every single item being statistically significant.

As evident, two variables are common to all scores, these are diabetes mellitus and vascular disease (considered also as previous ACS or PCI). Some others like heart failure, age and smoking, are common to 2 out of 3 scores. Diabetes mellitus and vascular disease are also the items with the higher OR or HR in every score and that means that they have more influence on the ischemic outcome.

Diabetes is a major independent risk factor for IHD[31], particularly for myocardial infarction. The pattern of coronary artery disease in diabetic patients is often complex, with multiple lesions and widespread involvement, making it difficult to achieve complete revascularization and adversely affecting long-term prognosis[31]. Several studies have also found a greater risk of death after ACS in patients with diabetes than in those without diabetes[32,33] in every subtype of coronary syndromes

Table 2 Bleeding risk scores items and HR/OR

Item	HR/OR (CI)
PARIS-MB (HR)	
Current smoking	1.94 (1.18–3.20)
CrCl < 60 mL/min	1.81 (1.16–2.82)
Age, per year increase	1.02 (1.00–1.04)
BMI	
< 25 kg/m^2	1.68 (1.09–2.60)
≥ 35 kg/m^2	1.79 (1.04—3.08)
Anemia	2.72 (1.83–4.04)
Triple therapy on discharge	1.93 (1.08–3.43)
CRUSADE (HR)	
Heart rate per 10 bpm increase	1.08 (1.07–1.10)
Systolic blood pressure	
≤ 110 mmHg	1.26 (1.16–1.36)
≥ 180 mmHg	1.24 (1.14–1.35)
Hematocrit < 36%	2.28 (2.11–2.46)
CrCl, per 10 mL/min decrease	1.12 (1.10–1.13)
Sign of HF	1.23 (1.15–1.31)
Vascular disease	1.19 (1.12–1.27)
Diabetes	1.16 (1.10–1.23)
Female sex	1.31 (1.23–1.39)
ACUITY (OR)	
Age, per 5 yr increase	1.17 (1.13–1.21)
Acute coronary syndrome	
NSTEMI	1.26 (1.04–1.54)
STEMI	1.92 (1.52–2.44)
White blood cell count, giga/L	1.10 (1.07–1.12)
Serum creatinine, per 0.1 mg/dL increase	1.09 (1.07–1.12)
Anemia	1.98 (1.65–2.37)
Bivalirudin monotherapy	0.56 (0.47–0.67)
Female sex	2.32 (1.98–2.72)
HAS-BLED (OR)	
Age > 65 yr	2.66 (1.33-5.32) NS
Systolic blood pressure >160 mmHg	0.60 (0.21-1.72) NS
Creatinine > 2.26 mg/dL or > 200 μmol/L or cirrhosis or bilirubin > 2 x normal with AST/ALT/AP > 3 x normal	2.86 (1.33-6.18)
Prior major bleeding or anemia	7.51 (3.00-18.78)
Medication predisposing to bleeding	0.81 (0.43-1.51) NS
Stroke	0.94 (0.32-2.86) NS
Labile INR	NR
Alcohol use, ≥ 8 drinks/wk	0.00 (0.00) NS
PRECISE-DAPT (OR)	
Hemoglobin, per 1 g increase	0.67 (0.53-0.64)

White-blood-cell count, per 103 cells per μL increase	1.06 (0.99-1.13)
Age, per 10 yr increase	1.34 (1.11-1.48)
CrCl, per 10 mL/min increase	0.9 (0.82-0.99)
Previous bleeding	4.14 (1.22-14.02)

CI: Confidence interval; CrCl: Creatinine clearance; HF: Heart failure; HR: Hazard ratio; NR: Not reported; NS: Not significant; OR: Odds ratio.

(unstable angina, STEMI and NSTEMI)[34,35].

The incidence of peripheral arterial disease (PAD) increased by 23.5% in the first 10 years of this century and 3%–12% of the earth's population is affected[36]. PAD patients share most of their atherosclerotic risk profiles with patients diagnosed with coronary artery disease. In the Global Atherothrombosis Assessment (AGATHA) study, approximately 50% of patients with PAD had IHD, and 20% of IHD patients was affected also by PAD[37]. Advanced stent technology and more potent antiplatelet agents and anticoagulant therapy have resulted in an improvement in outcomes among the overall population of patients undergoing coronary interventions. However, PAD patients demonstrated a lower benefit increase. Of note, their risk of major adverse cardiovascular events outcomes following PCI has remained unchanged across the early bare-metal stent (BMS) and drug-eluting stent (DES) eras: the only benefit has been demonstrated for a reduction in the rate of repeated PCI. Singh *et al*[38] found that patients with PAD that underwent PCI in the BMS era had an 84% relative-risk increase of an in-hospital mortality and a 48% relative-risk increase of death over a period of 3-years compared to patients without PAD. And this was evident also after adjustment for concomitant risk factors. In the Tirofiban and Reopro Give Similar Efficacy Outcome Trial (TARGET), PAD was independently associated with a 2- to 3-fold increase in mortality 12 mo after PCI. Similar to findings in the BMS era, in the DES era the study by Ramzy *et al*[39] suggests that PAD continues to be independently associated with approximately a two-fold increased risk of 12 mo mortality. Assessment of Dual AntiPlatelet Therapy with Drug Eluting Stents (ADAPT-DES) study was conducted with the aim to determine the relationship between platelet reactivity, PAD and subsequent adverse outcomes. In the study population, there was a 10.2% prevalence of PAD among the 8582 patients, all of whom received DESs. Data analysis showed PAD to be an independent predictor of MACE (adjusted HR = 1.34, P = 0.003)[40].

At last, we want to focus on Chronic Kidney Disease (CKD) which is only considered in the PARIS CTE score. As known, CKD is a well-known ischemic risk factor and bleeding risk factor at the same time[41]. Some studies have demonstrated that including CKD in known risk scores, increases the predictive value of the score. A modified CHA2DS2-Vasc score including CKD with a different definition showed a better discriminative capacity than the original score in mortality prediction in an ACS patient population[42].

However, the double association with ischemic and bleeding events in IHD patients is not simple to manage for the clinician and, according to this consideration, we move forward with the analysis of the bleeding risk scores, to put some lights on this risk factor.

Variables of some of the most adopted bleeding scores are summarized in Table 2. Prior bleeding/anemia and CKD are the only variables common to all scores. In particular, baseline anemia was assessed as one of the most important independent predictors of bleeding in PARIS MB and PRECISE-DAPT. As evident, HAS-BLED included some variables that were not statistically significant in the derivation cohort, like age, blood pressure, medication predisposing to bleeding and previous stroke: however, these variables were still included due to their known association with bleeding events derived from previous literature[28]. On the other hand, all scores do not consider some important variables known to be associated with increased bleeding risk because these are not common in patients with IHD or those undergoing PCI (like thrombocytopenia) or because they were rarely recorded in the derivation data. The mentioned differences in risk prediction scores are directly linked to heterogeneity in the populations studied, the variables assessed and the bleeding definitions used in the development cohorts.

Information about the subsequent bleeding risk in patients that undergo PCI with a history of prior bleeding event is scarce. Nonetheless, a prior spontaneous bleed at any time was assessed as an important predictor of bleeding in the PRECISE-DAPT score and, by itself, rises the patient bleeding risk in the highest quartile[30].

Anemia defined by World Health Organization criteria (hemoglobin < 13 g/dL in men and < 12 g/dL in women) is not uncommon in patients undergoing PCI and is directly related with the risk of future bleeding[43]. A meta-analysis of 44 studies including more than 230000 patients undergoing PCI, anemia (defined by World Health Organization criteria in the majority of studies) prevalence was 16% and was associated with a doubled risk of subsequent bleeding [as defined in individual studies; adjusted risk ratio, 2.31 (95%CI: 1.44–3.71)][44]. Furthermore, bleeding risk increased with increasing severity of anemia. In PARIS MB, anemia at baseline (defined as hemoglobin < 12 g/dL in men and < 11 g/dL in women) was assessed as an important predictor of 2-year BARC 3 or BARC 5 bleeding [9.5%

with *vs* 2.7% without anemia; adjusted HR = 2.72 (95%CI: 1.83–4.04); $P < 0.0001$][20]. In PRECISE-DAPT a reduction in the risk of TIMI major/minor bleeding at 1 year was independently associated with every 1 g/dL increase in hemoglobin between 10 and 12 g/dL [adjusted HR = 0.67 (95%CI: 0.53–0.84); $P = 0.001$][31].

Estimated glomerular filtration rate (eGFR) < 30 mL/min, which configures a severe or end-stage CKD, is considered a major ARC-HBR criterion, while eGFR between 30–59 mL/min (moderate CKD) is considered a minor ARC-HBR criterion. Unfortunately, patients with severe CKD have generally been excluded from randomized trials and only approximately 30% of patients undergoing PCI have an eGFR < 60 mL/min[45]. However, it has been demonstrated that the bleeding risk increases incrementally with worsening CKD and even mild CKD is an independent risk factor for bleeding after PCI [46-49]. In the PRECISE-DAPT score, eGFR < 30 mL/min by itself increases patients bleeding risk to the highest quartile, whereas milder CKD is associated with a slight to moderate risk. It must be noticed that in the DAPT score, CKD is not considered as a variable because the associated increased bleeding risk was balanced by an almost identical increased ischemic risk[22].

CONCLUSION

According to our analysis, it becomes clear that a single score can't be the real solution to balance the ischemic/bleeding risk of a patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD. In particular, we found that diabetes mellitus and vascular disease clearly increase the risk of ischemic events, while previous bleeding, anemia and CKD bring a high risk of further bleeding events. Some scores include too many variables that can mislead the clinician choice: since a perfect score could not exist we suggest clinicians apply the most user friendly and at the same time, evaluate the cited variables separately. As suggested by Guidelines, PRECISE-DAPT could be the most suitable bleeding risk score since it is more influenced by CKD, anemia and history of bleeding, while PARIS CTE should be the ischemic risk score of choice, including diabetes mellitus and vascular disease. However, the final result of a clinical reasoning should not be the right score result but the most fitted patient therapy.

ARTICLE HIGHLIGHTS

Research background

Bleedingsare an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention, representing a hazard equivalent to or greater than that for recurrent ACS. Dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events, but the benefit of such therapy is counteracted by the increased hemorrhagic complications.

Research motivation

An early and individualized patient risk stratification can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients.

Research objectives

In order to review existing literature and gain better understanding of the role of ischemic and hemorrhagic risk scores in patients with ischemic heart disease (IHD).

Research methods

The authors used a combination of terms potentially used in the literature describing the most common ischemic and hemorrhagic risk scores to search in PubMed, as well as references of full-length articles. The authors briefly describe the most important ischemic and bleeding scores that can be adopted in patients with IHD, focusing on GRACE, CHA2DS2-Vasc, PARIS CTE, DAPT, CRUSADE, ACUITY (Mehran *et al*), HAS-BLED, PARIS MB and PRECISE-DAPT score.

Research results

A single score can't be the real solution to balance the ischemic/bleeding risk of a patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD. In particular, we found that diabetes mellitus and vascular disease clearly increase the risk of ischemic events, while previous bleeding, anemia and CKD bring a high risk of further bleeding events. Some

scores include too many variables that can mislead the clinician's choice: since a perfect score could not exist we suggest the clinician apply the most user friendly and at the same time evaluate the cited variables separately. As suggested by Guidelines, PRECISE-DAPT could be the most suitable bleeding risk score, since it is more influenced by CKD, anemia and history of bleeding, while PARIS CTE should be the ischemic risk score of choice with diabetes mellitus and vascular disease.

Research conclusions

Risk scores by themselves can't be the single solution to balance the ischemic/bleeding risk of an IHD patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD.

Research perspectives

Future research should try to elaborate an omni-comprehensive score to be adopted in IHD and at the same time be easy to use and reliable.

FOOTNOTES

Author contributions: Persampieri S and Castini D participated in the development of the proposal to research the topic, performed literature search and review, and wrote the draft of the manuscript, reviewed, edited and approved the manuscript; Lupi A and Guazzi M participated in the supervision of the research on the topic, reviewed, wrote and revised the manuscript as senior authors.

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REVIEW

Fundamentals of percutaneous coronary bifurcation interventions

Tamer Kırat

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Abstract

Coronary bifurcation lesions (CBLs) account for 15%-20% of all percutaneous coronary interventions. The complex nature of these lesions is responsible for poorer procedural, early and late outcomes. This complex lesion subset has received great attention in the interventional cardiac community, and multiple stenting techniques have been developed. Of these, the provisional stenting technique is most often the default strategy; however, the elective double stenting (EDS) technique is preferred in certain subsets of complex CBLs. The double kissing crush technique may be the preferred EDS technique because of its efficacy and safety in comparative trials; however, this technique consists of many steps and requires training. Many new methods have recently been added to the EDS techniques to provide better stent scaffolding and to reduce early and late adverse outcomes. Intravascular imaging is necessary to determine the interventional strategy and postinterventional results. This review discusses the basic concepts, contemporary percutaneous interventional technical approaches, new methods, and controversial treatment issues of CBLs.

Key Words: Percutaneous coronary intervention; Coronary artery disease; Drug-eluting stents; Bifurcation lesion; Stenting technique; Left main intervention

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Core Tip: Coronary bifurcation lesions are one of the most challenging subsets in percutaneous interventions. Many different interventional techniques have been used to overcome the relatively poor procedural and long term outcomes of these lesions of great interest. In this review, basic aspects of coronary bifurcation lesions and step-by-step classical stenting techniques, as well as recently introduced techniques, modifications, trials and important issues in the latest guidelines are discussed.

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INTRODUCTION

Percutaneous interventions of coronary bifurcation lesions (CBLs) are not only technically challenging, with lower procedural success and higher complication rates, but also have higher thrombosis and restenosis rates than nonbifurcation lesions[1-3]. The broad anatomical (*i.e.*, bifurcation site and angle, and vessel diameters) and pathological (*i.e.*, severity, locations and lengths of the atherosclerotic plaques) spectrum of CBL, as well as dynamic changes (carina, plaque shift and dissection) during intervention are responsible for the complexity of these lesions[3,4]. Many stenting and other interventional techniques have been developed and are used to provide optimum stent scaffolding, resulting in fewer clinical adverse outcomes. Operators should be familiar with these techniques and the basic aspects of CBLs.

BASIC ASPECTS

Anatomy

In epicardial coronary arteries, bifurcations show a fractal geometry[5] (a fractal is a geometric shape in which every smaller structure is similar to the whole part). This geometry provides minimum energy consumption and the optimum amount of blood required for the underlying myocardium[6]. A coronary bifurcation consists of a flow divider (carina) and three vessel segments: The proximal main vessel (PMV), the distal main vessel (DMV) and the side branch (SB) (Figure 1). There is a constant relationship between these three vessels that was identified by Murray's law 95 years ago[7] as:

$(\text{Diameter of PMV})^3 = (\text{Diameter of DMV})^3 + (\text{Diameter of SB})^3$

Nearly a decade ago, this law was modified in human coronary arteries by the Huo-Kassab law[8] as:

$(\text{Diameter of PMV})^{7/3} = (\text{Diameter of DMV})^{7/3} + (\text{Diameter of SB})^{7/3}$

Nearly at the same time, Finet's formula was created by IVUS measurements in normal human coronary arteries[9] as:

(Diameter of PMV) = 0.678 (*i.e.*, approximately 2/3) × (Diameter of DMV + Diameter of SB)

Huo *et al*[10] compared these 2 Laws and Finet's formula in the epicardial coronary bifurcations of patients and swine in a later study. They found that Huo-Kassab law accurately predicts all size diameters of the epicardial coronary bifurcation vessels whereas Murray's law and Finet's formula can only do so in certain size subsets[10]. However, due to its simplicity, Finet's formula is the most commonly used in clinical practice in most angiography units.

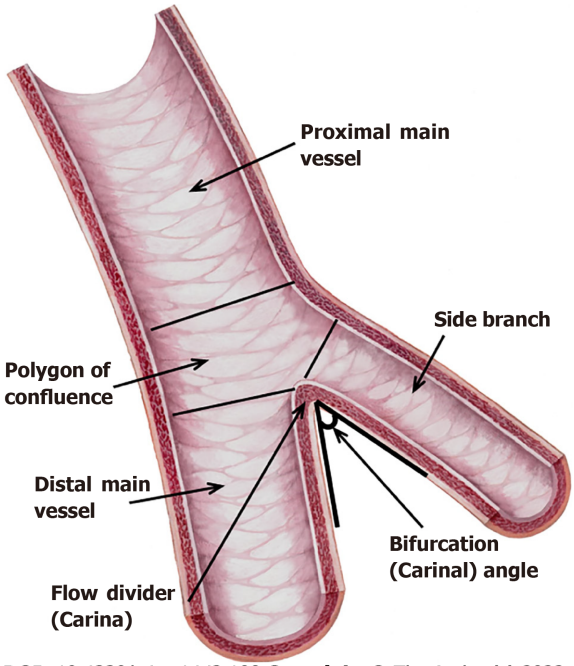
The polygon of confluence (POC) is an independent area between the PMV, DMV and SB whose boundaries are formed by the lines drawn vertically in the ostium of branches and at the end of the PMV (Figure 1)[11,12]. Finally, the bifurcation angle (carinal angle) is important in accessing the SB and in the decision of the stent treatment strategy.

Definition

A bifurcation lesion is a major epicardial coronary artery stenosis next to and/or including the ostium of a significant side branch[13,14]. A significant SB is a branch whose severe narrowing or acute occlusion before or during intervention can cause considerable ischemia or a new infarction area that will worsen the clinical course of a particular patient. To determine the significance of the SB, not only the diameter, length, location and collateral function of the SB but also the symptoms, left ventricular function and viability of the supplied myocardium should be evaluated[13,14].

Pathophysiology of atherosclerosis in CBL

Bifurcations are among the sites most affected by atherosclerotic processes in the coronary tree. *In vitro* and recent *in vivo* studies on the anatomy and flow patterns of coronary bifurcations have shown that local flow disturbances and thus endothelial shear stress (ESS) play the most important role in the localization and progression of atherosclerotic plaques[15]. ESS is the tangential force caused by the friction of the flowing blood on the endothelial surface[16]. The major determinants of ESS are the blood viscosity and the spatial gradient of the blood velocity. Endothelial mechanoreceptors sense ESS; and in response to high ESS, these receptors induce many intracellular signaling pathways resulting in the expression of many atheroprotective genes and suppression of many proatherogenic genes. Conversely, in the case of low or oscillatory ESS, atheroprotective genes are suppressed and proatherogenic genes that promote atherosclerosis are upregulated[15-17]. Indeed, in IVUS and autopsy studies of bifurcation



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Figure 1 Coronary bifurcation anatomy.

lesions, atherosclerosis was most frequently demonstrated in the lateral walls of MVs and side branches where ESS was low and oscillatory and uncommon in the carina where ESS was high[18]. Moreover, the carinal angle was found to affect the severity of atherosclerosis as larger angles have been correlated with increased plaque burden[19]. This is again explained by the role of ESS since larger angles produce lower and more oscillatory ESS in the lateral walls of the bifurcation vessels. Finally, in addition to its most important role in plaque initiation and progression, low ESS has also been found to be associated with rupture-prone atherosclerotic plaque formation[19]. Thus, CBLs have an increased tendency for plaque rupture, platelet aggregation and atherothrombosis[20].

Classification

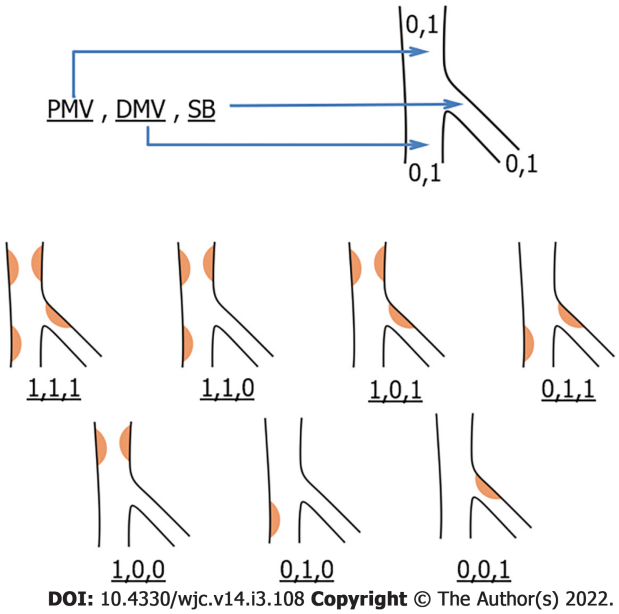
Various angiographic classifications of CBL have been proposed[21]. Because of its simplicity, the easiest to remember and most prevalently used is the Medina classification[22]. This classification is established on the presence ("1") or absence ("0") of significant stenosis (≥ 50%) in the proximal main vessel (MV), distal MV and SB in CBLs, respectively (Figure 2). According to this classification, two different types are described: "true" and "non-true " CBLs. Significant stenosis (≥ 50%) in both vessels (proximal MV and/or distal MV and SB), *i.e.*, Medina 1,1,1/1,0,1 and 0,1,1 classes are defined as "true", while all others are defined as "non-true" CBLs. "True" bifurcation lesions are more complex and more difficult to treat with poorer outcomes than "non-true" types[23]. However, in true bifurcation lesions, Medina 1,1,1 and 0,1,1 lesions were found to have a higher risk of cardiac death, myocardial infarction (MI), and more SB occlusion than Medina 1,0,1 lesions[23]; and only these two classes have been taken as the criterion or one of the criteria of complex true lesions in many bifurcation (especially left main) trials.

Finally, the Medina classification does not consider other important information that may direct treatment strategies, such as lesion size and length, calcification and bifurcation angles. Therefore, additional modalities such as multislice computed tomography (MSCT), intravascular ultrasound (IVUS), optical coherence tomography (OCT) and fractional flow reserve (FFR) or other functional tests may be necessary to clarify the true classification of a bifurcation lesion and to determine the treatment strategy[24].

PERCUTANEOUS CORONARY INTERVENTION (PCI) TECHNIQUES

Classification

Many stenting techniques have been developed and published. For simplicity, these techniques were classified by the European Bifurcation Club (EBC) as "MADS" in 2008. However, some techniques have been abandoned due to adverse outcomes or lack of effectivity. Therefore, an updated new classification called "MADS-2" was created by the EBC in 2020[25]. This classification is based on the location of the



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Figure 2 Medina classification. "1" indicates ≥ 50% stenosis, and "0" indicates < 50% stenosis. Atherosclerosis is most often seen in the lateral walls of vessels where endothelial shear stress is low and oscillatory. DMV: Distal main vessel; PMV: Proximal main vessel; SB: Side branch.

first stent implanted (as Main vessel, Across side branch, Double lumen in proximal MV or Side branch). Balloon applications and dedicated bifurcation stent types are added to the original form in this new classification[25].

Although MADS-2 involves many stenting techniques, the most widely used major bifurcation stenting techniques recommended by the EBC are as follows[25]: (1) One-stent techniques: The provisional stenting technique (PST) and inverted provisional stenting technique; and (2) Two-stent techniques (Elective, or bail-out in PST): (a) T/T and protrusion (TAP) stenting; (b) Culotte/inverted culotte stenting techniques; and (c) Double kissing (DK)-crush technique.

Vascular access and guiding catheter selection

In one-stent techniques, most CBLs can be treated transradially or transfemorally using a 6 Fr guiding catheter (GC). However, if a rotablator with a burr size ≥ 2 mm is used or more than two balloons are used simultaneously in the GC, a 7 Fr or larger GC is required[26]. Although transfemoral is the most preferred route in this situation, an increasing number of operators prefer the transradial route using slender sheaths or sheathless guiding catheters.

Two-stent techniques can also be performed using 6 Fr GC except when there are two stents in the GC at the same time, such as mini-crush, V or simultaneous kissing stenting techniques[27].

Due to the challenging interventional nature of CBLs, guiding catheters with strong support (such as extra back-up guiding catheters for the left coronary artery and AL 0.75, AL1 or AR2 for the right coronary artery (RCA)) should be preferred[28].

Optimal views for bifurcation lesions[28,29]: (1) Left main coronary artery (LMCA) bifurcation: (a) Working view: RAO caudal (0–30°, 25–30°); and (b) Side branch ostium visualization: LAO caudal (30–60°, 25–30°), AP caudal (0, 45-55°); (2) LAD-first diagonal bifurcation: (a) Working view: RAO cranial (10°, 40°); and (b) Side branch ostium visualization: AP/LAO cranial (0–45°, 25–70°); (3) For early diagonals: LAO caudal (45–55°, 25–30°); (4) LCx-first marginal: (a) Working view: RAO caudal (0–15°, 25°); (b) Side branch ostium visualization: AP caudal (0, 25°–40°), LAO caudal (45–55°, 25–30°); and (5) RCA-PDA/PL: (a) Working view: LAO 35–50°; and (b) Side branch ostium visualization: AP/LAO cranial (0–55°, 30-40°).

Which technique should be selected? The PST or the elective double stenting technique?

Most of the randomized comparative trials prior to the mid-2010s showed no difference in major adverse cardiovascular events (MACE) between the PST and elective double stenting (EDS) techniques [26,30,31]. Even, lower mortality rates were found for the PST compared to EDS in two recent meta-analyses[32,33]. As a result, the provisional stenting technique has been recommended as the default strategy for CBLs in the guidelines and consensus statements for more than 15 years. However, it should be noted that the EDS techniques in these trials and meta-analyses were the culotte, T, and crush techniques. After the introduction of the DK-crush technique, in 2011, Chen *et al*[34] showed that there was a significant reduction in target lesion revascularization (TLR) and target vascular revascularization (TVR) rates in favor of the DK-crush technique *vs* the PST with no MACE differences in complex true

bifurcation lesions in the DKCRUSH II trial. Later, the DKCRUSH III trial showed that the culotte stenting technique was worse than the DK-crush technique in terms of MACE in patients with unprotected left main (LMCA) bifurcation lesions[35]. Moreover, the DKCRUSH V study presented in 2017 found a lower rate of target lesion failure (TLF) at 1 year with the DK-crush technique than with the PST in complex true LMCA bifurcation lesions[36].

Recently, the 3-year outcomes of the DKCRUSH V trial were published and confirmed the one-year results and additionally showed a reduction in the stent thrombosis rate in favor of the DK-crush technique[37]. Crimi *et al*[38] found that the DK-crush technique lowered device-oriented clinical events (defined as a composite of cardiac death, target-vessel MI, stent thrombosis and TLR or TVR) *vs* the PST and other EDS techniques in their recent meta-analysis. In another concurrent network meta-analysis, Di Gioia *et al*[39] showed that TLR was significantly lower with the DK-crush technique than with the PST and other EDS techniques with no differences in cardiac death, MI or stent thrombosis rates. In addition, in this meta-analysis, a clinical benefit was observed with EDS techniques over PST in CBL with SB lesion lengths ≥ 10 mm. In the recently published DEFINITION II trial, complex bifurcation lesions were defined by the sum of various criteria, as shown in Table 1. In this trial, the EDS technique (DK-crush 77.8%, culotte 17.9%, and other 4.3%) provided a significant reduction in TLF (mainly driven by target vessel MI and clinically driven TLR) compared to the PST in the defined complex bifurcation lesions at one year[40].

Despite the favorable results of the DK-crush technique in randomized studies and two meta-analyses, the recent guidelines still recommend the PST as the default strategy for complex CBLs and a class IIb indication for the DK-crush technique over the PST in true LMCA bifurcations[25,41-43]. The reason for this may be some reservations that have been described[30]: (1) The DK-crush technique has multiple steps and is a challenging technique; (2) The DKCRUSH trials mostly come from the same group of interventional experts who have performed this procedure for many years; and (3) The PST results in these trials were worse than previously published ones, which might be associated with a high SB stenting rate (29%-47%) due to the high rate of long SB lesions (mean 15-17 mm).

When deciding between the PST and EDS, the high risk of SB occlusion should also be considered, as SB occlusion may result in serious adverse clinical outcomes[44]. SB occlusion predictors by angiography, IVUS and OCT have been described recently[44,45]. Angiographically, plaque on the same side of the SB, SB stenosis > 50%, POC stenosis > 50%, bifurcation angle > 70%, MV/SB diameter ratio (diameter of PMV+DMV/2×diameter of SB) > 1 and a low MV TIMI flow grade were found to be predictors of SB occlusion after MV stenting. A risk score was described based on these predictors[44]. According to this risk score, higher stenosis rates, larger bifurcation angles, larger MV/SB diameter ratios, a lower TIMI flow grade, and more predictors result in higher SB occlusion rates[44].

The recently published EBC-MAIN study, which compared the PST and EDS techniques in LMCA bifurcation lesions, showed that there were fewer MACE in the PST than EDS, although the difference was statistically insignificant. The authors consequently recommended the PST as the default strategy for LMCA bifurcation lesions. However, it should be noted that the DK-crush technique was used in only 5% of the EDS patients in this trial. In addition, the mean lesion lengths of the side vessels were not long: 5.8 cm and 7.9 cm in the PST and EDS patients, respectively[46].

Consequently, for non-true CBL, the default strategy is the PST[47]. In true complex CBL (Medina 1,1,1 or 0,1,1), if the SB is ≥ 2.5 mm and the SB lesion length ≥ 10 mm or the likelihood of SB occlusion is high or SB wiring is difficult, it is better to choose EDS; otherwise, the PST is preferred[38,39,41,45,48]. In true non-complex CBL (Medina 1,0,1), the inverted PST may be an appropriate treatment if there is no large difference between the SB and the PMV diameter[42]; otherwise, and in the case of the above risks, EDS may be preferred[39,45,48,49]. A proposed algorithm for choosing between the PST/inverted PST and the EDS technique is shown in Figure 3.

The ongoing BBK3 trial will provide more data on the outcomes of the PST or EDS techniques in non-LMCA bifurcation lesions[50].

The choice between the different EDS techniques depends partially on the bifurcation angle. The T technique can only be applied at bifurcation angles very close to 90°[25]. The TAP technique can be performed at bifurcation angles from 70°-90°. Culotte/inverted culotte stenting and the DK-crush techniques (unlike the crush technique) can be implemented regardless of the bifurcation angle[51,52]; however, applying the culotte technique at < 70° angles gives better results[35]. If the bifurcation angle is from 70°-90°, due to simplicity and familiarity, an increasing number of operators are using the T/TAP technique not only when a second stent is required in the PST[53] but also in the EDS technique as the first-line therapy and perform the culotte/inverted culotte or DK-crush techniques if the angle is < 70° [41,54].

In conclusion, in view of recent data, the DK-crush technique may be preferred over the other two-stent techniques regardless of the bifurcation angle; however, it is a complex procedure with many steps, and the operator's familiarity with a particular technique is an important factor in the choice of which EDS technique to perform and in obtaining the best result[45].

Table 1 DEFINITION criteria for a complex coronary bifurcation lesion[40]

Major criteria	Complex lesion definition	Minor criteria
For left main bifurcation (Major 1)	**Major 1 or Major 2 + any 2 minor criteria**	> Mild calcification
SB lesion length ≥10 mm and SB diameter stenosis ≥ 70%		Multiple lesions
		Bifurcation angle < 45° or > 70°
For non-left main bifurcation (Major 2)		MV-RVD < 2.5 mm
SB lesion length ≥ 10 mm and SB diameter stenosis ≥ 90%		MV lesion length ≥ 25 mm
		Thrombus-containing lesions

All bifurcation lesions are in Medina 1,1,1 or 0,1,1. MV: Main vessel; RVD: Reference vessel diameter; SB: Side branch

PST

The step-by-step PST is shown in Figure 4.

Wiring the vessels

In addition to the MV, the SB should also be wired in all CBLs. This wire helps to prevent SB occlusion after MV stenting, serves as a marker in case of SB occlusion, widens the angle between the PMV and SB for easier access, enhances support of the guiding catheter, and finally can be used as a rescue balloon guidewire that will be described later. To prevent the two wires from wrapping, the more difficult vessel (mostly the SB) should be wired first, and the second wire should be inserted without much manipulation.

Wire types and shaping

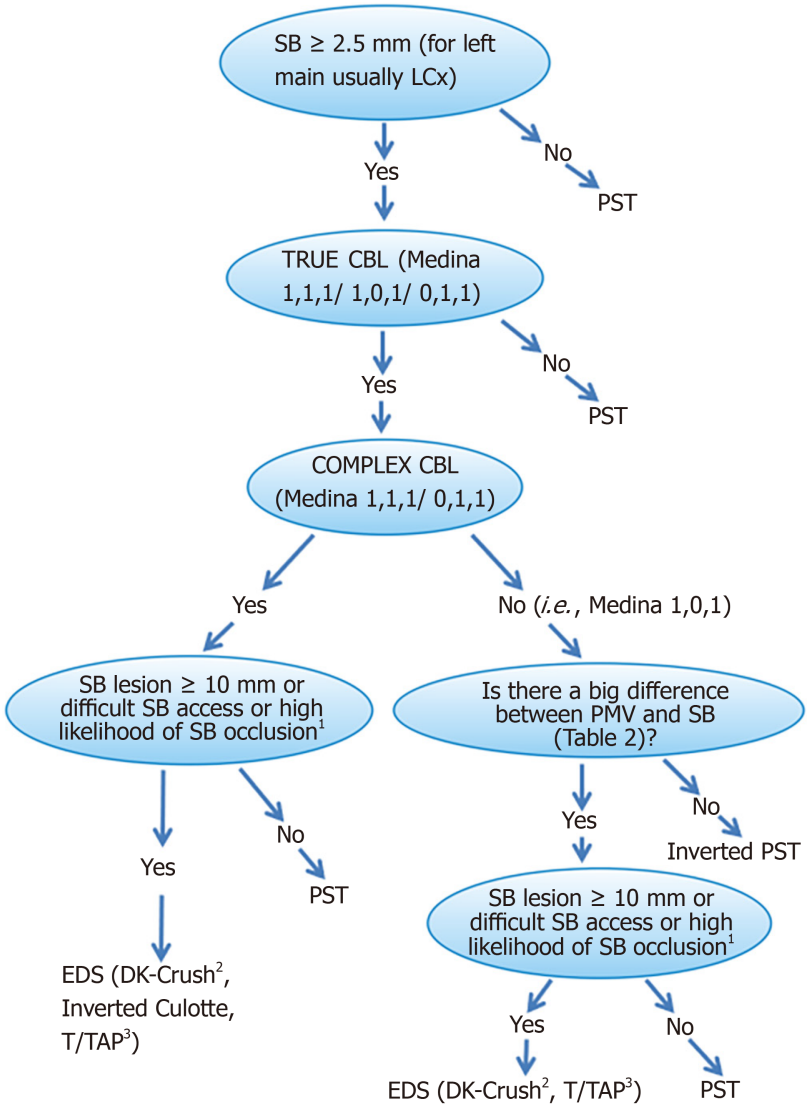
The types of wires are left to the operator's preference. Any type of wire (hydrophilic with or without polymer coating and hydrophobic) can be used[55,56]. One necessary point is not to jail the radiopaque tip part of the wire in the SB ostium during MV stenting.

Both wires should be ready for the exchange technique if needed after MV stenting. To accomplish this, the MV guidewire tip should be angled so that its length will be longer than the proximal MV reference diameter to reach the SB ostium. A 1-1.5 mm secondary bend can also be added to the tip to hook the struts of the MV stent[57]. The SB wire should be prepared as a sharp angled short tip that will make it easier to create a "U" shape to pass through the MV stent during wire exchange[58]. The MV wire should not be pushed too distally in order to maintain the shape of the tip for exchange and to reduce the risk of distal perforation or dissection that can occur during many maneuvers.

Troubleshooting SB wiring problems

SB wiring may be difficult in the following circumstances: a bifurcation angle greater than 70°-90°, severe ostial SB stenosis, MV stenosis or severe calcifications in the proximal MV and/or ostial SB. In addition, tortuosity before or at the SB take-off may flatten or change the angle of the wire, resulting in difficult SB wiring[58].

Possible solutions for solving the SB wiring problem are the following[52,58]: (1) If the problem is wide angulation, a wide smooth bend or double bend shape given to the tip can help; (2) The workhorse wire can be replaced with a stiffer or hydrophilic polymer-coated wire. Stiffer wires are preferred first because hydrophilic wires can easily go subintimally and cause dissection or perforation; (3) Pull-back wire technique: A wide smooth bent or double bent wire is advanced into the DMV and pulled back to intubate the SB ostium. After intubating, a gentle counterclockwise rotation allows the wire to advance in the SB; (4) Reverse wire technique: When the SB has an excessively angled take-off (greater than 90°), a polymer-jacket wire with a 3-5 cm tip bent 180°, like a hairpin, is used in this technique (Figure 5). The wire is advanced in the DMV and pulled back to the bifurcation, and an attempt is made to enter the SB ostium. After intubation, the wire is gently withdrawn and gently rotated counterclockwise to allow the wire to advance in the SB; (5) A dual lumen microcatheter, a steerable-tip microcatheter (Venture, Teleflex, Wayne, PA, United States) or an angled microcatheter (SuperCross 45-90-120°-XT, Teleflex) can be used to direct the wire to the SB; (6) When there is a large plaque burden that prevents wiring the SB, debulking techniques such as rotational/orbital atherectomy or laser may be used; (7) Balloon dilatation of the MV to modify the plaque is performed by many operators as a last effort. However, it can cause plaque and/or carina shift, resulting in SB occlusion; and (8) Finally, if the SB cannot be wired, the decision to abandon the procedure can be made based on the patient's clinicopathological condition.



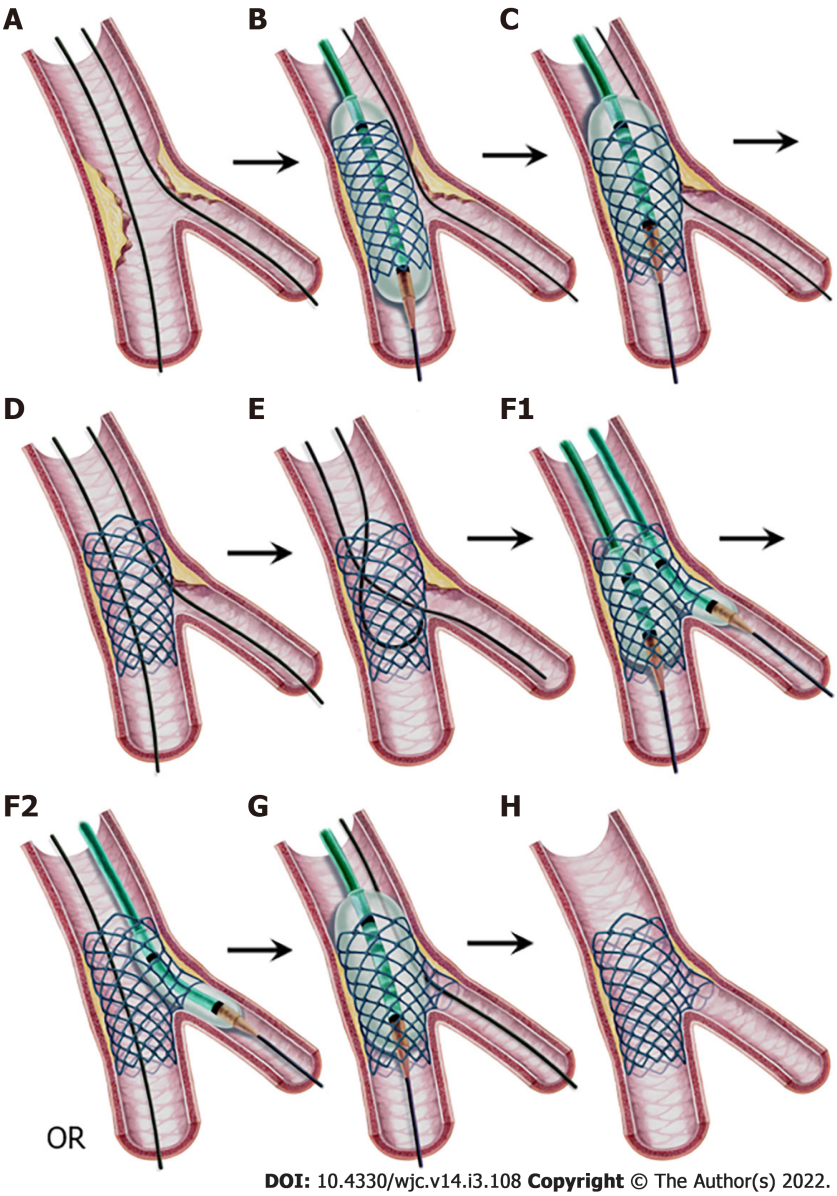
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Figure 3 Proposed algorithm for selecting an optimum percutaneous coronary intervention strategy in both left main coronary artery and non-left main coronary artery bifurcation lesions. [1]Plaque on the same side of SB, SB stenosis > 50%, POC stenosis > 50%, bifurcation angle > 70%, MV/SB diameter ratio (diameter of PMV+DMV/2×diameter of SB) >1 and low MV TIMI flow grade are predictors of a high likelihood of SB occlusion. The larger the size of the numbers and/or the lower the TIMI flow grade and/or the more predictors, the higher the risk of SB occlusion. A recently created SB occlusion risk score may be used[44]. [2]The DK-crush technique seems to be preferable to the other EDS techniques in view of the recent data; however, the operator's experience is decisive in the choice between the EDS technique and is important in obtaining the best result. [3]The TAP technique cannot be considered the upfront technique in cases with difficult SB access and a high risk of SB occlusion because of SB stenting after MV stenting. CBL: Coronary bifurcation lesion; EDS: Elective double stenting; LCx: Left circumflex artery; LMCA: Left main coronary artery; MV: Main vessel; POC: Polygon of confluence; PST: Provisional stenting technique; SB: Side branch.

Predilation of the MV and the SB

Optimal preparation of the MV is necessary before stenting. Therefore, the operator can decide to predilate the MV and/or perform any debulking procedure according to the MV lesion properties.

Routine predilation of the SB has been a controversial issue in the PST. Predilation aims to prevent SB closure after MV stenting; however, it can cause dissection that may prevent guidewire advancement during wire exchange or may require an extra stent in the SB. A prospective randomized study showed that SB predilation resulted in improved flow with less need to treat the SB[59]. However, another double-blind smaller randomized study and a recent meta-analysis of eight trials demonstrated the opposite: SB predilation increased SB intervention rates and made no difference in procedural angiographic and long-term major cardiovascular outcomes[60,61]. Consequently, it seems that routine predilation of the SB cannot be recommended currently. Conditions that favor SB predilation with an undersized non-compliant balloon are severe ostial SB narrowing, extensive SB calcification, difficult SB access or decreased flow after MB predilation and/or debulking[14,49].



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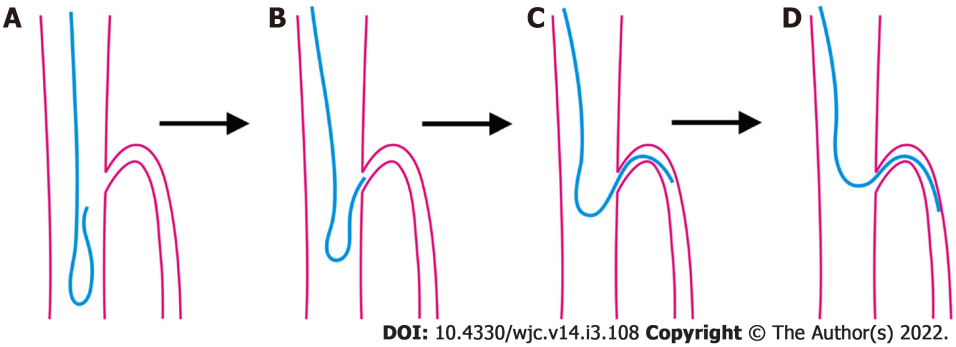
Figure 4 Provisional stenting technique, step-by-step. A: Both branches are wired; B: A stent sized to the distal MV diameter is implanted in the MV; C: Proximal optimization technique (POT) application with a balloon sized to the proximal MV diameter with its distal shoulder aligned to the carina; D: Stent view after POT. If the result is satisfactory, stop here. If not, proceed to step E; E: Guidewire exchange; First, the SB is wired through the most distal cell. Second, the retracted and released SB wire is advanced into the distal MV as a "U" shape; F1: Kissing balloon inflation sized to branch diameters, or F2: SB ostium ballooning as a part of the POT-side-POT technique; G: Final POT; and H: Final result. MV: Main vessel; POT: Proximal optimization technique; SB: Side branch.

When the SB is predilated, the angiographic result should be carefully evaluated before MV stenting. In situations where the SB is compromised, such as dissection or difficult SB access, the operator should be ready to change the stenting strategy to another strategy, such as the inverted PST or the DK-crush technique[49].

Newer side branch protection techniques

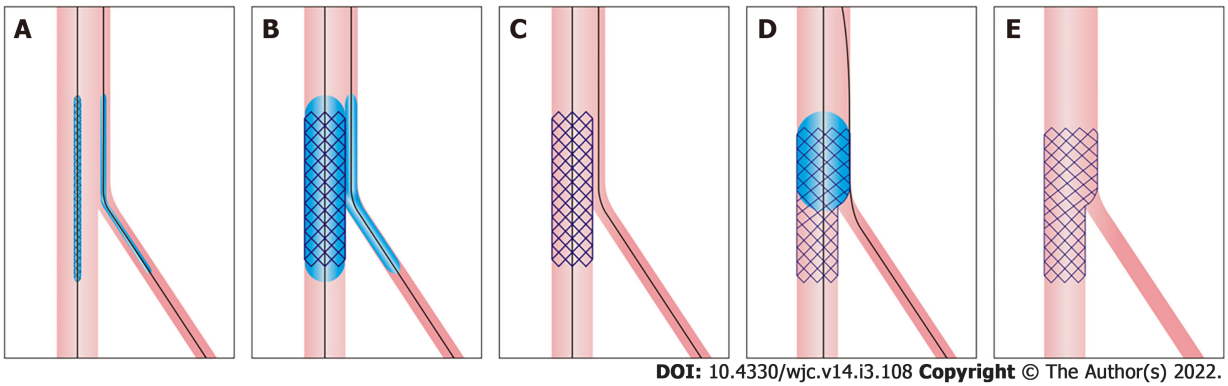
To prevent side branch occlusion during the PST, various novel techniques have been developed recently: the pre-kissing technique, jailed balloon, jailed semi-inflated balloon and modified jailed balloon techniques. The pre-kissing technique involves the simultaneous dilation of two undersized balloons (one in the MV and the other in the SB) whose proximal parts are aligned in the proximal MV before MV stenting. The aim of this technique is to sustain the central position of the carina while moving the atherosclerotic plaques away. Using first-generation drug eluting stents (DESs), this technique was shown to reduce SB-related complications in a small retrospective study[62].

The jailed balloon technique (JBT) and the jailed semi-inflated balloon technique (JSBT) involve implanting an MV stent while a semi-compliant balloon is in the SB protruding to the MV. The proximal marker of the SB balloon is positioned to align or 1-2 mm proximal to the marker of the MV stent (Figure 6). The SB balloon is uninflated (JBT) or inflated to low or moderate pressure (< 3 to 7 atm)



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Figure 5 Reverse wire technique. A, B: The wire shaped as a hairpin is advanced into the distal main vessel and withdrawn back to the carina; C, D: When the tip intubates the side branch (SB) ostium, slight withdrawal and gentle counterclockwise rotation allow the wire to advance in the SB.



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Figure 6 Jailed balloon technique and jailed semi-inflated balloon technique. A: A balloon is positioned in the side branch (SB) to align or 1-2 mm proximal to the main vessel (MV) stent in the proximal MV; B: The stent is deployed while the SB balloon is kept inflated at a low or moderate pressure (in the jailed semi-inflated balloon technique) or uninflated (in the jailed balloon technique); C: Both balloons are removed; D: Proximal optimization technique sized to the proximal MV diameter; and E: Final result.

(JSBT) during MV stent balloon inflation at nominal pressure. After MV stent implantation, if the SB flow is not compromised (*i.e.*, TIMI-3 flow), the uninflated SB balloon is inflated at low (< 3 atm) pressure in the JBT (not shown in Figure 6). If less than TIMI-3 flow in the SB is observed, the SB balloon is inflated at nominal pressure. After the balloons are removed, the proximal optimization technique (POT) is performed in the PMV[63,64].

In the modified jailed balloon technique (M-JBT), the MV stent is positioned across the SB, and a balloon is placed in the SB with its proximal end touching the MB stent (Figure 7). Both the MV stent and SB balloon are inflated at the same nominal pressure (*e.g.*, 12 atm) simultaneously. After deflation and removal of the balloons, the POT is performed in the PMV[65].

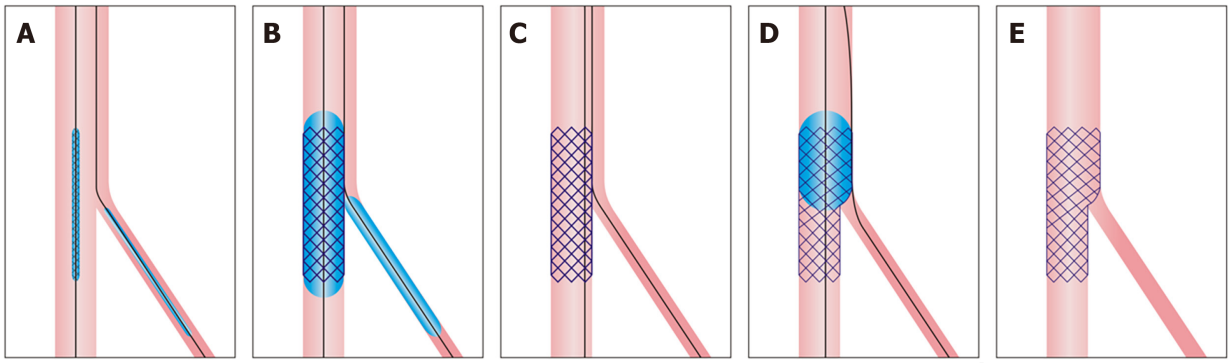
All three JBTs, the jailed semi-inflated balloon technique and the M-JBT were investigated in small-sized trials and found to have low SB loss, SB dissection and MACE rates[66,67]; however, larger randomized controlled trials are required for the routine use of these new techniques in the PST.

MV stenting

The preferred type of stent is new-generation DESs which reduce the risk of restenosis and repeat interventions compared to bare metal stents and early-generation DESs[68,69]. The diameter of the MV stent should be chosen at a 1:1 ratio according to the reference distal MV size (Figure 4B). The implantation of a larger stent can cause distal dissection and carinal shift, which can result in severe narrowing or even occlusion of the SB. The length of the stent should be selected so that its PMV part will be equal to or longer than the shortest balloon available (usually 6-8 mm) for the subsequent POT [25,48]. The stent should be implanted at nominal pressures, avoiding overexpansion, which is called the "distal optimization technique" (called "DOT" in the literature)[53].

POT

Since the diameter of the MV stent is chosen according to the diameter of the DMV, a semi-compliant or non-compliant balloon sized to the PMV diameter should be inflated in the PMV stent part to correct malapposition[25] (Figures 4B and 4C). The distal shoulder of the balloon (the point where balloon parallelism ends) should be aligned to the level of the carina so as to avoid stent underexpansion at the



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Figure 7 Modified jailed balloon technique. A: Semicompliant balloon in the side branch is positioned with its proximal end touching the main vessel (MV) stent; B: Both the MV stent and balloon are inflated at the same nominal pressure; C: Both balloons are removed; D: Proximal optimization technique sized to proximal MV diameter; E: Final result.

polygon of confluence (occurs when placed more proximally) and carinal shift (occurs when placed more distally)[70]. Many operators use the distal balloon marker as the distal shoulder; however, as the location of this marker varies between manufacturers, the operator should be familiar with the design of the balloon used to avoid misplacement[49,71]. The POT corrects the malapposition of the stent in the PMV, prevents understrut passing of subsequent wires, provides strut protrusion into the SB and widens the distance between struts in the SB ostium which facilitates subsequent wire and balloon passing into the SB.

When the POT balloon is shorter than the PMV stent part, the POT must be applied to the entire PMV stent part. Furthermore, the POT balloon should not be longer than the PMV part of the stent; otherwise, it can cause proximal stent edge dissection.

Finally, the overexpansion capacity of the available stent types should be known to select the correct stent in order to provide natural fractal anatomy of the coronary bifurcation with the POT [72] (Table 2).

Is routine kissing balloon inflation or POT-side-POT technique necessary after the first POT?

KBI involves the inflation of two non-compliant balloons (one in the MV and the other in the SB) whose proximal parts are aligned in the proximal MV. The aim of this procedure after MV stenting is to remove the stent struts at the SB ostium, to eliminate the stenosis in the SB, and to maintain the carina in its central position.

In a recent meta-analysis, routine final KBI resulted in a significant reduction in SB restenosis, but an increase in MV restenosis rates with no significant differences in clinical outcomes[73]. Another recent larger meta-analysis of final KBI *vs* no-final KBI in PST trials also showed similar results in that there was no difference in terms of MACEs and other outcomes[74].

SB dilatation to open the struts at the ostium of the SB after MV stent implantation was shown to cause stent distortion with malapposition of struts at the opposite side of the SB ostium in bench studies [75,76]. Therefore, the POT or KBI should be performed to correct this distortion[71,75,76]. POT-side-POT is a new technique that involves initial POT + SB balloon dilatation + final POT (or re-POT) and will be described later.

Presently, there are no convincing data for KBI and insufficient data for the POT-side-POT technique to recommend either of them for routine use after the first POT in PST.

When should we treat the SB after the POT?

After the POT, if the SB flow is TIMI-3 and there is < 75% stenosis in the ostium, or no dissection, then the operation is completed.

After MV stenting, the MV plaque and/or carina shift can create an angiographic image of SB ostial narrowing. However, angiography is unreliable with regard to the functional significance of SB stenosis in this situation. It was shown in a study that none of the < 75% and only 27% of the SB stenoses ≥ 75% were found to be significant with the FFR[77]. This situation can be explained by the oval shape of the SB ostium (the narrower the carinal angle, the more oval the ostium) (Figure 8), the edge effect originating from angiography[57] and the recently shown elliptical stretch of the SB ostium after MV stenting[78].

Consequently, severe stenosis (≥ 75%) in the SB ostium, FFR ≤ 0.8, less than TIMI-3 flow or dissection in the SB requires SB intervention.

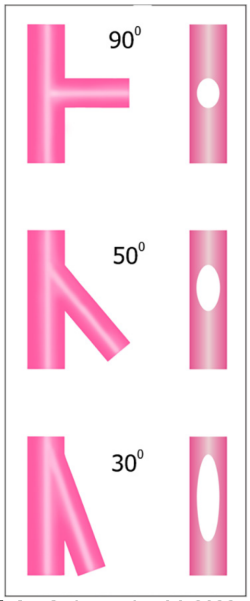
Technical steps of SB intervention after the POT

If the SB requires intervention after MV stenting and the POT, the sequential techniques and technical steps are as follows:

Table 2 Maximum-expansion capacity of stents

Manufacturer	Stent type	Stent size (mm)	Balloon[1] (bench test) (mm)	Maximum expansion (bench test) (mm)[72]	Maximum expansion (mm) (manufacturer recommendation)
Biosensors	Biomatrix A	3	5	4.1	-
		4	6	5.9	5.8
Medtronic	Resolute Onyx	2.5	4	3.3	-
		3	5	4.4	-
		4	6	5.6	-
		5	6	6	6
Biotronik	Orsiro	3	5	4	-
		4	6	5.3	4.4
Abbott	Xience	3	5	4.1	3.75
		4	6	5.6	5.5
Terumo	Ultimaster	3	5	4.3	-
		4	6	5.8	5.5
Boston Scientific	Synergy	2.75	5	3.6	3.5
		3.5	5	4.2	4.25
		4	6	5.7	5.75

[1]In the bench test, all balloons are inflated at 14 *atm*[72].



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Figure 8 Effect of bifurcation angle on side branch ostium ellipticity. Narrower angles result in more oval ostium shapes.

Guidewire exchange technique: The MV wire tip is pulled to the level of the carina and tried to pass into the SB through the most distal cell of the MV stent (carinal cell) at the SB ostium (Figure 4E). The passing of the wire through the distal cell is very important in the PST as subsequent balloon inflation will direct the struts to the non-carinal ostial segment of the SB, providing better scaffolding[26]. The jailed SB wire should not be retracted until the MV wire passes into the SB, since this wire indicates the SB ostium location and can be used when a rescue balloon is required as described next.

If the wire cannot be passed through the stent struts into the SB, the following options are available: (1) It can be reshaped; (2) The POT with a larger balloon can be performed again to open the cells and remove the struts at the SB ostium; (3) A hydrophilic polymer-coated or a stiffer wire can be used; (4) A

steerable-tip microcatheter (Venture, Teleflex), an angled microcatheter (SuperCross, Teleflex) or a dual lumen microcatheter can be used; and (5) Finally, a small balloon (1-1.5 mm) can be passed through the jailed wire under the stent struts and dilated at the ostium of the SB, which not only rescues the SB in case of occlusion but also allows the MV wire to enter the SB[26]. In extreme cases, the inverted crush technique can be implemented as a last effort to rescue the occluded SB.

After the MV wire is inserted in the SB, the jailed SB wire is withdrawn until it comes out under the stent struts and is then pushed forward into the stent. At this time, the tip should be formed into a "U" shape to easily cross the MV stent, avoiding passing under the struts (Figure 4E). While the jailed SB wire is being retracted, the guiding catheter may intubate deeply into the vessel, which can cause dissection and longitudinal stent deformation in the case of LMCA stenting[26]. Therefore, the guiding catheter tip should be withdrawn a few mm into the aorta beforehand; and while retracting the wire with right hand, the operator should control the guiding catheter with left hand while closely monitoring its tip[26].

Rarely, the jailed wire cannot be easily removed under the struts. In this case, a small balloon passed over the jailed wire with or without inflation at the jailed site may help.

Instead of the wire exchange technique, a third wire can be used to pass into the SB while the jailed wire is in place. The third wire is advanced into the DMV and then retracted back, and an attempt is made to enter through the most distal cell.

Kissing balloon inflation technique: After exchanging the wires, a non-compliant balloon sized to the SB diameter is inserted into the SB, and another non-compliant balloon sized to the DMV diameter is inserted into the MV. The balloons should be sufficiently short to prevent inflation outside the MV stent and disease-free regions in the SB. Moreover, minimal balloon overlap is recommended to keep elliptical stent deformation in the PMV to a minimum (Figure 4F1)[25,79]. First, the SB balloon is inflated at a high pressure to open the struts and eliminate the stenosis; and after deflation, the MV balloon is inflated to a high pressure. Subsequently, to maintain the carina in its central position, simultaneous inflation and deflation of both balloons is conducted using moderate pressures (at approximately 8-10 atm) as high pressures cause more oval distortion in the PMV segment of the stent[25].

A modified kissing balloon inflation (KBI) technique investigated in a bench test study was described by Mortier *et al*[80]. In this technique, the SB balloon is inflated to 12 atm and deflated to 4 atm. Then, the MB balloon is inflated to 12 atm; and finally, both balloons are deflated simultaneously. This technique was found to cause less elliptical stent deformation of the PMV segment with optimization of SB access compared to KBI with 12 atm inflation and deflation of both balloons simultaneously.

After KBI, to correct the oval (elliptical) stent deformation in the PMV segment, the POT should be performed again, which is termed the re-POT or final POT. In a recent bench test study, the position of the re-POT balloon was found to be an important factor in the alteration of the SB cell area size of the MV stent. The distal shoulder of the balloon positioned across the SB takeoff caused a reduction in the SB cell area whereas the distal shoulder positioned proximal to the SB takeoff did not[71]. The results of future *in vivo* tests and clinical studies of this approach are needed.

Balloon crossing problem to the SB: If the balloon does not cross to the SB through the stent struts, the following steps are performed[26,51]: (1) The first step is to check the position of the guiding catheter to determine whether it is at the ostium and coaxial to the vessel; (2) The second step is to use a smaller or the smallest balloon (1-1.5 mm) available; (3) It is suspected that the two wires are wrapped if the balloon cannot be forwarded to the SB ostium or if the MV wire is observed coming back while pushing the balloon. In this case, the MV wire is withdrawn back to the GC and inserted again into the DMV; (4) The next step is to inflate a balloon in the DMV stent part to increase the support of the GC (the anchor-balloon technique); (5) Performing the re-POT with a larger balloon to open the cells at the ostium of the SB is another choice; (6) Some operators advance a small balloon until it stops at the SB ostium, inflate it at high pressure with the objective of opening the struts, and then try to advance the balloon while deflating it[81]; and (7) As a last effort, the SB can be rewired from a different stent cell.

POT-Side-POT technique: After the first POT and exchanging wires, instead of the KBI, the POT-Side-(re)POT technique was proposed as an alternative and is increasingly used[82-84]. Technically, after the first POT, a balloon sized to the SB diameter is dilated in the SB to eliminate stenosis and remove the struts at the ostium, followed by the re-POT (Figures 4F2 and 4G). Because only one balloon is inserted and inflated at a time, this technique can be performed with 5 Fr guiding catheters, requires only one indeflator, and permits more proper balloon positioning. In a small recent clinical prospective registry using optical coherence tomography (OCT), the global strut malapposition, ellipticity index and SB occlusion rates were significantly reduced with a good sixth-month safety outcome[83].

Inverted PST

In Medina 0,0,1 bifurcation lesions with a very large SB (for ex., ostial circumflex or ostial diagonal lesion), a stent from the PMV to the SB may be implanted. This is called the "inverted PST"[25]. In addition, if there is no large difference between the PMV and the SB, this technique can also be performed in Medina 1,0,1 Lesions (Figure 3). The technical steps are the same as for the PST. The only difference is that the DMV is considered the SB and the SB is considered the DMV.

SIDE BRANCH STENTING FOLLOWING THE PST

After KBI or POT-side-POT techniques, if there is dissection, TIMI flow grade < 3 or FFR ≤ 0.8 in the SB, a second stent is required. Since there is a poor correlation between angiography and FFR measurements, when there is a suspicion of severe stenosis in the SB ostium after PST, it is better to use FFR to decide on SB stent implantation[14].

T/TAP stenting techniques

These stenting techniques are the simplest methods of second stent implantation in the PST. If the bifurcation angle is very close to 90°, then implanting a second stent in the SB as a "T form" is suitable. Technically, optimal angiographic views of the SB ostium should be obtained and stent augmentation tools should be used for successful T stenting[25].

Bench test studies and clinical practice have demonstrated that the bifurcation angle is usually not 90°; thus, the second stent may not completely cover the SB ostium with the T stenting technique, resulting in increased restenosis rates[25]. Therefore, the TAP stenting technique was developed. The TAP technique allows complete coverage of the SB ostium at the cost of creating a metallic neocarina. The length of the metallic neocarina depends on the bifurcation angle; the narrower the bifurcation angle is, the longer the length of the neocarina. For this reason, the TAP technique is generally not recommended at bifurcation angles < 70°.

The technical steps of the TAP technique in the PST are as follows[25] (Figure 9): (1) After the MV stenting and exchanging wires, the SB ostium is dilated with a balloon; (2) A DES of the SB diameter and appropriate length is positioned in the SB; (3) A balloon sized to DMV diameter is placed uninflated in the MV for use in subsequent KBI; (4) The SB stent is implanted with great care so that the non-carinal ostium is completely covered with minimal protrusion in the carinal segment (Figure 9B); (5) After the implantation of the SB stent, the stent balloon is slightly withdrawn and inflated at high pressure to provide optimum stent expansion in the SB ostium and postdilation of the stent (Figure 9C); (6) The uninflated, parked MV balloon and SB stent balloon are aligned in the PMV. Simultaneous KBI at moderate pressure and deflation are implemented to hold the neocarina in a central position; and (7) As a last step, the re-POT is performed to correct the oval shape if KBI has been implemented in a long segment in the PMV; otherwise, this step is not mandatory. It is of upmost importance that the re-POT balloon should not reach the metallic neocarina (Figure 9E). If this happens, the neocarina can bend to the SB side, which can result in rejailing and reduction in the SB ostial cell area[71].

Culotte stenting technique in the PST (classical culotte technique)

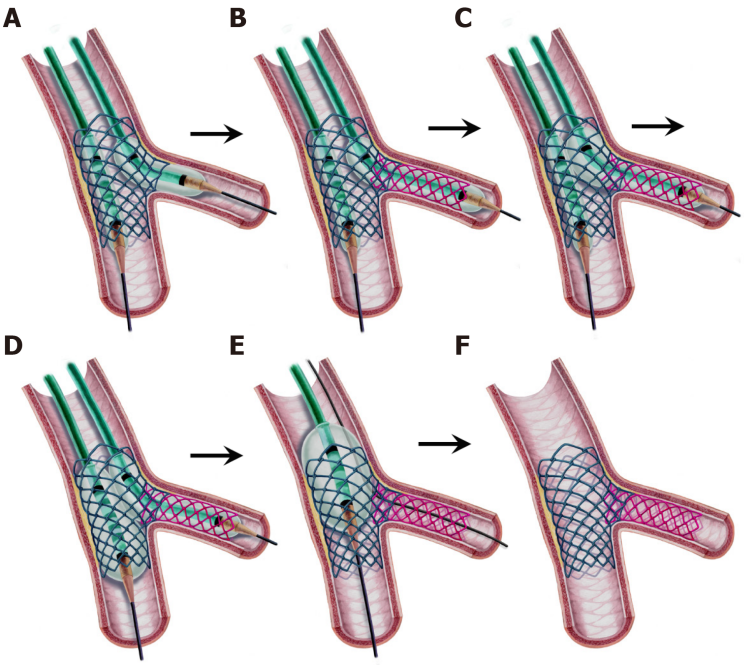
TAP is the most often used technique in the PST due to its simplicity; however, when the bifurcation angle is less than 70°, some operators prefer to use the culotte technique first introduced by Chevalier *et al*[85]. The culotte technique provides full coverage of the bifurcation; however, two layers of struts in the PMV are the disadvantage of this technique. Furthermore, before deciding to perform this technique, the overexpansion capacity of the available stent types should be known (Table 2)[72]. If the maximum expanded diameter of the available SB stent is less than the diameter of the PMV according to the table, then the culotte technique cannot be performed. This is especially the case when there is a large difference between the PMV and SB diameters.

The technical steps of culotte stenting in PST are the following[25] (Figure 10): (1) After the stages of the PST are completed (Figures 10A-C), wire exchange and balloon dilatation of the SB ostium is performed (Figures 10D and E); (2) A DES with the same diameter as the SB and an appropriate length that extends from the SB to overlap the proximal part of the MV stent is implanted while the MV wire is in place. The overlap part is long in the classical culotte technique but is kept at 1-3 mm in the "mini-culotte" technique (Figure 10F); (3) A new POT is performed through the SB wire with a non-compliant balloon sized to the PMV. The balloon distal shoulder should be aligned to the carinal level (Figure 10G); (4) Wire exchange should be performed for the second time. It should be noted that the SB wire must be passed from the cell closest to the carina into the DMV (Figure 10H). This allows the deployed SB stent struts to move to the lateral walls of the MV rather than the carina and the SB ostium during the next balloon inflation. The MV wire is retracted under the SB stent and advanced into the SB as a "U" shape; (5) A non-compliant balloon sized to the DMV and another non-compliant balloon sized to the SB are advanced into the relevant vessels, and the proximal balloon markers are aligned in the PMV. Each balloon is inflated at high pressure and deflated sequentially, followed by KBI at moderate pressures (Figure 10I); and (6) A last POT should be performed for correcting the oval shape created by previous KBI (Figure 10J).

ELECTIVE DOUBLE STENTING TECHNIQUES

Inverted culotte stenting technique

To maintain access to the SB during the procedure, the culotte stenting technique was modified to the "inverted culotte stenting technique" in elective double-stent implantation. Similar to the culotte



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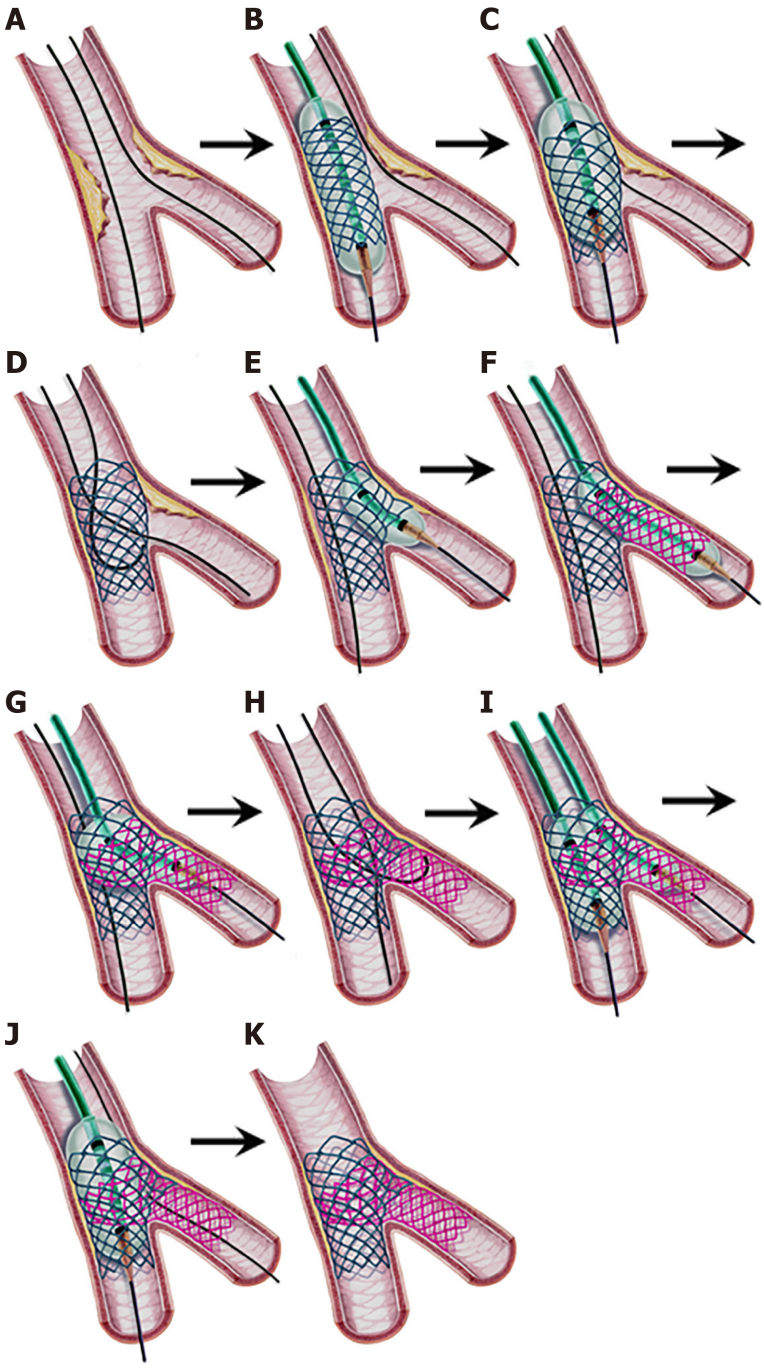
Figure 9 Step-by-step T and protrusion technique. A: After main vessel (MV) stenting, an uninflated balloon is positioned in the MV, and the side branch (SB) ostium is dilated by a balloon; B: The SB stent is deployed with minimal protrusion and covers the ostium completely; C: The stent balloon is withdrawn slightly and inflated at high pressure; D: Kissing balloon inflation; E: Proximal optimization technique with a short balloon not reaching the neocarina. (This step is not mandatory if the kissing balloon inflation area in the proximal MV is not long.); F: Final result.

technique, the inverted culotte technique provides full coverage of the bifurcation at the expense of two layers of struts in the PMV, and it cannot be performed when there is a large difference between the PMV and SB diameters.

The technical steps of inverted culotte stenting are as follows (Figure 11): (1) Both branches are wired, and MV predilation and/or debulking is performed with predilation of the SB; (2) A stent sized 1:1 to the SB diameter is deployed in the SB protruding into the PMV. The length of the stent is selected so that the PMV part is sufficiently long enough for the subsequent POT. In the "mini-culotte technique" introduced a decade ago, the PMV part of the SB stent is kept as short as 1-3 mm to reduce the length of the two stent layers[86,87] (Figure 11B). This technique was found to be associated with high procedural success and very good 9-month outcomes in a pilot study[88]. Randomized, controlled, larger comparative studies are needed to confirm the favorable outcomes of this method; (3) The PMV part of the stent is dilated with a non-compliant or semicompliant balloon sized to 1:1 to the PMV diameter. This is the first POT (Figure 11C); (4) Wire exchange (or a third wire advancement) should then be performed. The DMV should be wired from the closest cell to the carina for the reasons described above (Figure 11D); (5) Stent struts are opened by a DMV balloon. Instead, KBI, which is part of the recently introduced "DK-culotte technique", can be performed[89,90] (Figure 11E). This technique was found to achieve better morphological properties than classical culotte stenting in a bench test study[89], and it reduced the total procedural time with better strut apposition than the culotte and even the DK-crush techniques in another study[90]; (6) An MV stent sized 1:1 to the DMV diameter is advanced and implanted. The length of the PMV part should be sufficient to cover the PMV part of the SB and be at least equal to the shortest POT balloon (Figure 11F); (7) A second POT is performed in the PMV (Figure 11G); (8) A second wire exchange is performed by passing the MV wire through the closest cell to the carina into the SB and the U-shaped SB wire into the DMV (Figure 11H); (9) KBI is performed with short non-compliant balloons sized 1:1 to the branches. Before KBI, sequential balloon inflation is recommended. The SB balloon is first inflated to a high pressure; and after deflation, the MV balloon is inflated to a high pressure. Then, both balloons are inflated at moderate pressures (at approximately 8-10 atm) and deflated simultaneously (Figure 11I). A recent mini-KBI in culotte stenting was described in a bench test study[91]. In this technique, the SB balloon only protrudes into the MV at the upper edge of the SB, and the KBI is performed. Compared to classical KBI, this modification significantly prevented stent deformation and overexpansion in the MV stent and provided better apposition of the MV stent and better expansion of the SB stent[91]; and (10) A final POT is performed in the PMV (Figure 11J).

Double-kissing crush technique

The crush technique was first introduced by Colombo *et al*[92]. The aim of this technique was to provide full coverage of the ostium to lessen SB restenosis with immediate patency of both branches. However,

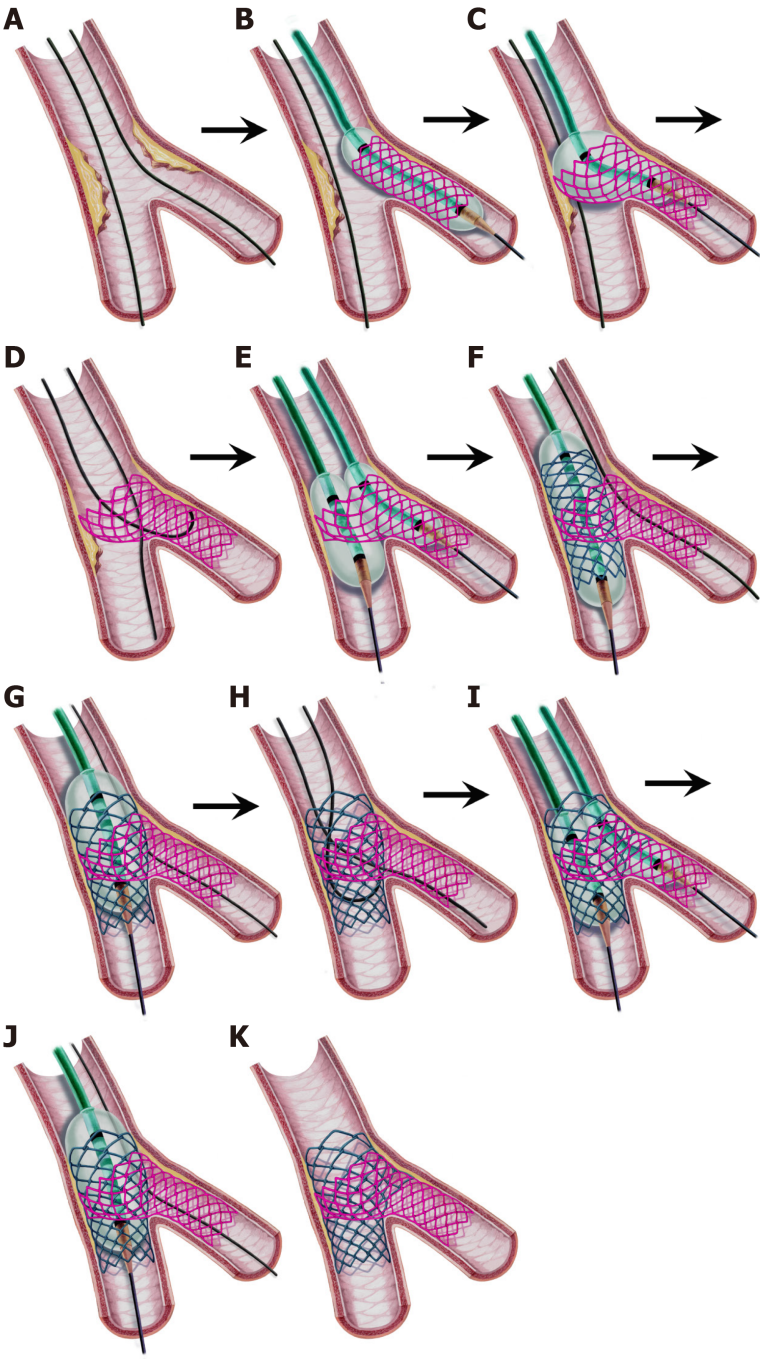


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Figure 10 Step-by-step classical (provisional) culotte stenting. A: Both vessels are wired; B: After predilatation, the main vessel (MV) stent sized to the distal MV is deployed; C: First proximal optimization technique (POT); D: Wire exchange; E: Balloon dilatation of the side branch (SB) ostium; F: Deployment of the SB stent protruding into the proximal MV (1-3 mm in "mini-culotte"(shown) or more in classical culotte technique); G: POT for the SB stent; H: Second wire exchange with wiring the distal MV through the closest cell to the carina, and the other wire tip is "U" shaped to cross the SB stent; I: Kissing balloon inflation; J: Final POT; K: Final result.

in clinical practice and in trials, the rate of achievable KBI was found to be low, leading to suboptimal long-term outcomes. Thus, this technique is no longer recommended[49]. Some modifications of this technique, such as "mini-crush"[93], "step-crush"[94], and "double-kissing (DK) crush"[95] were described. As described before, the DK crush technique has received great attention due to its high final KBI success rate and its efficacy with long-term safety in complex bifurcation lesions in a series of trials [25,34-36,96]. Nonetheless, this technique is complex with many steps that require proper training and experience.

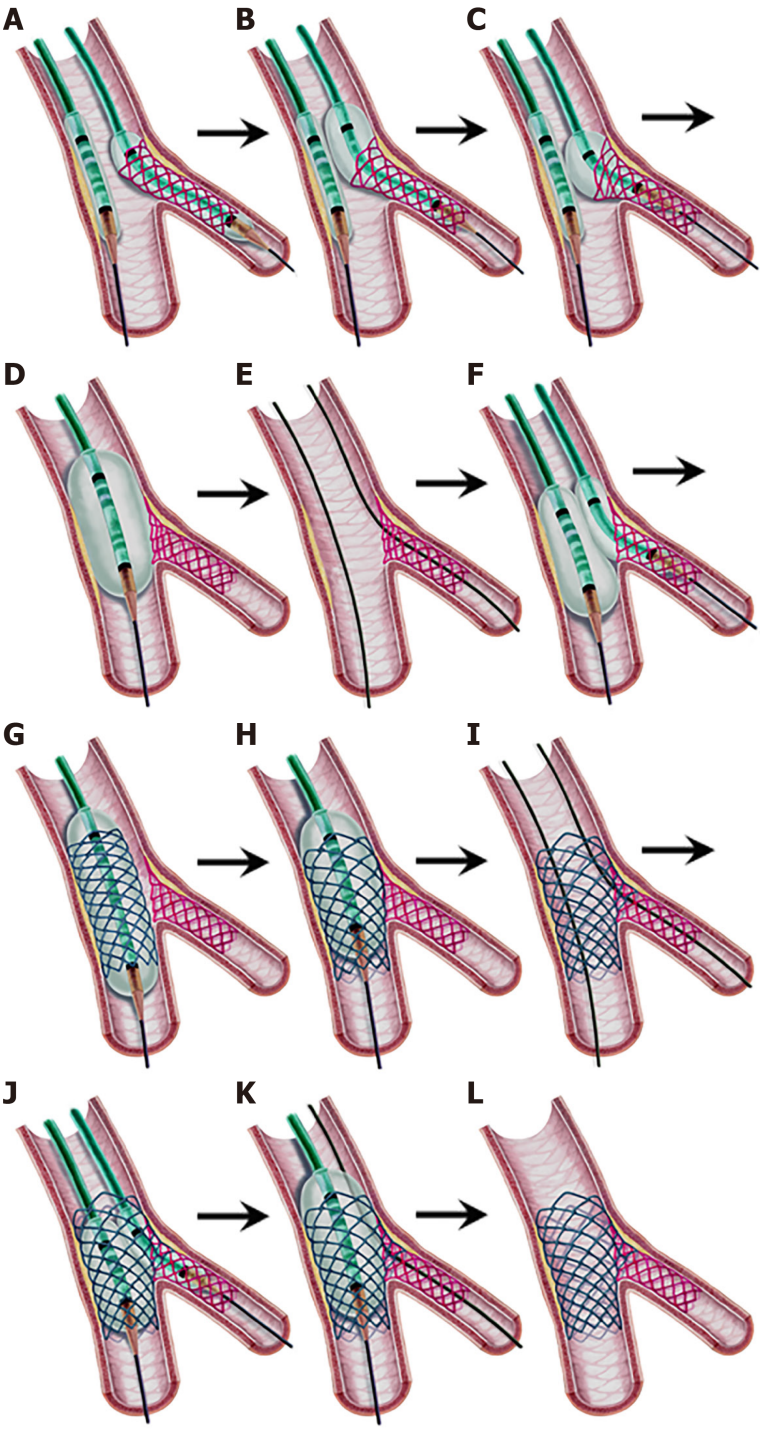
The technical steps of the contemporary DK-crush technique are as follows[25] (Figure 12): (1) After wiring the two branches, optimal preparation of the MV with balloon inflation and/or debulking with predilatation of the SB is performed; (2) A DES, sized to the SB diameter and with a length to ensure full coverage of the SB lesion, is advanced into the SB. The stent is positioned protruding 2-3 mm into the



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Figure 11 Step-by-step inverted culotte stenting. A: Both vessels are wired; B: The side branch (SB) stent protruding in the proximal main vessel is deployed (protrusion part is 1-3 mm in the "Mini-culotte technique"); C: Proximal optimization technique (POT) for the SB stent; D: Wire exchange. The distal main vessel (MV) wiring from the closest cell to the carina and the "U" shaped wire is advanced into the SB; E: Kissing balloon inflation (KBI) (in the "double kissing mini-culotte "technique) or classical balloon dilatation only in the distal MV ostium may be performed; F: MV stenting; G: POT for the MV stent; H: Second wire exchange. Wiring the SB through the closest cell to the carina and the "U" shaped wire crossing the MV stent; I: KBI; J: Final POT; K: Final result.

PMV (Figure 12A); (3) A balloon sized to the PMV is positioned in the MV to crush the stent later. This balloon will be kept uninflated until the crushing procedure (Figure 12A); (4) After the SB stent is implanted, a new method called the "proximal side optimization" described by Lavarra[97,98] and considered useful by the EBC[25] may be performed. In this method, the stent balloon is slightly withdrawn and inflated at 4-6 atm higher than the nominal pressure (Figure 12B); and after removing this balloon, a new NC balloon (0.25-0.5 mm larger than the SB stent) is again inflated in the protruding part of the stent and the SB ostium (Figure 12C). The purpose of this method is to achieve adequate expansion and apposition of the SB stent in the ostium and to provide a larger stent cell area for rewiring; (5) After the SB balloon is removed, angiography should be performed to evaluate the results of SB stent implantation, such as the stent expansion, flow pattern, distal dissection or new lesion development. If an additional stent is required, it should be implanted at this time as the SB wire will be



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Figure 12 Step-by-step double kissing-crush technique. A: After the preparation of the vessels, the side branch (SB) stent protruding 2-3 mm into the proximal main vessel (MV) is deployed while an uninflated proximal optimization technique (POT) balloon is positioned in the MV; B, C: "Proximal side optimization". A slightly withdrawn stent balloon is inflated at a higher pressure. Then, a new larger NC balloon is inflated in the protruding stent part to further open the struts; D: Crushing the stent by POT after the SB balloon and wire are removed; E: Wiring the SB through a non-distal cell; F: First kissing balloon inflation (KBI) after sequential inflation of the two balloons; G: MV stenting after the SB balloon and wire are removed; H: Second POT; I: Wiring the SB through a non-distal cell for the second time; J: Second KBI; K: Final POT; L: Final result.

removed in the next step and rewiring and stent advancement may be challenging in later steps[99]; (6) The SB wire is removed (some operators leave it in), and the pending uninflated MV balloon is positioned with its distal shoulder aligned to the carina. High-pressure inflation (POT) is performed to crush the protruding part of the SB stent, which is called "balloon crushing"[25]. It was demonstrated in bench tests that the POT is required to achieve total crushing. (Figure 12D); (7) The SB is rewired through a *non-distal* cell of the crushed stent (Figure 12E). Non-distal cell rewiring, the opposite of distal rewiring in the PST, is important because more frequent suboptimal KBI results and higher SB stent restenosis were found with distal wiring[100]. The mechanism of this is explained by the fact that the

KBI in the distal cell pushes the stent struts to the proximal side, causing incomplete coverage of the distal 1/3 of the SB ostium[100]. How to overcome wiring problems is explained in the relevant section of the PST; (8) An SB balloon sized 1:1 to the SB diameter and an MV balloon sized 1:1 to the DMV diameter are advanced. To perform the first KBI, the SB balloon is inflated at high pressure to open the struts; and after deflation, the MV balloon is inflated at high pressure. Eventually, simultaneous inflation and deflation of both balloons with moderate pressures (at approximately 8-10 atm) is conducted (Figure 12F). How to overcome balloon crossing problems is explained in the relevant section of the PST; (9) The two balloons and the SB wire are removed. A DES sized 1:1 to the DMV diameter is positioned across the SB covering all the distal and proximal MV lesions and deployed (Figure 12G). The PMV part of the DES should be at least equal to the shortest POT balloon; (10) After removing the stent balloon, a repeat POT with a balloon sized 1:1 to the PMV diameter should be performed (Figure 12H); (11) The SB is rewired again through a non-distal cell (Figure 12I); (12) A second KBI is performed (Figure 12J); (13) A final POT is performed to correct the oval shape of the PMV created by the previous KBI (Figure 12K).

Nano-crush technique

The "nano-crush" technique was first presented by Ray *et al*[101,102] at the 12th EBC meeting in 2016. Later, in 2017, Rigatelli *et al*[103] published a bench test and clinical outcome study of a technique with the same name. Although both procedures use a tiny SB stent part for crushing, the techniques are somewhat different from each other. Rigatelli *et al*[104] recently changed the name of their technique to the "nano inverted T stenting technique".

In the nano-crush technique described by Ray *et al*[105], the SB stent is positioned uninflated in the SB, and a non-compliant MV balloon is positioned across the carina and then inflated at a nominal pressure. While the MV balloon is inflated, the SB stent is pulled back until a small part protrudes into the MV and is deployed. However, in the nano-crush technique described by Rigatelli *et al*[103,104], 0.5-1 mm protrusion of the proximal part of the SB stent for crushing is adjusted visually by angiography. Moreover, the KBI numbers and techniques are also different. Where Ray *et al*[102] perform double "classical" KBI at high pressures without a final POT, Rigatelli *et al*[103-105] perform only one "snuggle" KBI, then a final POT. The other steps are similar to the DK-crush stenting technique described before. Finally, Rigatelli *et al*[103-105] use only ultrathin strut stents in their technique.

Both techniques provided complete coverage of the SB ostium with a tiny amount of metal at the carina in bench tests[106,107]. In a clinical study with a small number of patients, Ray *et al*[102] demonstrated short procedural times and no procedural complications with acceptable clinical outcomes with their technique. Rigatelli *et al*[104,108] showed a low incidence of TLF, no stent thrombosis and a good survival rate in left main bifurcation lesions in a small registry study and less contrast use and less procedural and radiation exposure time in comparison to the culotte technique in left main bifurcation lesions in an observational study.

Further controlled, randomized, larger studies are needed to confirm the favorable procedural and long-term clinical outcomes of these techniques in left main and non-left main bifurcation lesions.

OTHER DOUBLE STENTING TECHNIQUES

Mini-crush and step-crush techniques

The mini-crush technique is a version of the crush technique in which the crushed part of the SB stent is 1-2 mm instead of 3-4 mm. The main advantage of the crush and mini-crush techniques is that instant patency of both branches is secured[52]. However, the main disadvantage of these techniques is that a 7 Fr guiding catheter is required because two stents are positioned in the coronary arteries at the same time. After the SB stent is deployed, the stent balloon and wire are withdrawn, and the prepositioned MV stent is inflated while the SB stent is crushed. The SB is rewired followed by balloon dilatation of the ostial struts, KBI and a final POT, sequentially. Rewiring the SB and balloon passing can be challenging due to three layers of stent struts, which is the reason for the low KBI rate in classical crush trials resulting in more adverse outcomes.

The step-crush technique is the same as the DK-crush technique except that the first KBI is not implemented in this technique.

Reverse (internal) crush technique

When a second stent is required in the PST, some operators use the reverse (internal) crush technique [48]. A stent is positioned in the SB, and a balloon is placed in the MV. The stent is pulled back prolapsing 2-3 mm into the MV and implanted. After the stent balloon and wire is removed, the MV balloon is inflated at a high pressure to crush the SB stent. After rewiring, KBI and the POT are subsequently performed. In this technique, the crushed SB part is on the MV stent facing the lumen, unlike the other crushing techniques where it is under the stent and adheres to the vessel wall. There is no large study investigating the safety and efficacy of this technique.

Inverted DK-crush technique

When the SB is larger than the DMV, the inverted DK-crush technique may be performed. The technical steps are the same as those of the DK-crush technique with the only difference being that the DMV is considered the SB and the SB is considered the DMV.

In addition, in very rare PST cases, when the SB is occluded after MV stenting and cannot be rewired, this technique can be used to rescue the SB. The PMV stent part is crushed with a balloon passed through the jailed wire, followed by the DK-crush technique steps.

V and simultaneous kissing stent techniques

The V and simultaneous kissing stent (SKS) techniques consist of the simultaneous implantation of the MV and SB stents. The two stents are positioned so their proximal parts overlap in the PMV to form a neocarina. If the neocarina is ≤ 2 mm, the technique is called "V stenting"; however, if it is ≥ 3 mm, it is called "SKS"[28,109]. Due to the simultaneous implantation of two stents, at least a 7 Fr guiding catheter is required. The main advantage of these two techniques is that access to both branches is maintained throughout the procedure without the need to rewire any branches. Therefore, these techniques are easy and fast and may be preferable to the more complex double stenting procedures in emergencies such as acute LMCA occlusion.

There are also disadvantages of these techniques[52]: (1) The possibility of PMV dissection is relatively higher because of barotrauma during two-stent implantation or postdilation; (2) If a proximal dissection occurs during the procedure or proximal restenosis develops on follow-up, a stent cannot be implanted simply proximal to the stents since a gap between the new stent and the others is inevitable. In this situation, one of the branch stents (mostly the SB) should be crushed by the new stent, but this results in four strut layers in the ostium of the branch causing difficulty for rewiring; (3) If restenosis or lesions occur distal to the stents during follow-up, wiring can be difficult as the wire can pass under or between the struts in the neocarina; and (4) Finally, SKS causes a long neocarina that has been shown to transform into a thin diaphragmatic membranous structure over time; however, the long-term adverse outcomes of this structure are unknown.

The main application of the V stenting technique is Medina 0,1,1 Lesions where the PMV is free of disease and the carinal angle is < 90°. Although many authors recommend this technique in this situation[28,48,52], there is no large study investigating the acute and long-term clinical outcomes of this technique. Due to the long carina and the above disadvantages, the SKS technique is not approved by the interventional community for use in nonemergent bifurcation interventions[48,51].

PROCEDURAL COMPLICATIONS AND OUTCOMES OF CBL INTERVENTIONS

The PCI of CBLs has more procedural risks and higher rates of adverse outcomes and restenosis than non-CBLs[99,110]. In addition to classical PCI risks such as dissection, no-reflow and perforation, the procedural risks specific to CBL interventions include acute side branch closure (2.8%-5.2%), the fracture of a jailed wire, and SB stent embolism while passing or withdrawing it through the implanted MV stent [99,110]. Early (< 30 d) (especially more in the EDS techniques) and late stent thrombosis rates are higher than those for non-CBLs[111-113]. This may be due to higher rates of stent underexpansion and malapposition and more metallic and polymer burdens, which may provide stimuli for hypersensitivity and acute thrombogenicity reactions[99,111].

Long-term MACEs are also higher after successful DES implantation for CBLs compared to non-CBLs. Finally, distal LMCA interventions compared to non-LMCA bifurcations are associated with higher MACE (death and TVR) rates[2,99].

INTRAVASCULAR IMAGING IN CBLs

Since coronary angiography is two-dimensional lumenography, it has some limitations in evaluating lesion characteristics and post-intervention results. The intravascular imaging techniques IVUS and OCT provide accurate tomographic images and essential information that guides planning and optimizing PCI treatment[114,115]. OCT provides much higher resolution images of the luminal surface, calcifications, wire positions and SB ostium than IVUS[43]. On the other hand, IVUS has been used more, needs no extra contrast or vessel flushing and is better in evaluating the plaque burden[43].

Compared to angiography, better visualization of the location and extension of plaques using these imaging techniques before PCI can assist in selecting an appropriate stenting strategy and avoid unnecessary two-stent implantation[26]. In addition, proximal and distal vessel sizes and plaque locations can be determined more accurately to determine the stent size, and calcifications that require debulking before stenting can also be identified[47]. In patients without ostial side branch involvement (*i.e.*, Medina 1,1,0/1,0,0/0,1,0), the "eyebrow" sign identified by IVUS was found to be a strong predictor of SB narrowing or occlusion after MV stent implantation[116], in which case the intervention strategy

can be changed. After stenting, OCT can help rewire through the distal cell, which is required for optimal stent scaffolding by subsequent balloon or KBI[115]. Stent expansion and apposition status, distal or proximal stent edge dissection, or residual stenosis can be well identified by both IVUS and OCT[43].

The MAIN-COMPARE registry trial, comparing the use of IVUS in LMCA bifurcation lesions to angiography alone, showed a lower 3-year mortality rate; and the other registry trial SCAAR showed a significantly lower primary endpoint (all-cause mortality, restenosis, or definitive stent thrombosis)[117,118]. In addition, a recently published analysis of the British Cardiovascular Intervention Society Database has shown lower in-hospital MACE and lower 1-year death rates with the use of IVUS in LMCA interventions[119]. Finally, the results were found to be similar in two recent meta-analyses[120,121]. In view of these data, IVUS is recommended as the gold standard for PCI of LMCA bifurcation lesions; and although there are no large data, it has been reported that OCT is feasible in LMCA bifurcation lesions in recent guidelines[41,47].

In non-LMCA lesions, an observational PCI study found a lower 7-year cardiac death, MI and MACE rates in the IVUS guided compared to angiography alone in true bifurcation lesions[122]. There are no randomized trials confirming the clinical benefits of routine IVUS use in non-LMCA bifurcation lesions, but the EBC emphasizes the benefit of intravascular imaging in all CBLs in the latest guidelines[20,47].

Although OCT provides superior images compared to IVUS, there are limited clinical data that only come from observational trials with a small number of bifurcation patients[115]. The results of ongoing large randomized trials OCTOBER (comparing two-year MACE between OCT guided or angiography alone interventions in CBLs) and OPTIMUM (comparing 3D OCT guided *vs* angiography alone provisional stenting in terms of malapposed struts in bifurcation lesions) will shed more light on the benefits of OCT use in CBL interventions[123,124].

LEFT MAIN BIFURCATION LESIONS

LMCA stenosis is detected in 5-8% of patients undergoing diagnostic angiography[125], and left main bifurcation lesions (LM-BLs) account for approximately 80% of LMCA lesions[125,126]. The LMCA with its bifurcation has specific properties and requires some different technical approaches[26,42,43,126]: (1) The LMCA supplies > 75% of the blood of the myocardium in a right dominant coronary system, so any complication may result in catastrophic outcomes; (2) The LMCA diameter is between 3.5-6.5 mm with a mean of 4.75-5 mm, so the overexpansion capacity of the stent to be used should be known (Table 2); (3) The left circumflex artery (LCx) is usually the side branch and supplies > 10% of the blood of the myocardium in > 95% of cases, so its loss during PCI is unacceptable; (4) The bifurcation angle is wider than the other bifurcations with a mean value of 70°-80°, so LCx rewiring may be more difficult, and it should be noted that worse outcomes were found with culotte stenting than with the DK-crush technique in patients with bifurcation angles > 70° in LM-BLs[35]; (5) The guiding catheter is close to the LMCA stent, so wires can go behind the struts. In addition, during the withdrawal of jailed wires or balloons, the guiding catheter can enter the LMCA and cause longitudinal compression of the LMCA stent, which is associated with adverse outcomes if untreated[26,57,127]; (6) Diffuse LMCA disease can be overlooked when using angiography due to the lack of a reference segment. Due to the physical laws of coronary bifurcation, LMCA diffuse disease should be considered when the LMCA reference diameter is similar to that of the LAD; and (7) A total of 10%-15% of patients have trifurcation with the addition of an intermediate (ramus) branch, so the complexity of PCI increases, and larger guides are required for triple kissing inflations.

CABG is the gold standard treatment for LMCA lesions according to both recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines[41,128]. However, there are some differences in PCI implementation between these guidelines. The ESC/EACTS recommends PCI as a Class I indication for LMCA patients with SYNTAX scores < 22 (low risk), Class IIa with SYNTAX scores between 23-32 (intermediate risk), and Class III with higher scores. On the other hand, the AHA/ACC classifies LMCA lesions as ostial, trunk and bifurcation. LMCA bifurcation lesions with an increased risk of surgical outcomes (Society of Thoracic Surgeons (STS) score > 2) are Class IIb indications whereas ostial and trunk lesions with a very high risk of surgical outcomes (STS score ≥ 5) are recommended as Class IIa indications for PCI. After these guidelines, 5-year results of two important EXCEL and NOBLE trials have been published, which have caused intense debate about the treatment of LMCA disease with PCI *vs* CABG[129,130]. Repeat revascularization rates were higher in the PCI arms of both trials. Although mortality rates were similar between the CABG and PCI arms, PCI was inferior in terms of the nonprocedural MI in the NOBLE trial. On the other hand, no significant difference between CABG and PCI was found in the primary outcome (composite of death, stroke or MI) in the EXCEL trial. However, the primary outcome definition that does not include repeat revascularization and the MI definition that differs from the second or third universal definition of MI have been criticized[131]. Moreover, although the cardiac death rates were not different, a higher total mortality rate in the PCI arm was noted[47]. A meta-analysis of five randomized trials involving EXCEL

and NOBLE was recently published and found that individual total mortality, cardiac death, stroke and MI rates were not different between the CABG and PCI arms, and unplanned revascularization rates were significantly higher in the PCI arm, as expected[132]. Finally, the multidisciplinary heart team approach, which considers the anatomical and clinicopathological status of each patient and the experience of the operators, is required in the LMCA treatment decision[45,47].

LM-BLs that involves only one branch (*i.e.*, Medina 1,1,0 or 1,0,1) are considered non-complex lesions, and the default strategy is the PST[42]. Two-branch involvement (*i.e.*, Medina 1,1,1 or 0,1,1) in LM-BLs is a complex true lesion. The EBC still recommends the PST for the vast majority of these complex lesions [42], and recommends the EDS techniques in the case of long SB (usually LCx) lesions (≥ 10 mm) or difficult SB access[49]. Furthermore, EDS is preferred in cases where there is a high risk of SB occlusion [48]. Finally, as described before, preferring the DK-crush technique over the PST in complex-true LMCA lesions is a Class IIb indication in the 2018 ESC/EACTS myocardial revascularization guidelines [40].

As described before, the EBC-MAIN trial was recently published and showed that there was no statistically significant difference between the PST and EDS techniques in LM-BL interventions in short SB lesions. The DK-crush technique was used in only 5% of EDS patients in this trial[46].

In light of the latest data and expert opinions, the PST is most often the default strategy[37-39,46,48]. However, it is better to prefer EDS if the SB (usually LCx) is ≥ 2.5 mm and the lesion length is ≥ 10 mm or the likelihood of SB occlusion is high or SB wiring is difficult in complex-true (Medina 1,1,1; 0,1,1) LM-BLs; furthermore, if the operator is familiar with the technique, the DK-crush technique may be preferred over other EDS techniques (Figure 3).

Angiographical LMCA stenosis > 50% is considered significant; however, there are many cases of ambiguous lesions. FFR and/or IVUS should be used to decide on revascularization for these lesions. Collected data showed that if FFR > 0.8, then it is safe to defer revascularization; and if FFR ≤ 0.8, then revascularization of the LMCA is indicated[42,133]. On the other hand, an IVUS-derived minimum lumen area (MLA) of 6 mm^2 is usually considered to be the cut-off value of significant LMCA lesions [42]; however, this value was determined in Western populations who typically have larger body and vessel sizes, and an IVUS-derived MLA of 4.5 mm^2 was found to be the cut-off value in an Asian population study[134]. Consequently, in LMCA lesions, it is recommended to defer revascularization if the MLA > 6 mm^2, to revascularize if the MLA < 4.5 mm^2 and to evaluate with FFR measurement if the MLA is between 4.5 and 6 mm^2[135]. There is no defined cut-off value for OCT yet[42].

After LMCA stenting, IVUS-derived minimum stent area cut-off values for predicting angiographic restenosis were 5 mm^2 for the ostial LCx, 6.3 mm^2 for the ostial left anterior descending artery (LAD), 7.2 mm^2 for the polygon of confluence, and 8.2 mm^2 for the LMCA above the polygon of confluence (the so-called 5-6-7-8 rule) in a study[136]. However, this trial was conducted in Asian patients and it appears that larger LMCA cut-off values should be targeted in other populations and large body size patients [127]. Indeed, in an IVUS substudy of the EXCEL trial, the minimum LMCA stent area cut-off value for predicting angiographic restenosis was 9.8 mm^2; and in the NOBLE trial substudy, this value was found to be 13.4 mm^2[137,138].

After crossover stenting in the LMCA during the PST, whether the nonobstructed SB (usually LCx) ostium should be opened is a matter of debate[47]. A recent large registry, however, showed that there was no significant difference between the KBI and non-KBI arms in terms of TLR in patients with crossover stenting from the LMCA to the LAD[139].

The optimal PCI strategy for isolated ostial LAD lesions and ostial LCx lesions (Medina 0,1,0 and 0,0,1) is uncertain[25]. The extension of LMCA bifurcation plaques may not be detected by angiography, so IVUS/OCT is preferred for isolated ostial LAD or LCx lesions. Indeed, angiographic assessment was found to underestimate the extension and severity of lesions. Distal LMCA atherosclerotic plaques extended 90% to the LAD, 66% to the LCx, and 62% to both whereas isolated ostial plaque involvement of the LAD and LCx was only 9% and 17%, respectively, in an IVUS study[140]. In conclusion, if the anatomy is appropriate according to IVUS/OCT (the carinal angle is approximately 90°, the LMCA is free of plaque and there is certain visualization of the ostium of the other branch), then ostial stenting may be preferred to avoid LMCA stenting. Otherwise, the PST (from LMCA to LAD stenting) for isolated ostial LAD and the inverted PST (from LMCA to LCx stenting) for isolated ostial LCx seem to be the preferred options[25,47].

Finally, after successful LMCA stenting, late (3-12 mo) control angiography may be considered regardless of symptoms according to recent guidelines (Class IIb, level of evidence C)[41].

DRUG–COATED BALLOONS IN CBLs

Drug–coated balloons (DCBs) are a new technology intended for the prevention of restenosis as an alternative option to DESs[26]. The use of DCBs in CBL is attractive due to the high rate of restenosis after CBL intervention. Observational studies using a DES in the MB and a DCB in the SB showed good SB results[141]. The PEPCAD-BIF trial showed that DCBs provided very acceptable late lumen loss in SB lesions without both major dissections and significant early vessel recoil[142]. In the BABILON trial,

a DCB in the SB plus a bare metal stent in the MV was found to be worse than the provisional DES strategy in terms of MACE and TLR[26]. It should be noted that these and all the other studies to date on the use of DCBs in de novo CBLs are heterogeneous and include a small number of patients[47]. A recent meta-analysis that included four studies with 349 patients treated with DCBs *vs* standard balloon angioplasty, showed that the DCB reduced the SB late lumen loss, but the SB binary restenosis rates and the clinical outcomes (MACE and TLR) were not different[143]. Consequently, there still is insufficient conclusive data on the use of DCBs in de novo CBLs[48]. A new "POT-side DCB-POT" method was recently described in a case report[144], and more research is expected on the clinical consequences of this technique.

DCBs have been tested in in-stent restenosis (especially after two-stent implantation) and have been found to provide a good clinical outcome without requiring extra stent implantation[145]. Therefore, the method was reported as "feasible" in this case in the latest EBC guidelines[47].

DEDICATED BIFURCATION STENTS

The difficulties in accessing the SB after MV stenting, or vice versa, resulted in the development of dedicated bifurcation stents (DBSs). Although many types are available, 4 DBSs were studied in randomized trials: BiOSS Expert and BiOSS LIM (Balton, Warsaw, Poland), the Tryton stent (Tryton Medical, Durham, North Carolina) and the Axxess bifurcation stent (Biosensors International, Singapore).

The BiOSS Expert is a paclitaxel-eluting balloon-expandable dedicated bifurcation stent that is implanted in the MV and has an open side to the ostium of the SB. In the Polbos I trial, the BiOSS Expert was compared with many types of DESs using the PST. Although the MACE rates were similar, the TLR rate was higher in the BiOSS Expert group[146]. The BiOSS LIM is a sirolimus-eluting balloon-expandable dedicated stent. In the Polbos II trial, no difference was found between the BiOSS LIM and provisional DES techniques in terms of the MACE and TLR rates[147].

The Tryton stent is a balloon expandable dedicated cobalt chromium non-DES. This stent is implanted in the SB, and a DES is implanted in the MV through the open struts of this dedicated stent. A pooled analysis of the Tryton pivotal randomized controlled trial and post-approval confirmatory study comparing this stent with the PST with a DES showed that the Tryton stent was clinically non-inferior to the PST with good angiographic outcomes at 1 year[148].

The Axxess stent is a self-expandable biolimus-eluting dedicated stent that is designed for EDS. It is implanted in the proximal MV with its distal end aligned to the carina, allowing easy access to both the distal MV and the SB[149]. In the COBRA study, Axxess with two biolimus-eluting stents (in the distal MV and the SB) was compared to the culotte stenting technique with two everolimus-eluting stents and found no difference in stent coverage at 9 mo and similar favorable clinical outcomes at 5 years[150].

Consequently, DBSs have not yet been found to be superior to conventional bifurcation stenting strategies for routine use in CBLs[151].

ANTITHROMBOTIC THERAPY

Since the periprocedural and long-term risk of stent thrombosis (ST) of coronary bifurcation PCI is high [112], antithrombotic therapy is an important part of CBL treatment. The anatomical properties of bifurcations lead to a relatively high rate of strut malapposition, stent underexpansion and isolated strut noncoverage, resulting in thrombosis[113]. EDS, except for the DK-crush technique, has been found to cause higher ST risk than one-stent implantation. In addition, the ST rate of "bail-out" second stent implantation in the PST was shown to be higher than that in EDS[152]. Therefore, careful preselection of the stenting strategy is required. ST most often occurs acutely or in the first 30 d postprocedure rather than later[20].

Unfractioned heparin is the standard anticoagulant agent for every PCI procedure. Given the complex and time-consuming nature of bifurcation intervention, close monitoring of ACT values is required. In order to prevent ST in the acute and early phases, IV cangrelor may be preferred in $P2Y_{12}$ inhibitor-naïve patients (ESC Class IIb, LOE A recommendation)[40].

Dual antiplatelet therapy (DAPT) with $P2Y_{12}$ inhibitors and aspirin is the standard treatment after every coronary stent implantation. In acute coronary syndrome (ACS), the potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor are preferred over clopidogrel. Due to the results of the recent ISAR–REACT 5 trial, prasugrel is preferred over ticagrelor in the latest ESC guidelines (Class IIa)[153]. In stable coronary artery disease (CAD), although they have not been documented to be more efficient than clopidogrel, the potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor may be considered in high ST risk situations, such as LMCA interventions, according to the ESC guidelines (Class IIb, LOE C recommendation)[41].

The duration of DAPT depends on the clinical presentation (stable CAD or ACS) and the ST and bleeding risk. In both stable CAD and ACS interventions, high ST risk patients such as bifurcation PCI ≥ 2 stents and LMCA PCI, the duration of DAPT may be prolonged beyond 12 mo if the bleeding risk is not high (Class IIb indication for stable CAD and class IIa indication for ACS)[41,154]. However, in the case of high bleeding risk (*e.g.*, PRECISE-DAPT score ≥ 25), DAPT duration may be considered as 3 mo for stable CAD and 3-6 mo for ACS patients with the cessation of $P2Y_{12}$ inhibitor (Class IIa indication according to ESC and Class IIb indication according to the latest AHA/ACC guidelines, for both stable CAD and ACS)[41,154-156]. Finally, after the recent publication of 5 large trials that also included CBLs, the AHA/ACC recommends a class IIa indication for a shorter DAPT duration (1-3 months) followed by $P2Y_{12}$ inhibitor monotherapy to reduce the risk of bleeding events in selected patients [156].

CONCLUSION

Coronary bifurcation lesions are complex and require meticulous preplanning of the stenting strategy. The provisional stenting technique is the default strategy in most cases. However, two-stent techniques, especially the DK-crush technique, may be the upfront-stenting strategy in some patients with complex lesions. Multiple consecutive steps are required to perform a successful stenting procedure. During the procedure, intravascular imaging is an essential tool since it is not only helpful in the selection of the stenting technique but also necessary for optimization of the result. The results of ongoing and anticipated future trials are awaited to clarify various unresolved issues in percutaneous coronary bifurcation interventions.

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REVIEW

Arrhythmic risk stratification in ischemic, non-ischemic and hypertrophic cardiomyopathy: A two-step multifactorial, electrophysiology study inclusive approach

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Abstract

Annual arrhythmic sudden cardiac death ranges from 0.6% to 4% in ischemic cardiomyopathy (ICM), 1% to 2% in non-ischemic cardiomyopathy (NICM), and 1% in hypertrophic cardiomyopathy (HCM). Towards a more effective arrhythmic risk stratification (ARS) we hereby present a two-step ARS with the usage of seven non-invasive risk factors: Late potentials presence (≥ 2/3 positive criteria), premature ventricular contractions (≥ 30/h), non-sustained ventricular tachycardia (≥ 1episode/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5 ms) and reduced deceleration capacity (≤ 4.5 ms), abnormal T wave alternans (≥ 65μV), decreased heart rate variability (SDNN < 70ms), and prolonged QT_c interval (> 440 ms in males and > 450 ms in females) which reflect the arrhythmogenic mechanisms for the selection of the intermediate arrhythmic risk patients in the first step. In the second step, these intermediate-risk patients undergo a programmed ventricular stimulation (PVS) for the detection of inducible, truly high-risk ICM and NICM patients, who will benefit from an implantable cardioverter defibrillator. For HCM patients, we also suggest the

incorporation of the PVS either for the low HCM Risk-score patients or for the patients with one traditional risk factor in order to improve the inadequate sensitivity of the former and the low specificity of the latter.

Key Words: Arrhythmic sudden cardiac death; Risk stratification; Non-invasive risk factors; Electrophysiology study; Two-step approach; Arrhythmias in cardiomyopathy

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Core Tip: An effective arrhythmic risk stratification approach based on two steps is proposed for the detection of truly high arrhythmic risk patients among ischemic and non-ischemic cardiomyopathy groups: In the first step, patients are screened for several non-invasive risk factors (NIRFs). When even one of these NIRFs is present, patients proceed to the second step, *i.e.*, an electrophysiological study with programmed ventricular stimulation. An implantable cardiac defibrillator is offered to the inducible patients. We also suggest the incorporation of an electrophysiological study in the arrhythmic risk stratification approach among low-risk groups of hypertrophic cardiomyopathy patients.

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INTRODUCTION

Arrhythmic sudden cardiac death (SCD) could potentially pose a threat to patients with ischemic[1] (ICM), non-ischemic[2] (NICM), and hypertrophic[3] (HCM) cardiomyopathy. It occurs by a sudden heart rhythm disorder caused by either an abrupt shift of the normal rhythm to ventricular tachycardia (VT), which degenerates into ventricular fibrillation (VF), or rarely by direct VF[4]. One of the common substrates for this rhythm disturbance in ICM as well as in NICM and HCM is myocardial fibrosis[5]. Arrhythmogenic fibrotic areas are ubiquitous in the post-infarcted myocardial segments in ICM[5], in the left ventricular septum or left ventricular free wall in NICM[6], and interstitially in the left ventricular wall in HCM[7]. The annual SCD rate may range from 0.6% to 4% in ICM[8,9], 1% to 2% in NICM[6] and 1% in HCM[3]. Nevertheless, patients may be protected from arrhythmic SCD thanks to Dr. Mirowski, who conceived the idea, invented and implanted the first cardioverter defibrillator (ICD) back in 1980. However, prior to an ICD implantation, an effective arrhythmic risk stratification (ARS) of a large number of patients at potential arrhythmic risk is required in order to identify those at truly high risk[9] thus, avoiding unnecessary implantations with undue exposure to complications and health system resources exhaustion.

Current status of arrhythmic risk stratification and its limitations

Current European[10] and American Guidelines for SCD prevention are based on previous studies[1,2] with significant inherent design limitations. For the primary prevention of SCD in post-myocardial infarction (post-MI) patients, an ICD implantation is recommended in all patients with left ventricular ejection fraction (LVEF) ≤ 35% based on the MADIT II[1] study results, published 19 years ago. While 18 devices have to be implanted, to save one life during a 2-year follow-up with this strategy[11], a rather significant post-MI subpopulation demonstrating preserved left ventricular systolic function and LVEF > 35%, will be still exposed to SCD with an annual prevalence of malignant arrhythmias ranging between 0.6% to 1%[8]. Similarly, according to the results of SCD-HeFT and DEFINITE[2] studies, an ICD implantation for primary prevention of SCD is recommended for NICM patients with a reduced left ventricular systolic function (LVEF ≤ 35%)[10]. The usage of the LVEF ≤ 35% criterion for non-ischemic dilated cardiomyopathy patients' selection for ICD implantation bears two limitations: first, as the LVEF ≤ 35% criterion fails to identify the truly arrhythmic risk patients, the majority of the implanted ICDs within this spectrum are not expected to be activated, and, as the recent DANISH study has shown, survival may not be improved. Secondly, in a significant proportion of NICM patients with an LVEF>35%, fatal arrhythmic events may occur[6].

In HCM, the current European guidelines recommend the HCM Risk-SCD score calculation and an ICD implantation for patients with an estimated 5-year SCD risk > 6% (Class IIa)[10]. The HCM Risk-

SCD score, as a screening tool, also has inherent limitations. Since its dawn in the development study among 2082 patients (derivation cohort) and the subsequent application in the evaluation study of 1593 patients[12] (validation cohort), 84 SCD cases occurred during follow-up. An HCM Risk-SCD score > 4% was able to detect 60 out of these 84 SCD cases (71%) but failed to detect the rest (29%, *i.e.*, one out of three patients). This limited performance of the current arrhythmic risk stratification approaches in ischemic and non-ischemic cardiomyopathy is of no surprise because of their inability to estimate the underlying arrhythmic substrate by ignoring significant information from already existing and promising non-invasive[9] and invasive electrophysiology (EP) related techniques[13,14]. MADIT II[1] and SCD-HeFT studies were endeavors for proving the post-ICD implantation survival benefit based on an oversimplistic, rather hemodynamic than EP oriented approach, in coronary artery disease (CAD) and NICM populations, in whom an increased incidence of cardiac mortality was anticipated. In HCM, the development of a multivariate scoring system[12], with the inclusion of clinical, echocardiographic, and electrocardiographic markers, although it achieved some degree of satisfactory performance among patients with several risk factors as recommended in both the European and American guidelines, it failed to detect relatively low-risk patients exhibiting one either strong or rather loose traditional risk factor, and who are still at risk for SCD[15,16]. Furthermore, there is a significant discrepancy between the European and American guidelines, with the former being more specific but less sensitive[17].

Value of the left ventricular ejection fraction in arrhythmic risk stratification and the role of the non-invasive risk factors

Arrhythmic mortality is known to have an inverse correlation with the left ventricular systolic function [9,18]. The more LVEF declines, the more mortality increases: in relatively preserved LVEF > 30% the annual mortality is 3.2%, while in diminished LVEF 21%-30% it raises to 7.7%, and in seriously depressed left ventricular systolic function (LVEF < 20%) it launches, to 9.4%[9]. This inverse correlation between left ventricular systolic function and arrhythmic event rates was known and well described before the MADIT II[1] trial. In this study design, the cutoff point of LVEF ≤ 30% was selected as an enrolment criterion for the recruitment of post-MI patients with moderate to serious heart failure and highly-expected future arrhythmic events[18]. Indeed, the main hypothesis (*i.e.*, ICDs improve survival in post-MI patients) was confirmed within the next 20 mo of follow-up. Thereafter, guideline recommendations[10] for patient selection and ICD implantation were dominated by the enrolment criteria for the CAD patients of the MADIT II study[1], *i.e.*, impaired LVEF ≤ 30% and for the NICM patients by the enrolment criteria of the SCDHeFT study, *i.e.*, diminished LVEF ≤ 35%. It must be emphasized the significant limitations of the LVEF screening tool[9] considering the calculation of left ventricular systolic function may be affected by the intra- and interobserver variability during measurements and may also be affected by the temporal variability arousing from the natural evolution of the disease as well as from therapeutic interventions such as coronary artery bypass, percutaneous coronary intervention, and pharmacological treatment. Furthermore, the LVEF is more correlated with total mortality rather than with arrhythmic sudden cardiac death and it has low sensitivity, as only one-third of SCDs occur in patients with LVEF < 35%, while two-thirds of SCDs occur in patients with an LVEF > 35%.

It should also be noted that, despite the guideline recommendations for primary prevention of SCD, ICD implantation rates in patients with LVEF ≤ 35% seem to be below, both in the United States[19] and Europe[20]. Therefore, a reasonable question arouses: why does LVEF, an anatomic-functional index per se, also predicts future arrhythmic events[9]? Impaired left ventricular systolic function is the consequence of post-MI ischemia, myocardial cell necrosis, and myocardial tissue fibrosis. After the infarction of the left ventricle, both anatomic and electric remodelings are evolving. At the anatomic-functional tissue level, the fibrotic scar formation reduces the left ventricular systolic function, while at the molecular scale, the action potential is prolonged, the intracellular calcium homeostasis is affected, and the dispersion of repolarization is increased. Accumulation of connective tissue into the cellular gap junctions occurs in parallel with systemic neurohormonal activation and increased tone of the sympathetic limp of the autonomic nervous system[21]. As a consequence, the LVEF that quantifies the impaired left ventricular functionality also reflects the subsequent electrical instability, predisposing to VT/VF[9]. The more this anatomic-functional index LVEF decreases, the more it encapsulates hidden electric information occurring in electrophysiological and myocardial cell levels. This information is of some prognostic value but the LVEF criterion is raw, modest, and remote from a personalized estimation of the active presence of the arrhythmogenic mechanisms[9]. The need for effective ARS prior to an ICD implantation constitutes a great challenge; in addition to using LVEF, which is of limited sensitivity and specificity, our research group proposes that this hidden electric information should be discriminated and extracted from the impaired anatomic-functional performance of the left ventricle for personalized prognostic ARS by applying the appropriate methods[9]. Arrhythmic SCD is electric in its origin and the most appropriate ARS approach is the usage of conventional and advanced electrocardiography through recording the electric function of the myocardium and detecting the presence and activity of different arrhythmogenic mechanisms[9,22]. Conventional electrocardiographic (ECG) indices, such as late potentials from signal-averaged ECG[23], QTc interval duration[24], number of ventricular premature beats[24], and non-sustained VT episodes[24] per 24 h, as well as advanced ECG

indices such as standard deviation of normal to normal beats from heart rate variability (SDNN)[25], deceleration capacity of heart rate (DC)[26], heart rate turbulence (HRT)[27,28], and T-wave alternans (TWA)[29], may reveal this prognostic information that is related to different arrhythmogenic mechanisms[22]. The above ECG indices were named "non-invasive risk factors" (NIRFs) when applied during the first step in the PRESERVE-EF[24] study for the selection of patients who were further investigated with programmed ventricular stimulation (PVS) in the second step. The main limitation of NIRFs for SCD prediction is solely that each of these risk factors has low positive predictive accuracy by achieving low odds or hazard ratios**.** To support a decision for an ICD implantation with an acceptable number needed to treat, it has been advocated that a risk stratification index is required to achieve an odds ratio of 25-30. This limitation was effectively addressed in the PRESERVE-EF study[24], through the implementation of PVS in the second step which essentially augmented the performance of the total algorithm after the seven NIRFs had been investigated in the first step.

Cardiac magnetic resonance imaging

Assessment of the arrhythmogenic substrate of the myocardium can be also conducted through cardiac magnetic resonance (CMR). Magnetic resonance diagnostic imaging is based on the contrast between tissues created by the signal generated from the response of hydrogen atoms to the magnetic field. T1 relaxation is the recovery of the longitudinal net magnetization vector and T2 relaxation time is the recovery of the transverse net magnetization vector[30]. T1 mapping does not separate extracellular from cellular segments[31,32]. CMR imaging enhanced with intravenous contrast agents *e.g.*, Gadolinium-based contrast agents (GBCAs), multiplies the extracted information[33]. GBCAs cannot enter the intracellular compartment and are distributed only to the extracellular and interstitial space. After the first distribution, a progressive washout of CBCA is observed in the normal myocardium but this washout is delayed in abnormal fibrotic areas. While late gadolinium enhancement (LGE) expresses the difference between two areas, the extracellular volume (ECV) is reflecting histological changes early in the cardiomyopathies' course, independently of their cause. In CAD, the scar tissue following an acute coronary syndrome forms the arrhythmogenic substrate[34]. LGE detects focal myocardial fibrosis predisposing to arrhythmic risk[35,36]. While in the dense core of the scar the fibrotic areas are interrupted by viable fibers serving as slow conduction pathways, in the "grey zone" that surrounds the core of the scar, the hypoperfused myocardium conceals arrhythmogenic properties[37,38]. CMR by assessing and quantifying the heterogeneity of the scar and size of the border zone predicts malignant arrhythmias and appropriate ICD activations[39]. T1 mapping and ECV abnormal measurements are also correlated with an increased arrhythmic burden[40].

In NICM, both the existence and localization of LGE are independent predictors for arrhythmic SCD and hospitalization in all ranges of LVEF[6,41,42]. Septal LGE carries the worst prognosis, even if the fibrotic area is restricted, while the coexistence of septal with free wall LGE, as well as a subepicardial pattern of LGE, are all additive risk factors for fatal arrhythmias[6,41-43]. ECV reveals the early stages of the disease and represents an independent prognostic factor for cardiovascular death and appropriate ICD activations[44,45].

In HCM, the presence of scar, imaged by LGE, is considered to be a strong independent predictor for ventricular arrhythmias, ventricular remodeling, all-cause mortality, and cardiac death[46]. The extent of myocardial LGE involvement has been proposed as a better risk stratifier, with cutoffs oscillating from as low as 10% to as high as 20%, with the mean value of 15% attaining wider acceptance. The pattern of LGE distribution, patchy with multiple foci or diffuse, does not carry additional risk. Nevertheless, we are not aware of whether the decision for an ICD implantation for primary protection against SCD can be exclusively made based on the cardiac MRI; the specific criteria for such a decision are unknown, and we lack prospective information relevant to the rate of appropriate defibrillator activations among all the implanted devices at follow-up time to evaluate such kind of strategy[47]. The results of the ongoing GUIDE-CMR multicenter study[48] in Australia, a study randomizing both post-MI and NICM patients with relatively preserved LVEF 35%-50% upon CMR findings to ICD *vs* ILR, may provide the initial answers to these questions. In the electrophysiology perspective, CMR characterizes the cardiac tissue and detects the substrate that may be arrhythmogenic. This is a necessary condition for arrhythmogenicity, however, it is considered insufficient. The potential arrhythmogenic function of this scar substrate with the usage of CMR solely remains unknown. In order for this predictive information to be extracted, it is necessary that non-invasive and invasive electrocardiography with VPBs, NSVT, LPs, and inducibility upon PVS in electrophysiology (EP) lab is included in the ARS. CMR may classify an extended number of patients with a scar presence[6,47], and convert all of them to ICD candidates. Following such a strategy, a large number needed to treat may not be avoided, and as it happened with the devices implanted for two decades according to the LVEF criterion, only a small portion will be appropriately activated. While mere CMR is probably insufficient to staunchly support the decision for appropriate patient selection before an ICD implantation, it represents an excellent NIRF for the first initial screening of a two-step, EP inclusive approach.

Electrophysiology study with PVS

Ventricular arrhythmias leading to SCD can be studied in the EP Lab and can be triggered or reproduced in patients prone to arrhythmia. Since 1971, when Wellens *et al*[49] introduced the PVS in

the investigation of arrhythmias, it has been known that malignant VT and VF may be triggered in the EP Lab, with the patient being fully conscious in the supine position. This triggering procedure involves an intracardiac catheter, which has been percutaneously inserted and intravenously advanced into the right ventricle, to contact the myocardium. After the external connection of the catheter to a suitable pulse generator, and the assessment of the effective refractory period of that point of the myocardium, PVS with a specific protocol follows. To increase the sensitivity and specificity of the study, the procedure is usually performed and repeated at two different sites, *i.e.*, at the apex and the right ventricle outflow tract, while NICM patients additionally receive intravenously b-agonists. Myocardial fibrosis forms the substrate for a reentrant mechanism which, during programmed ventricular stimulation with the extra stimuli addition, may be activated and generate monomorphic ventricular tachycardia. Multiple programmed ventricular stimuli may act on the triggering mechanism and they may also cause ventricular tachycardia. The laboratory result of an induced or non-induced sustained ventricular tachyarrhythmia provides unique and valuable information for the management of such patients. This information cannot be extracted through other modalities and requires patients to be subjected to this specific protocol, which in the controlled EP Lab setting, is absolutely safe. Given the importance of the question and the risk of possible future exposure to SCD, there is not a single doubt that a patient's subjection to this invasive procedure is worthwhile. Inducible sustained monomorphic VT has been repeatedly proved to be a predictor of SCD in prospective trials[50]. In contrast, the existing data for polymorphic VT or VF induction are conflicting.

Some studies conclude that the induced polymorphic VT or VF are not associated with a high risk for SCD[50,51] but this point is conflicting, as other data support the aspect that such an arrhythmic response to PVS is also of prognostic value[13,14,52].

In addition, previous studies suggest a low risk of SCD in patients with relatively preserved left ventricular systolic function and LVEF > 40%, even in the presence of inducible VT[53], however, primary protection from major arrhythmic events was recently confirmed for these patients, when the implanted ICDs with the improved two-step, EP inclusive approach in PRESERVE EF study where appropriately activated[24]. In CAD, the ARS may be discerned at three different periods, considering the time pass after the myocardial infarction (MI): (1) the early phase (first 40 d); (2) the subacute phase (40 d–6 mo after the MI); and (3) the remote phase (> 6 mo after the MI).

Acute MI phase (< 40 d): Animal studies have shown that within two weeks after MI, the substrate for reentrant ventricular arrhythmias was formed in the myocardium. In terms of pathophysiology, the experimental results justify an early post-MI PVS investigation[54].

The BEST-ICD study[55] enrolled 143 survivors with left ventricular ejection fraction ≤ 35% and either frequent VPBs > 10/h or depressed SDNN < 70 ms from heart rate variability or abnormal signal-averaged ECG within a month after an acute MI. Of these, 138 were randomized, in a 2:3 ratio, to conventional strategy (n = 59) or PVS guided/ICD strategy (n = 79), with 24 ICDs implanted in the inducible patients. A nonsignificant survival benefit of this early PVS-guided strategy of ICD implantation was shown, but the study was underpowered to provide a definite conclusion for the performance of such an approach. It must be noted that this was a two-step ARS study, with the preselected patients exhibiting a combination of a depressed LVEF ≤ 35% and/or three basic NIRFS, while the PVS was performed after total sample randomization.

Two observational ICD studies found that a positive response on PVS is an efficient arrhythmia predictor. In the first one[56], which included ST-elevation MI patients who had received a primary percutaneous coronary intervention, a benefit from an early ICD implantation for the patients with an impaired LVEF and positive PVS was shown, while in the second one[57], which enrolled post-MI patients with a depressed left ventricular systolic function, the PVS study effectively discriminated - in the long term - patients with a protective ICD implantation (PVS positives) from the vast majority of those at significantly lower risk of arrhythmic events without a defibrillator (PVS negatives).

Furthermore, a negative PVS predicted survival in the absence of an ICD implantation[56]. Despite the negative results produced by IRIS and DINAMIT studies, whose design failed to detect the truly early post-MI high arrhythmic risk patients and, thus, failed to prove a survival benefit for the ICD recipients', consequently withholding such patients from an ICD implantation with a class III recommendation[10], the arrhythmic SCD risk in early post-MI phase exists and this is well known and described. The acknowledgment of this risk explains the paradox: while guidelines that are based on the IRIS and DINAMIT studies reject ICD implantation in early post-MI patients with a Class III recommendation[10], the same guidelines, propose screening these early post-MI patients at potential arrhythmic risk with PVS with a Class IIb recommendation. This specific clinical issue questioning the most appropriate ARS strategy is under investigation by the PROTECT-ICD trial[58], which recruits early post-MI patients with LVEF ≤ 40% and randomizes them to either PVS-guided early ICD implantation or a control standard care arm.

Subacute and remote phases after MI phase (≥ 40 d): Data for the utility of PVS in remote phases after an MI comes from both randomized and observational studies. MADIT I study, 1996, included 196 post-MI patients at increased risk for ventricular tachyarrhythmias. Enrollment was focused on patients fulfilling the inclusion criteria of LVEF < 35%, non-sustained VT, and the inducibility of VT in PVS.

These patients were randomly assigned to receive either an implanted defibrillator (n = 95) or conventional medical therapy (n = 101). A 54% reduction in overall mortality was observed for the ICD treatment arm with a 27-mo follow-up. The MUSTT study[59], 1999, investigated a population at relatively increased arrhythmic risk consisting of patients with a prior MI, LVEF% < 40%, and non-sustained VT that was inducible in PVS (n = 704). After randomization, 351 of them were assigned to EP-guided therapy and 353 were assigned to no antiarrhythmic therapy. The five-year estimates of the incidence of the primary endpoint of cardiac arrest or death from arrhythmia were 25% for the EP guided therapy receivers and 32% for the patients assigned to no antiarrhythmic therapy with a relative risk: 0.73, representing a 27% risk reduction. In this study, a combination of LVEF<40% and inducibility in the PVS resulted in a greater reduction in mortality than the one observed in the MADIT II trial[1], which used the LVEF as the sole criterion for selecting patients for ICD implantation. These two randomized trials have demonstrated the utility of PVS in combination with a reduced LVEF and other variables in the appropriate selection of the candidates before an ICD implantation. MADIT II study[1] in 2002, extended the prophylactic use of an ICD to a broader post-MI patients spectrum under a less arrhythmic risk compared to the MUSST[59] population with an LVEF < 30% as the only pre-implantation criterion. In the MADIT II trial[1], a PVS was not considered necessary for the initial study. These 1232 post-MI patients with significant heart failure were randomly assigned in a 3:2 ratio to receive either an ICD (n = 742) or conventional medical therapy (n = 490). An improvement in survival was observed in the ICD group during an average follow-up of 20 mo with a 0.69 hazard ratio. Although a PVS was not an inclusion criterion for patient selection in the initial study, its performance was examined in a MADIT II sub-study[51] and inducibility was found to be related to subsequent ICD-detected arrhythmias. In that study, while an inducible monomorphic VT predicted future arrhythmic episodes, the induction of polymorphic VT or VF appeared less relevant. These data were retrospectively acquired, with many study-centers contributing only 2–4 cases and without having used a standardized PVS protocol. On the other hand, high PVS predictive accuracy was consistently shown when the EP study was performed in dedicated centers in the context of single-center studies, using standardized protocols[13,14,52]. The prospective observational Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction - CARISMA trial in 2009, investigated 312 post-MI phase patients with a mean LVEF of 31% ± 6% with application of NIRFs (Heart rate variability/turbulence, ambient arrhythmias, signal-averaged electrocardiogram, T-wave alternans) and PVS, applying the NIRFs and the PVS rather independently in a parallel screening than in a two-step sequential approach. Induction of sustained monomorphic VT predicted the future occurrence of VT/VF (adjusted HR = 4.8, P = 0.003).

PVS in NICM and HCM

In NICM, the role of PVS has been disputed[60] for years. However, this view was recently challenged by a prospective study of 157 NICM patients[13,61,62], who were evaluated with PVS for primary prevention; during long-term follow-up, appropriate ICD intervention or SCD occurred significantly more frequently among PVS positive NICM patients. This PVS-guided approach was incorporated for the first time in current ESC guidelines[10], albeit at a class IIb recommendation. In HCM, the ESC guidelines[10] for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, following ESC HCM guidelines that are based on an expert opinion level of evidence, do not recommend a PVS for ARS. However, recent results[15] support its use in a study that investigated 203 HCM patients with ≥ 1 NIRFs who were submitted to PVS and received an ICD. During a median follow-up period of 60 mo, the primary endpoint was observed in 20 patients, of whom 19 were inducible in a procedure that was proven safe and they had an ICD implanted. Inducibility at PVS predicted SCD or appropriate device therapy while non-inducibility was associated with prolonged event-free survival. The addition of an EP/PVS risk estimation[15], among HCM patients demonstrating one traditional risk factor, may improve the frequently observed rather poor performance[15,63] of either the American or the European guidelines in this subgroup of HCM patients. Considering the time course for the evolution of research in the field of SCD ARS, one could say that data from previous studies have now dried up, leaving significant gaps in the management of such patients[60], gaps that we do not know if and how they will be filled in by methods such as MRI [17] or Virtual PVS[64] in the future. Nevertheless, the latest results published[24] describe a two-step SCD ARS strategy: in the first step of this strategy, if the included bloodless non-invasive ECG markers (NIRFs) are positive, we proceed with the second step of PVS for the patient selection before an ICD implantation. Similar results based on a two-step, EP inclusive approach, were documented in patients across the entire spectrum of ischemic and organic cardiomyopathy, in post-MI patients with preserved LVEF[24], in patients with heart failure and moderately impaired left ventricular systolic function[65], in NICM[13], and HCM[15] patients, noteworthy with correct ICDs activation of the devices implanted. This strategy has been applied in sudden cardiac death ARS by the First Department of Cardiology and EP Lab, National and Kapodistrian University of Athens at Hippocration Hospital of Athens, Attica, Greece[66], over the last twenty years, thus contributing to the final decision for the appropriate patient selection for ICD implantation across all the ICM[24,65] and NICM[13] and HCM[15] patients' spectrum.

Table 1 Abnormal values and connection of every non-invasive risk factors with the arrhythmogenic mechanisms

Non-invasive risk factors	Abnormal values	Mechanisms
SAECG, LPs	2/3 positive criteria	Fibrotic areas, slow conduction, reentry
QTc	≥ 440 ms (♂), ≥ 450 ms (♀)	Prolonged repolarization, EAD, DAD
TWA	≥ 65 μV (2-channels)	APD and Ca^{2+} alternans, steep APDR and CVR, steep FSRCR
VPBs	≥ 30/24 h	Automaticity (Ca^{2+}oscillations), reentry
NSVT	≥ 1 episode/24 h	Automaticity (Ca^{2+}oscillations), reentry
SDNN/HRV	≤ 75 ms	Enhanced sympathetic tone, autonomic imbalance
DC/HRT	DC ≤ 4.5 ms	Vagal and sympathetic ANS dysfunction
	HRT onset ≥ 0%	
	HRT slope ≤ 2.5ms	

ANS: Autonomic nervous system; APD: Action potential duration; APDR: Action potential duration restitution; CVR: Conduction velocity restitution; DAD: Delayed afterdepolarization; DC: Deceleration capacity from heart rate dynamics; EAD: Early afterdepolarization; FSRCR: Fractional sarcoplasmic reticulum Ca^{2+} release; HRT: Heart rate turbulence; LPs: Late potentials from signal-averaged electrocardiogram; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SAECG: Signal-averaged electrocardiogram; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

TWO-STEP, NON-INVASIVE RISK FACTORS ELECTROPHYSIOLOGY STUDY INCLUSIVE, RISK STRATIFICATION ALGORITHM

Initially, the concept of the two-step multifactorial, EP inclusive approach had been successfully introduced for the risk stratification and management of post-MI patients, incorporating NIRFs such as heart rate variability, LVEF, late potentials, and complex ventricular arrhythmias[67,68]. Indeed, such studies identified a high-risk group of post-MI patients, predominantly among those with reduced LVEF that are usually offered an ICD, based on current guidelines. This strategy was further refined and improved in the PRESERVE EF study[24] applying an accurate algorithm with multiple advanced ECG markers[9] that reflect the presence and activity of diverse arrhythmic mechanisms to detect high-risk post-MI patients after a limited myocardial injury without any evidence of ongoing myocardial ischemia or significant left ventricular dysfunction. In the first step, the advanced form of the algorithm [24] determined the presence of seven NIRFs, while in its simplified, yet equally effective form[65], it appears to be working well even in the simple presence of only three fundamental NIRFs. Upon detecting the presence of at least one of the NIRFs, patients are referred for PVS. The advantage of ARS using multiple NIRFs during the first step is that they reflect the presence and activity of multiple different arrhythmogenic mechanisms, such as fibrotic areas with late conduction properties predisposing for re-entry (SAECG late potentials)[23], prolonged action potential repolarization duration (QTc)[24], electrical instability with T wave alternations during repolarization (TWA)[29], increased sympathetic tone (SDNN)[25], decreased parasympathetic tone (DC[26] and HRT[27,28]), triggered activity on a substrate that predisposes to and maintains ventricular arrhythmias (VPBs and NSVT)[24]. The pathophysiological connection for every NIRF with the arrhythmogenic mechanisms[22] is presented in Table 1, while its prevalence in the total sample, in the truly high-risk group that was detected after the two-step, EP inclusive approach, and in the 9 patient subgroup with SCD equivalent major arrhythmic events during a 32 mo of follow-up, as investigated in the PRESERVE EF study[24], are presented in Table 2. The results of the implementation of this two-step risk stratification strategy were described in this study in 575 post-MI, relatively not aged (mean age = 57 years) with preserved left ventricular systolic function (LVEF = 50.8%) patients. In this study, 9 major arrhythmic events (MAEs) were observed during a 32 mo follow-up. The MAE prevalence in the total sample of 575 patients was 1.5%. The implementation of the first step of the algorithm determined an intermediate risk subpopulation of 204 patients out of 575 patients in total, with at least one NIRF present. In this intermediate-risk subpopulation with positive NIRFs, who were risk-stratified using the first step, the MAE prevalence increased from 1.5% to 4.4%. When this subpopulation underwent PVS as per the second step, 41 out of 152 patients developed arrhythmia (out of the 204 patients of the intermediate-risk group who gave their informed consent to participate in the EP study). This third group of 41 PVS-positive patients represented the subpopulation at actual high risk with the MAE prevalence accounting for 22% (Figure 1). It is realistically feasible that by this approach, out of the general population of the ischemic, the NICM and the HCM patients, the subpopulation at actual high risk for SCD who could undergo ICD implantation can be defined in 2 steps, whereas the rest of the patients can safely be excluded from implantation[24,60,69]. This approach will be tested in NICM patients in the

Table 2 Prevalence of non-invasive risk factors in the total sample, in the truly high-risk group, detected after the two-step, electrophysiology inclusive approach, and in patients with major arrhythmic events during a 32-mo follow-up, as investigated in the PRESERVE EF study[24]

NIRF	Prevalence in the total preserve-EF study (*n* = 577)	Prevalence in the high-risk group (*n* = 41)	Prevalence in 9 MAE/SCD patients
LPs (%)	13.8	51.2	78 (7/9)
NSVT (%)	8.6	46.3	66 (6/9)
QTc (%)	13.6	36.6	55 (5/9)
VPBs (%)	10.8	39	33 (3/9)
TWA (%)	6.8	24.4	11 (1/9)
SDNN (%)	2.8	9.8	0 (0/9)
HRT and DC (%)	2.8	9.8	0 (0/9)

DC: Deceleration capacity from heart rate dynamics; HRT: Heart rate turbulence from heart rate dynamics; LPs: Late potentials from signal-averaged electrocardiogram; MAE: Major arrhythmic event; NIRF: Non-invasive risk factor; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

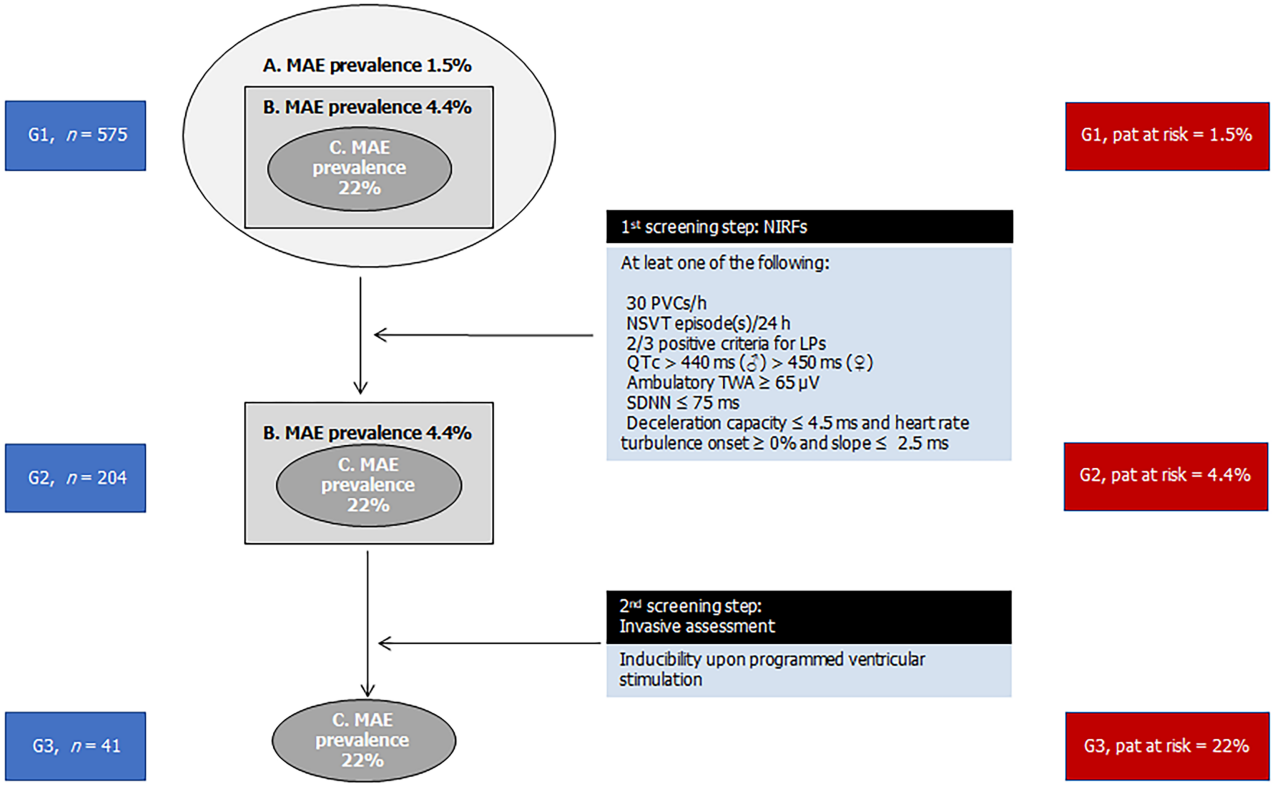


Figure 1 The PRESERVE EF[24] study's two-step arrhythmic risk stratification algorithm. In the total sample of patients the estimated prevalence of major arrhythmic events (MAE) during the 32-mo follow-up was 1.5%. Implementation of the algorithm with the detection of the NIRFs in the first step determines the intermediate-risk subpopulation, with the MAE prevalence accounting for 4.4%. In the second step, the Programmed Ventricular Stimulation determines the actual high-risk subpopulation, with a prevalence reaching 22%. Of the 37 patients with implantable cardioverter defibrillator, there were 9 true activations during the 32-mo follow-up. Neither sudden cardiac death(SCD) nor inappropriate ICD activations were observed during follow-up. (Modified with permission from EHJ[24]).

ReCONSIDER study[70]. An overview of a two-step, non-invasive, EP inclusive ARS approach, for ICM, NICM, and HCM is depicted in Figure 2.

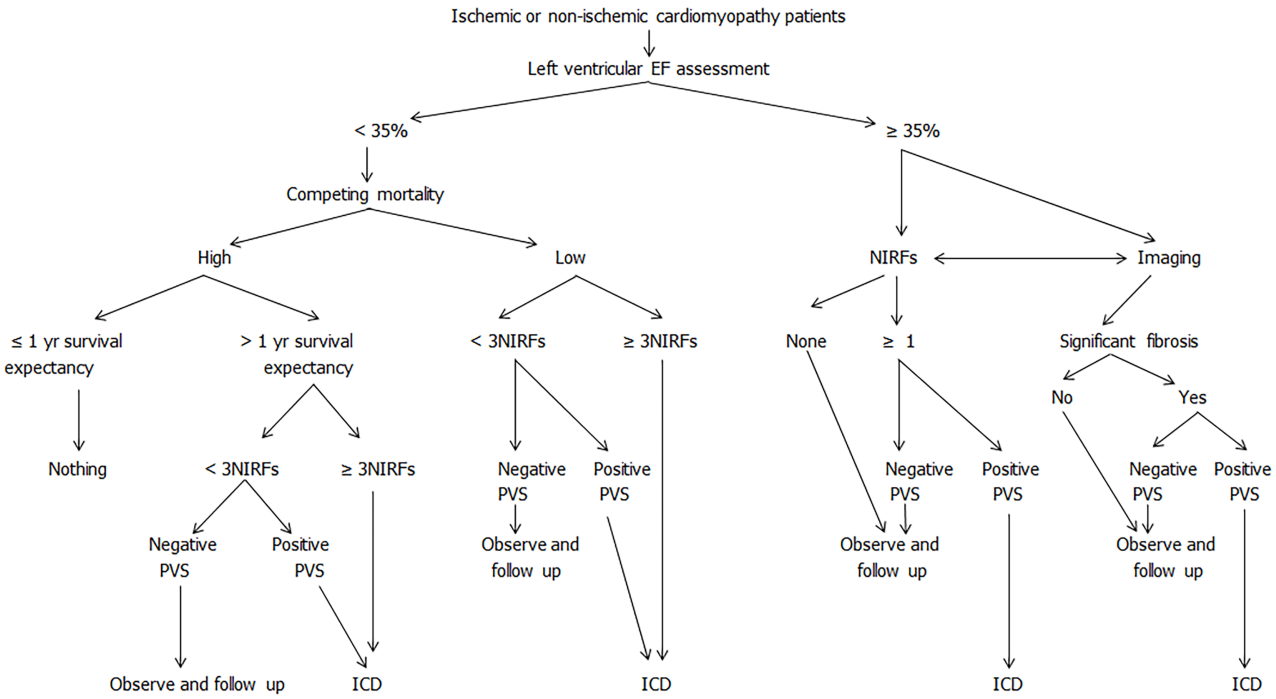


Figure 2 Emerging new sudden cardiac death risk stratification paradigm. It is based on newer evidence, incorporating competing mortality assessments, as well as non-invasive and invasive tests. Non-invasive tests are performed before programmed ventricular stimulation (PVS) to assess the likelihood of functional circuit formation. PVS is pivotal in determining the potential for arrhythmia sustainability and guiding treatment, especially in intermediate and low-risk patients. "Observe and Follow-up" involves repeating tests for NIRF annually and PVS every 3–5 yr. NIRFs (noninvasive ECG risk factors) including the presence of late potentials (≥ 2/3 criteria), frequent premature ventricular contractions (≥ 30/h), non-sustained VT (≥ 1/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5ms) and reduced deceleration capacity (≤ 4.5 ms), positive T wave alternans (≥ 65 μV), decreased heart rate variability (SDNN < 70ms), prolonged QT_c interval (> 440 ms in males and > 450 ms in females). (Modified after permission from ANE[60]).

CONCLUSION

The arrhythmic risk stratification for SCD in Ischemic, Non-Ischemic, and Hypertrophic cardiomyopathy for ICD implantation patient selection may be improved with the proposed two-step algorithm. This broad spectrum of patients shares arrhythmogenic mechanisms. Appropriate screening of all these patients with basic and advanced electrocardiographic indices in the first step may detect the subpopulation of intermediate SCD risk. When this subpopulation is subjected to programmed ventricular stimulation in the second step, the truly high SCD risk patients may be detected and effectively protected with an ICD.

FOOTNOTES

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REVIEW

Climatic influences on cardiovascular diseases

Maurizio Giuseppe Abrignani, Alberto Lombardo, Annabella Braschi, Nicolò Renda, Vincenzo Abrignani

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Abstract

Classical risk factors only partially account for variations in cardiovascular disease incidence; therefore, also other so far unknown features, among which meteorological factors, may influence heart diseases (mainly coronary heart diseases, but also heart failure, arrhythmias, aortic dissection and stroke) rates. The most studied phenomenon is ambient temperature. The relation between mortality, as well as cardiovascular diseases incidence, and temperature appears graphically as a ''U'' shape. Exposure to cold, heat and heat waves is associated with an increased risk of acute coronary syndromes. Other climatic variables, such as humidity, atmospheric pressure, sunlight hours, wind strength and direction and rain/snow precipitations have been hypothesized as related to fatal and non-fatal cardiovascular diseases incidence. Main limitation of these studies is the unavailability of data on individual exposure to weather parameters. Effects of weather may vary depending on other factors, such as population disease profile and age structure. Climatic stress may increase direct and indirect risks to human health *via* different, complex pathophysiological pathways and exogenous and endogenous mechanisms. These data have attracted growing interest because of the recent earth's climate change, with consequent increasing ambient temperatures and climatic fluctuations. This review evaluates the evidence base for cardiac health consequences of climate conditions, and it also explores potential further implications.

Key Words: Weather; Climate; Meteorology; Cardiovascular diseases; Myocardial infarction; Angina pectoris

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Core Tip: Climatic stress may determine some risks to human health *via* complex pathophysiological pathways. Meteorological factors may influence coronary heart diseases, but also heart failure, arrhythmias, aortic dissection and stroke rates. The most studied phenomenon is temperature. The relation between mortality, as well as cardiovascular diseases incidence, and temperature appears graphically as a ''U'' shape. Other variables, such as humidity, atmospheric pressure, sunlight hours, wind strength and direction and rain/snow precipitations have been studied. These data have attracted growing interest because of the recent earth's climate change. This review evaluates the evidence for cardiac health consequences of climate conditions.

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INTRODUCTION

Despite considerable advances in identifying the conditions that may predispose to atherosclerosis, less information is known about the incident events leading to plaque rupture. Classical risk factors only partially account for variations in cardiovascular disease incidence and mortality. Therefore, also other so far unknown features, among which meteorological factors, may influence cardiovascular diseases rates.

AMBIENT TEMPERATURE AND MORTALITY

Seasonal peaks in respiratory, cardiovascular, and cerebrovascular mortality, with a winter increase in deaths, have been reported in different countries, referred to as ''excess winter mortality''[1-3]. This phenomenon has been strongly linked to changes in temperature[4-8].

The relation between environmental temperature and health has been known for a very long time. Several disorders, such as heat stroke and hypothermia, are directly linked to temperature extremes. Low seasonal temperatures increase the odds of mortality[9,10]. An association between extreme high temperatures and mortality has also been demonstrated[11,12], as confirmed by recent data[13-16]. Actually, a number of ecological time-series studies suggest that the relation between mortality and ambient temperature appears graphically as a ''U'' shape, with mortality rates lower on days in which the average temperatures range between 15° to 25°C, rising progressively as the ambient temperature becomes hotter or colder[17-20]. Most of mortality linked to heat occurs during first days after temperature increase, while the effect of cold has been prolonged for several weeks[21-23]. Spatial and temporal differences have been described in this phenomenon[24-27]. Many heat-related deaths occur in people before they come to medical attention[28]. Investigations carried out in a large number of cities have shown that temperature level corresponding to the minimum mortality varies from place to place and country to country according to the usual climate (heat thresholds were generally higher in communities closer to the equator), probably reflecting adaptations of the population to the usual range of temperature[29]. High respiratory, cardiovascular and influenza mortality in winter leads to lower temperature effects in the following summer[30]. There was a progressive reduction in temperature related deaths over the 20th century, despite an aging population[31-33]. This trend is likely to reflect improvements in social, environmental, behavioural, and health-care factors[34,35]. In the recent COVID-19 pandemic, there was a negative correlation between the cumulative relative risk of death and temperature[36]. Table 1 shows main studies on the relations between weather and general mortality.

In particular, various epidemiological studies have reported greater coronary heart disease (CHD) and acute myocardial infarction (AMI) mortality both in winter[37-40] and in extremely hot summers [25,41,42]. Many authors have postulated that weather-related variables may also explain these seasonal trends, as well as substantial geographic variations in CHD mortality. Cold climate is independently associated to coronary mortality[43-45], but a U-shaped relationship between ambient temperature and cardiovascular mortality has been also described even in milder regions, where either low temperatures or heat waves are exceptional[46-48], with few exceptions[49]. Consensus is lacking, however, on whether this phenomenon reflects variations in incidence or in case fatality rate. Cold effect seems delayed, whereas heat effect is acute, both of which last for several days[34,46,50]. The delay between peak of cold is lower for all-cause mortality and CHD causes than for respiratory ones[51]. Mean temperature had better predictive ability than minimum and maximum one[35,46]. Table 2 shows main studies on the relations between weather and cardiovascular mortality.

Table 1 Main studies on the relations between weather and general mortality

Ref.	Setting and population	Year	Main results
Chung *et al* [11]	Fifteen cities in Northeast Asia	1972-2010	Cold effects had longer time lags (5–11 d) than heat effects, which were immediate (1–3 d). Both cold and heat effects were more significant for cardiorespiratory mortality than for other causes of death
Curriero *et al*[4]	Eleven large eastern United States cities	1973-1994	Current and recent days' temperatures were the weather components most strongly predictive of mortality. Mortality risk generally decreased as temperature increased from the coldest days to a certain threshold temperature, which varied by latitude, above which mortality risk increased as temperature increased. Strong association of the temperature-mortality relation with latitude, with a greater effect of colder temperatures on mortality risk in more-southern cities and of warmer temperatures in more-northern cities
Fernández-Raga *et al* [18]	Castile-Leòn, Spain	1980-1988	Temperatures with lower death risk for patients with cardiovascular diseases (16.8°C) are apparently lower than those for patients with respiratory diseases (18.1°C)
Achebak *et al*[31]	47 major cities in Spain	1980-2015	Reduction in relative risks of cause-specific and cause-sex mortality across the whole range of summer temperatures
Gemmel *et al*[2]	Scotland, United Kingdom	1981-1993	A 1°C decrease in mean temperature was associated with a 1% increase in deaths 1 wk later
Guo *et al*[15]	400 communities from 18 countries/regions	1984-2013	Heat waves had significant cumulative associations with mortality but varied by community. The higher the temperature threshold used to define heat waves, the higher heat wave associations on mortality. The association between heat waves and mortality appeared acutely and lasted for 3 and 4 d. Heat waves had higher associations with mortality in moderate areas than in cold and hot areas
Gasparrini *et al*[22]	305 locations in 9 countries: Australia, Canada, China, Italy, Japan, South Korea, Spain, United Kingdom, and United States	1985-2012	Strong evidence of a reduction in risk over the season. Relative risks for the 99th percentile versus the minimum mortality temperature were in the range of 1.15–2.03 in early summer. In late summer, the excess was substantially reduced or abated, with relative risks in the range of 0.97–1.41
Gasparrini *et al*[27]	384 locations in Australia, Brazil, Canada, China, Italy, Japan, South Korea, Spain, Sweden, Taiwan, Thailand, United Kingdom, and United States	1985-2012	7.71% (95%CI: 7.43–7.91) of mortality was attributable to non-optimum temperature in the selected countries within the study period, with substantial differences between countries, ranging from 3.37% (3.06 to 3.63) in Thailand to 11.00% (9.29 to 12.47) in China. The temperature percentile of minimum mortality varied from roughly the 60th percentile in tropical areas to about the 80–90th percentile in temperate regions
Aylin *et al* [5]	Great Britain	1986-1996	Significant association between mortality and temperature with 1.5 higher odds of dying for every 1°C reduction in winter temperature
The Eurowinter Group[1]	Men and women aged 50–59 and 65–74 in north Finland, south Finland, Baden-Württemburg, the Netherlands, London, and north Italy	1988-1992	Percentage increases in all-cause mortality per 1°C fall in temperature below 18°C were greater in warmer regions than in colder regions. High indices of cold-related mortality were associated with high mean winter temperatures ($P < 0.01$ for all-cause mortality and respiratory mortality; $P > 0.05$ for mortality from ischaemic heart disease and cerebrovascular disease)
Rocklöv *et al* [30]	Stockholm, Sweden	1990-2002	A high rate of respiratory and cardiovascular mortality in winter reduced the heat effect the following summer. The cumulative effect per 1°C increase was 0.95% below and 0.89% above a threshold (21.3°C) after a winter with low cardiovascular and respiratory mortality, but -0.23% below and 0.21% above the threshold after a winter with high cardiovascular and respiratory mortality
Ragettli *et al* [32]	Switzerland	1995-2013	Significant temperature-mortality relationships were found for maximal (1.15; 1.08–1.22); mean (1.16; 1.09–1.23), and minimal (1.23; 1.15–1.32) temperature. Mortality risks were higher at the beginning of the summer. Recent non-significant reduction in the effect of high temperatures on mortality
Chen *et al* [10]	All deaths among residents in Ontario, Canada	1996-2010	In warm seasons, each 5°C increase in daily mean temperature was associated with a 2.5% increase in nonaccidental deaths (95%CI: 1.3%-3.8%) on the day of exposure (lag 0). In cold seasons, each 5°C decrease in daily temperature was associated with a 3.0% (95%CI: 1.8%-4.2%) increase in nonaccidental deaths, which persisted over 7 d. Cold-related effects were stronger for cardiovascular-related deaths (any cardiovascular death: 4.1%, 95%CI: 2.3%-5.9%; CHD: 5.8%, 95%CI: 3.6%-8.1%). Each 5°C change in daily temperature was estimated to induce 7 excess deaths per day in cold seasons and 4 excess deaths in warm seasons
Oudin Åström *et al* [24]	Eastern Esthonia	1997-2013	Immediate increase in mortality associated with temperatures exceeding the 75th percentile of summer maximum temperatures, corresponding to approximately 23°C. This increase lasted for a couple of days
Bell *et al*[21]	Mexico City, Mexico; Sao Paulo, Brazil; Santiago, Chile	1998-2002	Elevated temperatures (in particular same and previous day apparent temperature) are associated with mortality risk
Chan *et al* [12]	Hong Kong, China	1998-2006	An average 18°C increase in daily mean temperature above 28.2°C was associated with a 1.8% increase in mortality. Non-cancer related causes such as cardiovascular and respiratory infection-related deaths were more sensitive to high temperature

Xu *et al*[34]	Barcelona, Spain	1999-2006	The effect of three consecutive hot days was a 30% increase in all-cause mortality (RR = 1.30, 95%CI: 1.24-1.38)
Guo *et al*[23]	Chiang Mai city, Thailand	1999-2008	Both hot and cold temperatures resulted in immediate increase in all mortality types and age groups. Generally, the hot effects on all mortality types and age groups were short-term, while the cold effects lasted longer. The relative risk of mortality associated with cold temperature (19.35°C, 1st centile) relative to 24.7°C (25th centile) was 1.29 (95%CI: 1.16, 1.44) for lags 0–21. The relative risk of mortality associated with high temperature (31.7°C, 99th centile) relative to 28°C (75th centile) was 1.11 (95%CI: 1.00, 1.24) for lags 0–21
Oudin Åström *et al*[24]	Population over 50 years in Rome, Italy, and Stockholm, Sweden	2000-2008	The percent increase in daily mortality during heat waves as compared to normal summer days was 22% (95%CI: 18%-26%) in Rome and 8% (95%CI: 3%-12%) in Stockholm
Zafeiratou *et al*[8]	42 Municipalities within the Greater Athens Area, Greece	2000-2012	Significant effects of daily temperature increase on all-cause, cardiovascular, and respiratory mortality (*e.g.*, for all ages 4.16% (95%CI: 3.73%, 4.60%) per 1 C increase in daily temperature (lags 0–3)
Fu *et al*[14]	India	2001–2013	Mortality from all medical causes, stroke, and respiratory diseases showed excess risks at moderately cold temperature and hot temperature. Moderately cold temperature was estimated to have higher attributable risks [6.3% (95% empirical CI 1.1 to 11.1) for all medical deaths, 27.2% (11.4 to 40.2) for stroke, 9.7% (3.7 to 15.3) for IHD, and 6.5% (3.5 to 9.2) for respiratory diseases] than extremely cold, moderately hot, and extremely hot temperatures
Zeng *et al*[9]	15973 elderly residents of 866 counties and cities, China	2002-2005	Low seasonal temperatures increase the odds of mortality
Argaud *et al*[25]	Lyon, France	2003	Independent contribution to mortality from heatstroke if patients used long-term antihypertensive medication (HR, 2.17; 95%CI: 1.17-4.05), or presented at admission with cardiovascular failure (HR, 2.43; 95%CI: 1.14-5.17)
Zhang *et al*[35]	Wuhan, China	2003-2006	U-shaped relationship between temperature and mortality. Cold effect was delayed, whereas hot effect was acute, both of which lasted for several days. For cold effects over lag 0–21 d, a 1°C decrease in mean temperature below cold thresholds was associated with a 2.39% (95%CI: 1.71, 3.08) increase in non-accidental mortality, 3.65% (95%CI: 2.62, 4.69) increase in cardiovascular mortality, 3.87% (95%CI: 1.57, 6.22) increase in respiratory mortality, 3.13% (95%CI: 1.88, 4.38) increase in stroke mortality, and 21.57% (95%CI: 12.59, 31.26) increase in CHD mortality. For hot effects over lag 0–7 d, a 1 °C increase in mean temperature above the hot thresholds was associated with a 25.18% (95%CI: 18.74, 31.96) increase in non-accidental mortality, 34.10% (95%CI: 25.63, 43.16) increase in cardiovascular mortality, 24.27% (95%CI: 7.55, 43.59) increase in respiratory mortality, 59.1% (95%CI: 41.81, 78.5) increase in stroke mortality, and 17.00% (95%CI: 7.91, 26.87) increase in CHD mortality
Gómez-Acebo *et al*[7]	Cantabria (northern Spain)	2003-2006	Raising maximum or minimum temperatures by 1ºC was associated with a 2% excess in mortality risk throughout the warm period. No effect in mortality on the cold season
Gómez-Acebo *et al*[17]	Cantabria (northern Spain)	2004-2005	The higher OR for cancer mortality was seen on the first day of exposure (OR = 4.91; 95%CI: 1.65–13.07 in the whole population). Cardiovascular (OR = 2.63; 95%CI: 1.88–3.67) and respiratory mortality (OR = 2.72; 95%CI: 1.46–5.08) showed a weaker effect
Analitis *et al*[26]	9 European cities	2004-2010	In the warm season, the percentage increase in all deaths from natural causes per ◦C increase in ambient temperature tended to be greater during high ozone days. For the cold period, no evidence for synergy was found.
McMichael *et al*[19]	Urban populations in Delhi, Monterrey, Mexico City, Chiang Mai, Bangkok, Salvador, Sao Paulo, Santiago, Cape Town, Ljubljana, Bucharest and Sofia.	2007	Most cities showed a U-shaped temperature-mortality relationship, with clear evidence of increasing death rates at colder temperatures and with increasing heat. Heat thresholds were generally higher in cities with warmer climates, while cold thresholds were unrelated to climate
Rabczenko *et al*[20]	Warsaw, Poland	2008-2013	Analysis of dependence between temperature and mortality for whole population as well as for subpopulations with respect to sex and age demonstrated its similar U-shape. Comfort varied between 20 and 24°C, with slight tendency to be higher for woman
Can *et al*[13]	Istanbul, Turkey	2013-2017	Three extreme heat waves in summer months of 2015, 2016, and 2017, which covered 14 days in total, significantly increased the mortality rate and caused 419 excess deaths in 23 d of exposure
Oray *et al*[16]	Izmir province, Turkey	2016	During the study period, the mean number of ED visits and mortality rates were significantly higher than the previous year's same period [320 ± 30/d *vs* 269 ± 27/d, (P < 0.01), and 1.6% *vs* 0.7%, (P < 0.01)]. Although the admission rate was similar between the study period and the other 21 d of June 2016 [320 ± 30/d *vs* 310 ± 32/d, (P = 0.445)] in-hospital mortality rate was significantly higher [1.6% *vs* 0.7%, (P < 0.01)]

CHD: Coronary heart disease; CI: Confidence interval; OR: Odds ratio.

AMBIENT TEMPERATURE AND CARDIOVASCULAR AND NON-CARDIOVASCULAR DISEASES

Weather exposure beyond certain thresholds affects human health negatively[52]. Both cold and heat temperature significantly increased risk of hospitalization for several diseases[53]. However, heat waves have documented a higher impact on mortality than on morbidity (hospital admissions)[41,54,55]. This phenomenon could be explained by the hypothesis that deaths from circulatory disease occur rapidly patients reach a hospital[56]. There are relationships between temperature (in particular its short-term variability) and hospital admissions due to various forms of heart disease[57-61]. Hot and cold temperature are a risk factor for a wide range of cardiovascular, respiratory, and psychiatric illness; yet, in few studies, the increase in temperature reduced the risk of hospital admissions for pulmonary embolism and angina pectoris[62]. Table 3 shows main studies on the relations between weather and hospital admissions.

AMBIENT TEMPERATURE AND ACUTE CORONARY SYNDROMES

Seasonal variations in emergency admission rates and trial recruitment of patients suffering from acute coronary syndromes (ACS) are well described[37], and a number of epidemiological studies have reported a greater winter ACS incidence, with similar seasonal trends in all studied cohorts, including men and women, middle-aged and elderly patients, and patients from northern and southern hemispheres[4].

Over the past few decades, a growing body of epidemiological studies found the effects of ambient temperature on cardiovascular disease, including risk for ACS[63-66]. Inverse relationship between temperature and ACS is well known[67-71], even regardless of season[37,72,73]. In a previous study, we correlated the daily number of AMI cases admitted to a western Sicily hospital and weather conditions on a day-to-day basis over twelve years, showing a significant association between daily number of ACS hospital admission and minimal daily temperature[74]. Effects of low temperature on total ACS cases were more pronounced in years with higher average temperatures and also during summer, suggesting not a pure "cold effect" but an influence of unusual temperature decreases[64,75].

This relation, moreover, could be actually U-shaped, with higher short-term risk of ACS also in extremely hot summer[67,76-79]. Very few studies failed to demonstrate an association between temperature and ACS incidence[80]. A recent meta-analysis, however, confirmed that cold exposure, heat exposure, and exposure to heat waves were associated with an increased risk of ACS[81].

It has been hypothesized that angina's worsening occurs in cold weather, but few studies have investigated variations in hospitalizations due to angina pectoris in relation to climatic variables[3,59]. We showed a significant association between daily number of angina hospital admission and temperature [82]. Table 4 shows main studies on the relations between weather and hospital admissions for ACS.

Main limitation of these studies is the unavailability of data on individual exposure to temperature variability[57]. These seasonal changes, besides, do not seem universal[43,76], as they are absent near the equator or in subpolar regions, with less temperature fluctuations than in temperate regions. For this reason, it seems inadequate to extrapolate results to different environments.

ACS AND OTHER METEOROLOGICAL PHENOMENA BEYOND TEMPERATURE

Ambient humidity

We observed a negative significant relationship between the number of ACS admissions and maximal humidity[74]. This was confirmed as regards angina admissions only in males, in whom we showed also a positive significant relationship between angina and minimal humidity[82]. Previous data for ACS were confounding: although some studies showed an association with low humidity[83,84], and other no association[69], more researches showed high humidity being related to CHD in northern countries[68,76] and in other Mediterranean[48,78], Asian[75], and Oceanian[54] settings. Fernández-Raga *et al*[18] suggested as the optimal relative humidity 24% for patients with respiratory diseases, and 45% for cardiovascular ones.

Atmospheric pressure.

Consequences of atmospheric pressure on cardiovascular diseases have been studied less frequently. Associations between an increase in CHD occurrence and low atmospheric temperatures have been reported from mortality data and hospital admission registries. A morbidity registry (Lille-WHO MONICA Project) detected a linear V-shaped relationship with a minimum at 1016 mbar: a 10-mbar decrease and a 10-mbar increase were associated with significant 12% and 11% increase in event rates, respectively[73]. Ambient pressure had a statistical impact on the incidence of angina or ACS also in Sweden[72], Serbia[83], Slovenia[68], Lithuania[85], and Switzerland[86], but in Mediterranean

Table 2 Main studies on the relations between weather and cardiovascular mortality

Ref.	Population and setting	Year	Main results
Gyllerup *et al* [44]	Men aged 40–64 from 259 municipalities in Sweden	1975-1984	Coronary mortality is more strongly associated with cold climate than with other explanatory factors such as cholesterol, socioeconomic factors, or tobacco
Crawford *et al*[43]	Deaths in Northern Ireland, United Kingdom	1979-1998	Low temperature is associated with highest mortality rates from myocardial infarction
Gerber *et al* [45]	Olmsted County, Minnesota, United States	1979-2002	RR of sudden death, but not of myocardial infarction, was increased in low temperatures (1.20, 95%CI: 1.07-1.35, for temperatures below 0°C *vs* 18°C-30°C). These associations were stronger for unexpected sudden death ($P < 0.05$)
Wichmann *et al*[49]	Gothenburg, Sweden	1985-2010	No evidence of association between temperature and CHD deaths in the entire year, warm or cold periods
Enquselassie *et al*[3]	Australian community-based register of heart disease (the WHO MONICA Project)	1992	Coronary deaths were more likely to occur on days of low temperature (and to a much lesser extent, of high temperature. Patterns of sudden and non-sudden deaths were not associated with weather conditions. Both longer-term seasonal effects and daily temperature effects exist
Dilaveris *et al* [48]	AMI deaths in Athens, Greece	2001	The best predictor was the average temperature of the previous 7 d; the relation between daily myocardial infarction deaths and 7-d average temperature (R2 0.109, $P < 0.001$) was U-shaped
Zhang *et al* [35]	District of Wuhan, China	2003-2010	For cold effects over lag 0–21 d, a 1°C decrease in mean temperature below the cold thresholds was associated with a 3.65% (95%CI: 2.62, 4.69) increase in cardiovascular mortality and 21.57% (95%CI: 12.59, 31.26) increase in CHD mortality. For hot effects over lag 0–7 d, a 1°C increase in mean temperature above the hot thresholds was associated with a 34.10% (95%CI: 25.63, 43.16) increase in cardiovascular mortality and 17.00% (95%CI: 7.91, 26.87) increase in CHD mortality
Wang X *et al* [47]	Beijing and Shanghai, China	2007–2009	The cold effects on cause-specific cardiovascular mortality reached the strongest at lag 0–27, while the hot effects reached the strongest at lag 0–14
Yang J *et al*[6]	Nine Chinese mega-cities	2007–2013	Statistically significant nonlinear associations between temperature and mortality were observed, with a total of 50658 deaths from myocardial infarction attributable to non-optimal temperatures
Yin Q, Wang J[50]	Beijing, China	2010-2012	When extremely high temperatures occur continuously, at varying temperature thresholds and durations, adverse effects on CVD mortality vary significantly. The longer the heat wave lasts, the greater the mortality risk is. When the daily maximum temperature exceeded 35 °C from the fourth day onward, the RR attributed to consecutive days' high temperature exposure saw an increase to about 10% ($P < 0.05$), and at the 5th day, the RR reached 51%

AMI: Acute myocardial infarction; CHD: Coronary heart disease; CVD: Cardiovascular diseases; CI: Confidence Interval; OR: Odds ratio; RR: Relative risk.

population we did not observe any significant relation[82].

Sunlight

The amount of sunlight hours seems inversely related to winter mortality and ACS risk[72]. Our study in a Mediterranean area did not confirm any relation between sunlight hours and ACS daily admissions [74].

Wind, rain, and snow

ACS incidence during southern wind periods seems significantly greater than during the northern ones [75]. Also, the amount of rain and wind speed seems inversely related to winter mortality and ACS incidence[72,75,85,86]. We, however, failed to observe any significant relationship between wind force and direction, rain, and the number of hospital ACS admissions[74], suggesting these variables are not strong triggers, according to other authors[43]. It is likely that rain intermixed with snow may trigger increased mortality from cardiovascular disease. Snow is somewhat more significant in triggering deaths from heart disease than is air temperature, influencing mortality, mainly in males[87,88]. Snow fall exceeding 2 cm/d was identified as a significant predictor for ACS admission rates[89]. Snow- and rainfall had inconsistent effects in another study[87].

Combination of weather factors

The assessment of air temperature does not allow evaluation of actual discomfort perception caused by the combination of different meteorological parameters. Alternative biometeorological approaches consider Apparent Temperature Index in summer and New United States/Canada Wind Chill Temperature Index in winter, which combine air temperature, relative humidity and wind velocity[90], the presence of anticyclonic and cyclonic air mass[91], as well as specific local climatic conditions, such as the Arctic Oscillation[92].

Table 3 Main studies on the relations between weather and hospital admissions

Ref.	Population and setting	Year	Main results
Ebi *et al*[59]	Three Californian regions, United States	1983-1998	Association between temperature and hospitalizations varied by region, age, and gender
Michelozzi *et al*[41]	Twelve European cities participating in the Assessment and Prevention of Acute Health Effects of Weather Conditions in Europe (PHEWE) project	1990-2001	For an 18°C increase in maximum apparent temperature above a threshold, respiratory admissions increased by 14.5% (95%CI: 1.9–7.3) and 13.1% (95%CI: 0.8–5.5) in Mediterranean and North-Continental cities, respectively. In contrast, the association between temperature and cardiovascular and cerebrovascular admissions tended to be negative and did not reach statistical significance
Vaneckova and Bambrick [52]	Sidney, Australia	1991-2009	On hot days, hospital admissions increased for all major categories. This increase was not shared homogeneously across all diseases. Admissions due to some major categories increased one to three days after a hot day (e.g., respiratory and cardiovascular diseases) and on two and three consecutive days
Goldie *et al* [54]	Darwin, Australia	1993-2011	Nighttime humidity was the most statistically significant predictor ($P < 0.001$), followed by daytime temperature ($P < 0.05$). Hot days appeared to have higher admission rates when they were preceded by high nighttime humidity
Linares and Diaz[28]	Daily emergency admissions between May and September in the Hospital General Universitario Gregorio Maranòn, Madrid, Spain	1995-2000	The temperature above which hospital admissions soar coincides with the temperature limit above which mortality sharply rises, which, in turn, coincides with 95th percentile of the maximum daily temperature series
Chan *et al*[53]	Hong Kong, China	1998-2009	During summer, admissions increased by 4.5% for every increase of 1°C above 29°C; during winter, admissions increased by 1.4% for every decrease of 1°C within the 8.2–26.9 °C range. Admissions for respiratory and infectious diseases increased during extreme heat and cold, but cardiovascular disease admissions increased only during cold temperatures. During winter, for every decrease of 1°C within the 8.2–26.9 °C range, admissions for cardiovascular diseases rose by 2.1%
Yitshak-Sade *et al*[61]	Respiratory, cardiac and stroke admissions of adults ≥ 65 (2015660), New England, United States	2001-2011	The short-term temperature effect was higher in months of higher temperature variability as well. For cardiac admissions, the PM2.5 effect was larger on colder days (0.56% versus −0.30%) and in months of higher temperature variability (0.99% *vs* −0.56%)
van Loenhout *et al*[55]	the Netherlands	2002-2007	Positive relationship between increasing temperatures above 21 °C and the risk for urgent emergency room admissions for respiratory diseases. For admissions for circulatory diseases, there is only a small significant increase of risk within the 85+ age group for moderate heat, but not for extreme heat
Ponjoan *et al* [58]	Catalonia, Spain	2006-2016	The overall incidence of cardiovascular hospitalizations significantly increased during cold spells (RR = 1.120; 95%CI: 1.10–1.30) and the effect was even stronger in the 7 d after the cold spell (RR = 1.29; 95%CI: 1.22–1.36). Conversely, cardiovascular hospitalizations did not increase during heatwaves
Shiue *et al*[60]	Ten percent of daily hospital admissions across Germany	2009-2011	Admissions due to diseases of pericardium, nonrheumatic mitral and aortic valve disorders, cardiomyopathy, atrioventricular block, other conduction disorders, atrial fibrillation and flutter, and other cardiac arrhythmias peaked when physiologically equivalent temperature was between 0 and 10°C
Tian *et al*[57]	184 cities in China	2014-2017	a 1˚C increase in short-term temperature variability (calculated from the SD of daily minimum and maximum temperatures) at 0–1 days was associated with a 0.44% (0.32%–0.55%), 0.31% (0.20%–0.43%), 0.48% (0.01%–0.96%), 0.34% (0.01%–0.67%), and 0.82% (0.59%–1.05%) increase in hospital admissions for cardiovascular disease, ischemic heart disease, heart failure, heart rhythm disturbances, and ischemic stroke, respectively

CHD: Coronary heart disease; CVD: Cardiovascular diseases; CI: Confidence interval; PM: Particulate matter; RR: Relative risk; SD: Standard deviation.

WEATHER AND OTHER CARDIOVASCULAR DISEASE BEYOND CHD

Heart failure

Environmental exposure is an important, but underappreciated, risk factor contributing to development and severity of heart failure. In European warm period (from June to October), there are significant less admissions than that in the cold period (from December to March). Air temperature is the most significant environmental factor related to heart failure hospital admissions, showing an inversed correlation[93,94]. Heart failure admissions peaked when temperature was between 0 and -10°C[68]. Every 1°C decrease in mean temperature and every 1hPa decrease in air pressure were associated, respectively, with an increase in the daily number of emergency admissions for heart failure by 7.83% (95%CI: 2.06-13.25) and 3.56% (95%CI: 1.09-5.96)[71]. Some other features, such as precipitation, are also relevant[94].

Table 4 Main studies on the relations between weather and acute coronary syndromes

Ref.	Population and setting	Year	Main results
Mirić *et al*[78]	Coastal part of middle Dalmatia (Croatia)	1981-1987	Significant association of acute myocardial infarction incidence with increased air temperature four days before, and on the day of the incident ($P < 0.05$)
Danet *et al*[73]	Morbidity registry (Lille-WHO MONICA Project) monitoring 257000 men Aged 25-64 years.	1985-1994	The events rate decreased linearly with increasing atmospheric temperature: a 10°C decrease was associated with a 13% increase in event rates
Wichmann *et al*[49]	AMI hospitalisationsin Gothenburg, Sweden	1985-2010	A linear exposure-response corresponding to a 3% and 7% decrease in AMI hospitalisations was observed for an inter-quartile range increase in the 2-d cumulative average of temperature during the entire year and the warm period, respectively
Abrignani *et al*[74]	Hospital admissions for acute myocardial infarction in Trapani, Italy	1987-1998	Significant association as regards the incidence relative ratio between daily number of myocardial infarction hospital admission and minimal daily temperature
Abrignani *et al*[82]	Hospital admissions for angina pectoris in Trapani, Italy	1987-1998	Significant association between daily number of angina hospital admission and temperature. Significant incidence relative ratios (95%CI) were, in males, 0.988 (0.980–0.996) ($P < 0.004$) for minimal temperature. The corresponding values in females were 0.973 (0.951–0.995) ($P < 0.017$) for maximal temperature and 1.024 (1.001–1.048) ($P < 0.037$) for minimal temperature
Marchant *et al*[37]	633 consecutive patients with myocardial infarction admitted to a coronary care unit in London, United Kingdom	1988-1991	Excess of infarctions on colder days in both winter and summer
Bayentin *et al*[77]	Quebec, Canada	1989-2006	Cold temperatures during winter and hot episodes during summer are associated with an increase of up to 12% in the daily hospital admission rate for CHD. In most regions, exposure to a continuous period of cold or hot temperature was more harmful than just one isolated day of extreme weather
Wolf *et al*[64]	Myocardial infarctions and coronary deaths in the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in Augsburg (MONICA/KORA) Registry, Germany	1995-2004	A 10°C decrease in 5-d average temperature was associated with a relative risk of 1.10 (95%CI: 1.04-1.15). Effect of temperature on the occurrence of nonfatal events showed a delayed pattern, whereas the association with fatal forms was more immediate
Madrigano *et al*[70]	Patients with a possible discharge diagnosis of AMI in 11 acute care general hospitals serving residents of the Worcester metropolitan area (Worcester Heart Attack Study), United Kingdom	1995, 1997, 1999, 2001, 2003	A decrease in an interquartile range in apparent temperature was associated with an increased risk of acute myocardial infarction on the same day [HR = 1.15 (95%CI: 1.01–1.31)]. Extreme cold during the 2 d prior was associated with an increased risk of acute myocardial infarction [1.36 (1.07–1.74)]. Exposure to heat increased the risk of dying after an AMI
Mohammad *et al*[72]	All myocardial infarctions reported to the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)	1998-2013	The most pronounced association was observed for air temperature, where a 1-SD increase (7.4°C) was associated with a 2.8% reduction in risk of myocardial infarction (incidence ratio, 0.972; 95%CI: 0.967-0.977; $P < 0.001$). Results were consistent for non–ST-elevation as well as ST-elevation myocardial infarction and across a large range of subgroups and health care regions
Messner *et al*[76]	Subarctic area of Northern Sweden	2001	A 1°C temperature rise was associated with an 1.5% increase in the number of nonfatal acute myocardial infarctions
Chang *et al*[69]	Myocardial infarctions among women aged 15–49 from 17 different countries in Africa, Asia, Europe, Latin America, and the Caribbean	2003	Overall, a 5°C drop in temperature was associated with a 12% increase in admissions for heart attack (incidence rate ratio 0.88 (95%CI: 0.8-0.97)
Misailidou *et al*[65]	Five rural Greek regions (Karditsa, Lamia, Chalkida, Kalamata and Zakinthos)	2003-2004	For an 18°C decrease in temperature there was a 1.6% (95%CI: 0.9%–2.2%) increase in admissions for CHD
Bhaskaran *et al*[63]	84010 hospital admissions for myocardial infarction in the Myocardial Ischaemia National Audit Project (15 conurbations in England and Wales, United Kingdom)	2003-2006	Broadly linear relation between temperature and myocardial infarction, without a threshold: each 1°C reduction in daily mean temperature was associated with a 2.0% (95%CI: 1.1%-2.9%) cumulative increase in risk of myocardial infarction over the current and following 28 d, the strongest effects being estimated at intermediate lags of 2-7 and 8-14 d. Heat had no detrimental effect
Nastos *et al*[80]	Crete, Greece	2004-2007	The impact of weather variability on the ACS incidence is not statistically significant
Ravljen *et al*[68]	ACS treated with coronary emergency catheter interventions in Slovenia	2008-2011	Daily average temperature, atmospheric pressure and relative humidity all have relevant and significant influences on ACS incidences for the entire population. However, the ACS incidence for population over 65 is only affected by daily average temperature

Hori *et al*[71]	Japan	2010	Every 1°C decrease in mean temperature was associated with an increase in the daily number of emergency admissions for ACS by 7.83% (95%CI: 2.06-13.25)
García-Lledó *et al*[66]	Madrid, Spain	2013-2017	The minimum incidence rate of myocardial infarction was observed at the maximum temperature of 18°C. Warmer temperatures were not associated with a higher incidence (RR, 1.03; 95%CI: 0.76-1.41), whereas colder temperatures were significantly associated with an increased risk (IRR, 1.25; 95%CI: 1.02-1.54)
Lin *et al*[67]	Hospitalizations for CHD in New York State, United States	2015	Extremely low universal apparent temperature in winter was associated with increased risk of AMI, especially during lag4-lag6
Sharif Nia *et al*[75]	Hospital admission for AMI in Mazandaran Province, Iran	2015-2016	Daily minimum temperature correlated with ACS events [RR = 0.942 (95%CI: 0.927-0.958), $P < 0.001$]

ACS: Acute coronary syndromes; AMI: Acute myocardial infarction; CHD: Coronary heart disease; CI: Confidence interval; RR: Relative risk; SD: Standard deviation.

Arrhythmias

Current paradigm in sudden cardiac death (SCD) requires an abnormal myocardial substrate and an internal or external transient factor (such as a cold spell, an unusually cold weather event) that triggers cardiac arrest. An increased risk of ischaemic SCD was significantly associated with a preceding cold spell[95], and cardiac arrest admissions peaked when temperatures were between 0° and -10°C[60]. These associations were stronger for unexpected SCD than for SCD with prior CHD[45]. However, also higher average daily temperature and larger variation in humidity were associated with increase in appropriate ICD interventions in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy[96].

Aortic dissection

Days with spontaneous type A aortic dissections were significantly colder than those without dissections[97]. There appears to be a significant correlation between mean low monthly pressures and rupture incidence[98].

Stroke

Significant associations between temperature and hospital admission rates for stroke were apparent and generally stronger than in other cardiovascular disease[99-101]. Both increases and decreases in temperature had a marked relationship with stroke deaths, while hospital admissions were only associated with low temperature[102,103]. Overall, a 5°C drop in temperature was significantly associated with a 7% increase in admissions for stroke[69]. Every 1°C increase in mean temperature during the preceding 24 h was associated with a significant 2.1% increase in ischaemic stroke admissions. A fall in atmospheric pressure over the preceding 48 h was associated with increased rate of haemorrhagic stroke admissions. Higher maximum daily temperature gave a significant increase in lacunar stroke admissions than in other ischaemic strokes[100]. In another study, every 1°C decrease in mean temperature was associated with an increase in the daily number of emergency admissions by 35.57% for intracerebral haemorrhage and by 11.71% for cerebral infarction. An increase of emergency admissions due to intracerebral haemorrhage was observed at every 1 hPa decrease in air pressure[71]. A recent metanalysis, finally, confirmed that lower mean ambient temperature is significantly associated with the risk of intracerebral haemorrhage, but not with ischemic stroke and subarachnoid haemorrhage [104].

AGE, SEX, OTHER FACTORS AND CLIMATIC VARIABLES

Effects of weather vary depending on other factors, such as the population disease profile and age structure[19,74]. People with pre-existing medical conditions such as cardiovascular disease or carrying out physically demanding work, and the elderly, particularly those in nursing and care homes, are particularly vulnerable[68,105-108].

Mortality's increase with cold or heat was greater for older age groups[21,63,109]. Diurnal temperature range are related to hospital admissions for all cardiovascular and cerebrovascular disease among elderly, namely in males[59,83,110]. In the elderly, cardiovascular disease curve was U-shaped, showing higher values for cold stress than for heat one[107,109,111,112]. In general, longer duration of heat waves increases the risks of cardiovascular mortality for the elderly[113]. Main predictors of death are: The use of home public-integrated assistance, a higher comorbidity, a higher degree of disability [114], lack of thermal insulation and sleeping right under the roof[113], being confined to bed or unable to care for oneself and pre-existing cardiovascular diseases[115]. Home air-conditioning, visiting cool

environments, dressing lightly, and increasing social contact were instead strongly associated with better outcomes[113,115]. Weak correlation between atmospheric air wind speed and ACS morbidity in older populations was determined[111].

Diurnal temperature range was significantly associated with hospital admissions for all cardiovascular disease, ischemic heart disease and cerebrovascular disease among elderly females[110]. We showed that, in females, a reduction in maximal temperature is associated with more hospital angina admissions[82], whereas the number of angina admissions is positively correlated with an increase in minimal temperature, as observed also by Ebi[59]. Increased outside temperature and sunshine hours were identified as strong positive predictors for ACS occurrence in women[89], as they tend to present with AMI at a later age than men, they will tend to exhibit a more marked seasonal variation[107-109]. A weak correlation between atmospheric air wind speed and MI morbidity in women was determined[111]. Snow fall was identified as a positive predictor for ACS admission rates with a significant effect in men, but not in women[89]. Other studies failed to detect significant difference according to sex[65].

Risk of heat-related death was significantly higher among Black people[112,116] and Australian indigens[105].

Heat-related mortality varied with sociodemographic characteristics such as in people living in low socioeconomic districts[12,106,107,117].

People living in areas with high PM2.5 concentration showed higher vulnerabilities to cold-ACS effects than other groups did[67].

MECHANISMS

Up to date, there are not clear pathophysiological links between weather and cardiovascular diseases. Climatic stress may increase direct and indirect risks to human health *via* different, complex pathophysiological pathways and exogenous and endogenous mechanisms. The pattern of well-known conventional risk factors (such as blood pressure, serum lipids, haematological and coagulation factors, body weight, glucose tolerance), a number of hormones including steroids, environmental factors (such as air pollution) as well as acute infections shows a marked seasonal variation, with a winter clustering of peak values[118,119]. In addition, humans display different seasonal behaviour in diet, activity, housing and smoking habits, psychosocial factors and mood disorders in winter[120]. Other factors, such as overindulgence, or stress on Christmas holidays, might also contribute[121].

Cold

Mechanisms leading to possible influence of cold on ACS or angina onset are most likely multifactorial. Different heart and circulation adjustments occur when humans are acutely exposed to low outdoor temperatures. Increase in circulating levels of catecholamines, secondary to cutaneous thermoreceptor activation[122]. lead to peripheral vasoconstriction and then to increase in blood pressure[123], heart rate, and left ventricular end-diastolic pressure and volume[3,124,125] with, in turn, increased cardiac work and peripheral resistance, greater heart oxygen requirement and reduction of ischemic threshold [3]; they may be clinically relevant when coronary circulation is already compromised[126]. People with normal cardiovascular function, in fact, are unaffected by cold stress, whereas those with IHD may be crippled, although rarely, by exposure to cold, especially if they perform physical work[122]. At the same time, reduced myocardial perfusion may lead to earlier ischemia, angina, and impaired performance. Also having a heart failure deteriorates submaximal and maximal performance in cold conditions[127]. In cold conditions also a greater sodium intake lead to an increase in blood pressure. Cold-induced vasoconstriction results in an early return of reflected pressure waves from the periphery and an increase in central aortic systolic pressure, with increase of central aortic augmentation index [128]. Endothelial dysfunction may be another mechanism. Brachial flow-mediated dilation would vary by temperature (in the Framingham Offspring cohort it was highest in the warmest and lowest in the coldest outdoor temperature quartiles)[129]. Moreover, coronary artery spasm could occur if vasoconstriction extends to the heart vessels. Cold-intolerant patients had a steeper heart rate response in cold conditions and developed ischemia and angina earlier. In cold-tolerant patients, this increase may be offset by a reduction in heart rate if baroreceptor function is normal. Baroreceptor function was impaired in cold-intolerant patients. If baroreceptor function is abnormal, heart rate may not decrease in response to a cold-induced increase in blood pressure. This mechanism may account for some of the variability in tolerance to cold exposure that affects patients with exertional angina[124].

More dramatic events, such as sudden death, may be due to increased frequency of cardiac arrhythmias, or, perhaps through rises in blood pressure, to abrupt rupture of atherosclerotic plaques [3].

Cold, besides, exerts other biological negative effects on inflammatory markers, haemostasis, rheological factors, and lipids (probably related to haemoconcentration), alcohol consumption, and body weight gain[40,124,125,130,131]. A 10°C decrease in temperature led to an increase in platelet counts and fibrinogen and a decrease in C-reactive protein in CHD patients[131]. In cold weather, a

greater tendency to clot in circulatory system has been demonstrated[119,132,133]. This could be related to plasma volume contraction (haemoconcentration) [119,126,134], induced by peripheral vasoconstriction, which can in part also explain the increase in serum lipids. These acute responses to cold conditions could trigger ACS.

Cold conditions may increase also the risk of respiratory infections through suppression of immune responses and direct effects on respiratory tree, and although no association can be claimed between respiratory infections and coronary deaths during cold season[124], a theory links pulmonary inflammation to stroke[99].

Finally, other causes hypothesized to explain the impact of cold are socioeconomic, mainly housing conditions[12,34].

Heat

During summer, ACS patients working outdoors show abnormal hemorheology (high haematocrit and blood viscosity)[135], as dehydration is more likely to occur[29]. Outdoor heat is associated with decreasing blood pressure, and cardiovascular vulnerability may vary primarily by central air conditioning[136]. Higher ambient temperature is associated with decreases in heart rate variability during warm season but not during cold one[137]. Hot weather is associated with an increase in systolic pressure at night in treated elderly hypertensive subjects, likely because of a nocturnal blood pressure escape from effects of a lighter summertime drug regimen[133].

Humidity

When air contains a high percentage of humidity, perspiration and the processes of temperature homeostasis may be hindered, making more difficult the automatic processes of internal temperature control, thus increasing respiratory fatigue and heart rate. However, this mechanism may be important only in more severe ischemic forms.

Rain and wind

A reduction of outdoor excursions when it is raining and windy prevents outdoor cold stress.

Sunshine

Several studies have demonstrated significantly lower levels of vitamin D, synthesized by skin following exposure to ultraviolet radiation, in subjects with CHD, particularly in winter[138]. It has been suggested that vitamin D may be a confounding factor in the association between cholesterol, structurally like it, and CHD risk. This is corroborated by findings of a strong, positive association between latitude and mean blood cholesterol, and a strong negative association between hours of sunshine and CHD mortality[120]. Association between vitamin D levels and CHD, however, has been shown to be independent of total serum cholesterol[138].

Age

With increasing age, winter peak increased. This is likely to reflect a combination of factors: poorer temperature autonomic control, lower physical activity levels, less use of protective clothing, greater time spent at home, more sensitivity to seasonal influenza and blood pressure changes, and poorer household heating and insulation. The predominance of effects of meteorological factors in the elderly could be also explained by the lower impact of genetic AMI determinants.

Sex

Different effects of weather on women may be related to different coronary anatomy in the female sex, as woman have less extensive coronary atherosclerosis, lower coronary size, and lower collateral circulation than males.

Pollution

Interaction between air pollution and weather is often missed in literature[139]. Studies show that ambient temperature and air pollution may interact to affect cardiovascular events *via* autonomic nervous system dysfunction[137]. Much higher PM10 effects on mortality were observed during warmer days[26,140-142], and the hypothesis that such an effect is attributable to enhanced exposure to particles in summer could not be rejected[143].

CONCLUSION

Implications and conclusions

Weather influences on heart diseases remind us that climatic stress can be considered as a new potential risk factor for cardiovascular events and even mortality[3,125]. Such an understanding has several potential implications for developing civil protection policy towards allocation of public healthcare

resources and planning appropriate measures to prevent cardiovascular events[59,116]. Weather-related health effects have sharply attracted growing interest because of the recent observed and predicted earth's climate change, with consequent increasing ambient temperatures and climatic fluctuations, extremes of precipitation (floods and droughts), air pollution, and infectious diseases. Contrary to current predictions, this may mean a paradoxical increase in seasonal cycle of events with greater winter peaks, even as overall global temperatures rise[93]. Thus, increases in heat-related mortality due to global warming are unlikely to be compensated by decreases in cold-related mortality[112]. In a global environment of rapid and extreme climatic events, more populations will be exposed to conditions they are not readily adapted to from a bio-behavioural perspective[60,144]. Adaptation to such changes, that are expected to further increase, would seem to be imperative for medical professionals, health institutions, and general public[41,70].

Public health educational, behavioural and social measures[28,43] have been proposed to reduce adverse cardiovascular consequences of climate variability. We wish here to summarize the most important ones.

High risk identification: Prevention programs must be based around rapid identification of high-risk conditions and people, such as frails with cardiovascular disease, or the elderly[53,107]. Protective measures, in fact, should be directed towards susceptible groups, rather than the population as a whole, with the creation of an up-to-date database and care of vulnerable high-risk individuals[21,24,110,114].

Specific interventions: In the community, at home, and in institutions that care for elderly or vulnerable people, such as hospitals, a comfortable temperature should be granted[63,65]. Educational measures should be suggested to high-risk people. During the passing atmospheric front, as well as in extreme ambient temperature periods, *i.e.*, coronary patients should stay at home, and avoid both physical and psychological stress[78].

Provision of targeted advice: Many weather-related diseases may be preventable by and appropriate response to emergencies. Operative health weather watch/warning systems link public health actions to meteorological forecasts of dangerous weather. We need development of a short-term forecast system of daily demand using weather variables.

Remodulation of health services offer: During severe climatic conditions, it should be granted a greater deployment of ambulance services and an adequate reinforcement of health personnel in order to meet the unexpected increase in demands, and to avoid potential mismatch between the occurrence of acute cardiovascular events and medical service capacities[108].

Future perspectives: In the long term, improvements in infrastructures, residential architecture, working environment and urban planning must be adapted[113].

In conclusion, the problem of climate change is serious, urgent and getting worse[144]. Fairly obvious connections between climate change and cardiovascular health have been outlined in this article. Medical professionals, and societies of medical professionals, easily capable of understanding the physical and statistical methods used by climatologists, are in a good position to give politicians and leaders in industry and agriculture their necessary support[144].

Further large, exhaustive, population-based cohort research with consistent methodology over long periods in geographical areas with homogeneous meteorological variables should be carried out to further clarify climatic influences on CHD occurrence, to identify underlying pathophysiological mechanisms, to show vulnerable populations and individuals and to develop cost-effective strategies to promote resilience against provocations of climate change[86,113].

FOOTNOTES

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MINIREVIEWS

Predictors of persistence of functional mitral regurgitation after cardiac resynchronization therapy: Review of literature

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Abstract

Functional mitral regurgitation is a common finding among heart failure patients with ischemic and non-ischemic dilated cardiomyopathies. The presence of moderate or severe mitral regurgitation is associated with higher morbidity and mortality. Heart failure patients meeting electrocardiogram and left ventricle function criteria are good candidates for cardiac resynchronization therapy, which may reduce the degree of functional mitral regurgitation in the short and long term, specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. In this article, we analyze data from the literature about predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

Key Words: Functional mitral regurgitation; Cardiac resynchronization therapy; Predictors; Mitral regurgitation improvement; Dyssynchrony

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Core Tip: Functional mitral regurgitation is a common finding among heart failure patients and, if moderate or severe, is associated with higher morbidity and mortality. Cardiac resynchronization therapy, as a therapy for a subset of heart failure patients, may determine a reduction of the degree of functional mitral regurgitation specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. Here, we analyze predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

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INTRODUCTION

Functional mitral regurgitation (FMR) is a common finding of left ventricular (LV) dysfunction and remodeling, occurring both in ischemic and non-ischemic heart disease[1]. The prevalence of FMR varies from 20% to 50% of heart failure (HF) patients[2,3], with 40% of patients presenting with moderate or severe mitral regurgitation (MR)[4]. Data from the literature suggest that any degree of FMR is associated with increased morbidity and reduced survival in patients with LV dysfunction[3-5]. In this setting, there is no conclusive evidence for a survival benefit after mitral valve intervention. The limited data regarding FMR result in a low level of evidence for treatment recommendations and highlight the importance of decision-making by the patient's heart team. According to the latest guidelines, surgery is indicated in patients with severe secondary mitral regurgitation undergoing coronary artery bypass graft and LV ejection fraction > 30%[6,7]. When revascularization is not indicated, optimal medical therapy in line with the HF guidelines should be the first step. Furthermore, patients with HF and FMR eligible for cardiac resynchronization therapy (CRT) could benefit from resynchronization in terms of reduction of the degree of FMR[8,9]. Unlike medical therapy, CRT specifically targets myocardial dyssynchrony, which is an important factor of FMR onset. However, in a subset of CRT patients, significant MR persists and may even worsen.

The purpose of this paper is to provide a comprehensive review on predictors of improvement in FMR after CRT.

ACUTE AND LONG-TERM EFFECTS OF CRT ON FMR IN THE PRESENCE OF DYSSYNCHRONY

FMR results from multiple factors: ventricular remodeling, decreased contractility, impairment of mitral annular function, imbalance between tethering and closing forces, and mechanical dyssynchrony. LV mechanical dyssynchrony could be a potential contributing factor to FMR through several mechanisms. First, LV dilatation due to dyssynchrony leads to displacement of papillary muscles with consequent lack of leaflet coaptation. Second, uncoordinated regional mechanical activation due to dyssynchrony results in distorted mitral valve apparatus geometry[10]. Lastly, LV dyssynchrony generates a positive pressure gradient between the LV and the left atrium, leading to a diastolic FMR during incomplete mitral valve closure[11].

CRT effects may be distinguished as acute or chronic. Acute, short-term FMR reduction occurs suddenly after CRT implantation, while chronic, long-term FMR reduction occurs weeks to months after CRT implantation. Immediately after CRT device implantation, global LV contraction efficiency improves and closing forces increase consequently. Breithardt *et al*[12] first showed that an increase in LV dP/dt after CRT is directly correlated to MR reduction. Indeed an increase in LV dP/dt leads to an increase in transmitral pressure gradients that facilitate mitral valve leaflet coaptation. Furthermore, CRT acutely determines resynchronization of the papillary muscles leading to a shortening of MR duration and later onset of MR. Indeed, Kanzaki *et al*[13] showed that the inter-papillary muscleactivation time delay is the main determining factor related to MR in HF patients with left bundle branch block and that this delay is immediately improved by CRT.

Data from the literature suggest that short-term reduction in FMR after CRT implantation predicts a favorable clinical response, whereas FMR persistence is associated with reduced survival[14]. In addition to the early effect of CRT on FMR, long-term beneficial effects on FMR have been described. They are mainly represented by the increase of the closing forces and the global LV remodeling. Specifically, LV dimensions, shape and function are main determinants of FMR, and CRT attenuates LV remodeling, which therefore improves FMR. These results could be achieved after 3–6 mo of CRT on top of optimized medical treatment and are even more evident during longer follow-up[15].

Large randomized trials have confirmed short and long-term reduction of FMR following CRT implantation, although the magnitude of this reduction is modest (20%–35% using different quantification methods)[16,17]. In 20%–25% of CRT patients, significant MR persists and may even worsen in 10%-15%. Specifically, this concerns patients with grade ≥ 2 FMR who have a significantly worse outcome than other CRT patients. This subset of patients is often found to be CRT non-responders, and the reasons why these patients do not benefit from CRT are still unclear.

PREDICTORS OF IMPROVEMENT OF FMR AFTER CRT IMPLANTATION

Data from the literature show that reductions in MR occur mainly in patients with response to CRT. However, FMR reduction was also demonstrated in CRT non-responders. Porciani *et al*[18] reported that FMR may improve even in CRT non-responders because of the reversal of LV dyssynchrony. Reversal of LV mechanical dyssynchrony, especially at the papillary muscle level, has been suggested as one of the mechanisms implicated in CRT-induced FMR improvement[19]. Reviewing the literature, several predictors of MR improvement in CRT patients were found and can be distinguished by patient, clinical, imaging and electric-targeting LV lead-related predictors.

PATIENT-RELATED PREDICTORS

Karaca *et al*[20] analyzed142 patients who received biventricular pacemaker devices and found that ΔQRS (baseline - paced) after CRT [hazard ratio (HR): 1.242, 95% confidence interval (CI): 1.019-1.465, P = 0.028] was associated with LV reverse remodeling and reduced FMR at 6 mo. There were also lower rates of death or hospitalization at midterm follow-up. The cut-off ΔQRS value to predict FMR response after CRT was 20 mo, with a sensitivity of 72% and a specificity of 85%. Multivariate analysis found that ΔQRS was an independent predictor of FMR response at 6 mo. The same authors observed that non-ischemic HF etiology [odds ratio (OR): 3.13, 95%CI: 1.169-8.380, P = 0.021] and the baseline presence of left bundle branch block morphology (OR: 2.49, 95%CI: 1.086-5.714, P = 0.032) were independent predictors of "reverse mitral remodeling" and predictors of MR amelioration[21]. The abovementioned preoperative features are those that the majority of previous CRT studies found as "classical" predictors of CRT response.

Sadeghian *et al*[22], in a small study of 69 patients, found that independent predictors of early MR improvement (48 h after CRT implantation) were older age and longer baseline QRS duration. Among the MR improvement group, the mean age was 60 ± 7 years (*vs* 55 ± 12 years in the no MR improvement group), and baseline QRS width was 172 ± 31 ms (*vs* 147 ± 28 ms).

Profibrotic biomarkers were also evaluated as potential predictors of FMR reduction. It was found that at the time of CRT device implantation, elevated concentrations of gal-3, a protein (lectin family) upregulated in HF that is involved in fibrogenesis, are associated with a lack of MR amelioration (OR: 0.14, 95%CI: 0.03-0.58, P = 0.007)[23]. These result are consistent with molecular changes in HF settings where fibroblast proliferation and collagen production have a pivotal role on LV remodeling and consequently in mitral annulus dilatation/dysfunction.

IMAGING-RELATED PREDICTORS

Sitges *et al*[24] found that baseline mitral valve tenting area, as a remodeling parameter of the mitral valve, was a powerful independent predictor of MR reduction with CRT(OR: 8.05, 95%CI: 1.15-56.60, P = 0.03). A cut-off value > 3.8 cm^2yielded sensitivity of 53% and specificity of 89% to predict the absence of a significant reduction in MR with CRT. Similar results have been reported for predicting the success of restrictive annuloplasty in patients with functional MR who undergo surgery. Indeed, Magne *et al*[25] reported that a tenting area > 2.5 $cm^2$was associated with failed mitral valve repair in these patients. Results described by Sitges *et al*[24] were confirmed subsequently by Karaca *et al*[21]. In that study, baseline tenting area was identified as an independent predictor of FMR response at 6 mo (HR: 2.011, 95%CI: 1.268-2.754, P = 0.012). Values of tenting area differed significantly in FMR responders compared with non-responders (4.68 ± 1.02 cm^2 *vs* 3.22 ± 0.88 cm^2, P = 0.002). These data suggest that the more advanced the LV remodeling and the more distorted the LV geometry, the lower the probability of effective treatment for functional MR.

Subsequently, studies were performed with tissue Doppler imaging (TDI) and speckle tracking echocardiography to elucidate the role of myocardial dyssynchrony in the genesis of FMR in HF patients. Sadeghian *et al*[22] showed that septolateral delay by TDI was a significant predictor of MR improvement. In a previous small study with moderate/severe MR patients, Karvounis *et al*[26] showed that inferior papillary muscle time delay (R^2 = 0.945, P = 0.04) together with an increase in posterior papillary muscle longitudinal negative strain (R^2 = 0.727, P = 0.01) (both evaluated with TDI) were significant predictors of reduction in MR volume post-CRT implantation.

Naqvi *et al*[27] found that septolateral delay of > 60 ms was a univariate but not a multivariate predictor of MR reduction and demonstrated that the combined presence of delayed longitudinal strain in the mid inferior LV segment along with preserved systolic strain in the basal and mid posterior segments predicted reduction in MR severity post-CRT. The sensitivity and specificity of this composite variable to predict follow-up MR was 88% and 93%, respectively. These aforementioned findings added important information about acute MR reduction post-CRT. Indeed, patients who developed significant MR reduction had discoordination at the mid ventricle level. Therefore, the mid anterolateral segments were the earliest, and the mid inferoposterior segments were the most delayed as well as viable

segments. This suggested delayed posterior papillary muscle compared to anterior papillary muscle contraction resulted in malcoaptation of mitral leaflets and MR. Therefore, CRT in the MR improvement group probably reduced MR by correcting the mid inferoposterior wall delay and by improving function in these viable segments as assessed by strain and strain rate.

Unlike these studies, Goland *et al*[28] evaluated radial instead of longitudinal strain and used a two-dimensional method of strain assessment instead of TDI. It was found on multivariable logistic analysis that time to peak two-dimensional radial strain between inferior and anterior LV segments of > 110 ms (OR: 8.4, 95%CI: 8.4–54.0, P = 0.02) and two-dimensional radial strain in the posterior segment of > 18% were significant predictors of early post-CRT MR improvement (OR: 7.6, 95%CI: 1.2–72.4, P = 0.006). These results confirmed the role of viability and dyssynchrony of the areas adjacent to posterior papillary muscle. Obviously, the presence of non-severe MR predicted MR reduction after CRT as suggested by MR jet area/Left area ratio (OR: 8.1, 95%CI: 1.2–52.4, P = 0.02).

Onishi *et al*[29], in a large series, showed that anteroseptal to posterior wall radial strain dyssynchrony > 200 ms (OR: 2.65, 95%CI:1.11–6.30, P = 0.0277) and end systolic dimension index < 29 mm/m^2 (OR: 2.53, 95%CI: 1.03–6.20, P = 0.0420) predicted MR improvement at 6 mo after CRT implantation. Therefore, the present study combined the presence of radial dyssynchrony and lack of excessive LV dilatation (simply measured by end-systolic diameter index) with strong amelioration of significant MR. Furthermore, it added another important element: the lack of echocardiographic scar at the papillary muscle insertion site (wall motion score index ≤ 2.5) that resulted as a significant predictor of MR improvement (OR: 2.59, 95%CI: 1.06–6.30, P = 0.0360).

An interesting study was recently conducted by Galand *et al*[30]. It included 54 HF patient candidates for CRT who underwent dual-source computed tomography (CT) scan imaging in order to guide the CRT implantation procedure. Cardiac dual-source computed tomography is an ideal non-invasive imaging modality with very fast features, so patients receive less radiation. It also creates sharper images. This study evaluated the impact of LV wall thickness using dual-source CT in response to CRT and MR improvement. In multivariable analysis, an area ≥ 25% of LV wall thickness < 6 mm including at least one papillary muscle insertion was the only predictor of no MR improvement at 6 mo (OR: 16.82, 95%CI: 1.72–164.2, P = 0.015). The study confirmed the crucial role of papillary muscle insertion site and suggested that normal wall thickness could promote a mitral valve apparatus remodeling after CRT.

ELECTRIC-TARGETING LV LEAD-RELATED PREDICTORS

Among invasive electric predictors of the response to CRT, a commonly studied measure of electric delay is the QLV interval, which is the time from the onset of the QRS complex on the surface electrocardiogram to the local LV activation at the site of the LV lead[31]. Previous studies demonstrated the predictive value of QLV interval as a measure of LV electric delay for acute hemodynamic changes and clinical outcome with CRT[32]. Recently, Upadhyay *et al*[33] provided an interesting link between a simple electric measurement, such as QLV, and improvement in MR. They demonstrated that greater changes in MR were achieved by targeting the LV lead in regions of longer QLV at implant (multivariate β coefficient = 0.0040, P = 0.0072).

Chatterjee *et al*[34] analyzed data from patients enrolled in the SMART-AV study[29] and provided strong evidence of the association between baseline QLV and reduction in MR after CRT. After multivariable adjustment, increasing QLV was an independent predictor of MR reduction at 6 mo as reflected by an increased odds of MR response (OR: 1.13, 95%CI: 1.03–1.25/10 ms increase QLV, P = 0.02).

STUDY LIMITATIONS

This was not a systematic review. Heterogeneity among included studies was widespread. Studies included showed variations in study design, cohort characteristics and response definitions. Another source of heterogeneity is that CRT implantation techniques and indications have evolved over the last 20 years. These limitations are particularly important to consider in future research studies.

CONCLUSION

Over the past two decades, numerous invasive and non-invasive predictors of the response to CRT have been proposed, and it was shown that reductions in MR occurred mainly in patients with response to CRT (Table 1). However, not all CRT responders are "MR responders," and FMR reduction was also demonstrated in CRT non-responders, hence the importance of identifying MR improvement predictors after CRT implantation. Among "MR predictors" proposed, the possibility to recognize viability and dyssynchrony by imaging, especially near papillary muscles, is very useful. Also the measurement of

Table 1 Variables that predict mitral regurgitation improvement or lack of improvement

Predictor category	Predictors of MR improvement	Ref.	HR	*P* value
Clinical parameters	ΔQRS (at least 20 ms) after CRT	[20]	1.242	0.028
	Non ischemic HF etiology	[20]	3.13	0.021
	Baseline presence of LBBB morphology	[20]	2.49	0.032
	QRS narrowing after CRT	[21]	NA	0.001
	Older age	[23]	NA	0.001
	Baseline longer QRS duration	[23]	NA	0.001
Echo imaging	Septal-lateral delay by TDI	[23]	NA	0.001
	Baseline tenting area < 3.8 cm^2	[24]	NA	0.02
	Baseline tenting area	[21]	NA	0.01
	Septal-lateral delay by TDI	[22]	NA	0.001
	Baseline inferior papillary muscle time delay	[26]	NA	0.04
	Increase in posterior papillary muscle longitudinal negative strain	[26]	NA	0.01
	Combined presence of delayed longitudinal strain in the mid inferior LV segment and preserved systolic strain in the basal and mid posterior segments	[27]	NA	0.001
	Time to- peak 2-DRS between inferior and anterior LV segments of > 110 ms	[28]	8.4	0.02
	Preserved radial strain in posterior segments assessed by 2-DRS	[28]	7.6	0.006
	MR jet area/left atrium area ratio < 40%	[28]	8.9	0.02
	Anteroseptal to posterior wall radial strain dyssynchrony > 200 ms	[29]	NA	0.028
	Lack of severe left ventricular dilatation (end-systolic dimension index < 29 mm/m^2)	[29]	NA	0.042
	Lack of echocardiographic scar at papillary muscle insertion sites	[29]	NA	0.036
Electric-Targeting LV Lead	Degree of delay at the LV lead site	[34]	1.13	0.02
	Predictors of lack of MR improvement			
CT imaging	≥ 25% of LVWT < 6 mm inclusive of at least one papillary muscle insertion using CT	[30]	1.04	0.032
Biomarkers	Higher levels of galectin 3	[23]	0.16	0.01

CRT: Cardiac resyncronization therapy; TDI: Tissue Doppler imaging; 2DRS: 2D radial strain; MR: Mitral regurgitation; LVWT: Left ventricular wall thickness; CT: Computed tomography; LV: Left ventricular; NA: Not available.

LV electric ventricular delay, such as QLV, is simple, does not require echocardiography or surface electrocardiographic measurements and has the potential to be measured automatically by devices that would further simplify lead optimization.

The concept that more advanced LV remodeling remains valid. Therefore, the lower the probability of successful CRT treatment for FMR and other treatment strategies to reduce MR should be evaluated. Long-term results in a larger cohort together with new imaging techniques, such as three-dimensional imaging, are needed to keep track of the developments and the changes in this exciting field.

FOOTNOTES

Author contributions: Russo E and Russo G contributed equally to this work and performed the conceptualization and writing of the original draft; Braccio M and Cassese M contributed to writing, reviewing and editing the manuscript.

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Retrospective Study

Risk profiles and outcomes of patients receiving antibacterial cardiovascular implantable electronic device envelopes: A retrospective analysis

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Abstract

BACKGROUND

Cardiovascular implantable electronic devices (CIEDs) are implanted in an increasing number of patients each year, which has led to an increase in the risk of CIED infection. Antibacterial CIED envelopes locally deliver antibiotics to the implant site over a short-term period and have been shown to reduce the risk of implant site infection. These envelopes are derived from either biologic or non-biologic materials. There is a paucity of data examining patient risk profiles and outcomes from using these envelope materials in the clinical setting and comparing these results to patients receiving no envelope with their CIED implantation.

AIM

To evaluate risk profiles and outcomes of patients who underwent CIED procedures with an antibacterial envelope or no envelope.

METHODS

After obtaining Internal Review Board approval, the records of consecutive patients who underwent a CIED implantation procedure by a single physician between March 2017 and December 2019 were retrospectively collected from our hospital. A total of 248 patients within this period were identified and reviewed through 12 mo of follow up. The CIED procedures used either no envelope (n = 57), a biologic envelope (CanGaroo®, Aziyo Biologics) that was pre-hydrated by the physician with vancomycin and gentamicin (n = 89), or a non-biologic envelope (Tyrx™, Medtronic) that was coated with a resorbable polymer containing the drug substances rifampin and minocycline by the manufacturer (n

= 102). Patient selection for receiving either no envelope or an envelope (and which envelope to use) was determined by the treating physician. Statistical analyses were performed between the 3 groups (CanGaroo, Tyrx, and no envelope), and also between the No Envelope and Any Envelope groups by an independent, experienced biostatistician.

RESULTS

On average, patients who received any envelope (biologic or non-biologic) were younger (70.7 ± 14.0 *vs* 74.9 ± 10.6, $P = 0.017$), had a greater number of infection risk factors (81.2% *vs* 49.1%, $P < 0.001$), received more high-powered devices (37.2% *vs* 5.8%, $P = 0.004$), and were undergoing more reoperative procedures (47.1% *vs* 0.0%, $P < 0.001$) than patients who received no envelope. Between the two envelopes, biologic envelopes tended to be used more often in higher risk patients (84.3% *vs* 78.4%) and reoperative procedures (62.9% *vs* 33.3%) than non-biologic envelopes. The rate of CIED implant site pocket infection was low (any envelope 0.5% *vs* no envelope 0.0%) and was statistically equivalent between the two envelope groups. Other reported adverse events (lead dislodgement, lead or pocket revision, device migration or erosion, twiddler's syndrome, and erythema/fever) were low and statistically equivalent between groups (biologic 2.2%, non-biologic 3.9%, no envelope 1.8%).

CONCLUSION

CIED infection rates for biologic and non-biologic antibacterial envelopes are similar. Antibacterial envelopes may benefit patients who are higher risk for infection, however additional studies are warranted to confirm this.

Key Words: Cardiovascular implantable electronic device envelope; Defibrillator; Extracellular matrix; Implantable cardioverter-defibrillator; Infection; Pacemaker

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Core Tip: This retrospective study was performed to determine risk profiles and clinical outcomes of patients who underwent cardiovascular implantable electronic device (CIED) procedures with a biologic or non-biologic antibacterial envelope, or no envelope. A total of 248 patient records were reviewed containing 89 biologic, 102 non-biologic, and 57 no envelope patients. Pre-procedurally, patients who received any envelope (biologic or non-biologic) were at higher infection risk than patients who received no envelope. Biologic envelopes tended to be used more often in higher risk patients than non-biologic envelopes. The rate of CIED pocket infection was low and equivalent between the two envelopes.

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INTRODUCTION

Expanding indications for cardiovascular implantable electronic devices (CIEDs) have increased the number of these devices that are implanted[1], but considering the common comorbidities seen in this patient population, complications such as infection are also increasing[2-4]. Reported infection rates of de novo CIED implantation range between 0.7%-4.6%, and can be as high as 7% for re-operations[5]. Thus, a better understanding of patient risk factors and available prophylactic techniques could potentially lower the risk of infection in this population[5-8]. CIED envelopes are intended to securely hold pacemakers or defibrillators when implanted in the body, and antibacterial CIED envelopes additionally provide short-term local antibiotic delivery which can reduce the risk of infection at the device implant site[9]. Available antibacterial CIED envelopes are either fabricated from biologic material (extracellular matrix hydrated with antibiotics by physician choice) or from non-biologic material (synthetic mesh coated with antibiotics by the manufacturer). The biologic envelope (CanGaroo®, Aziyo Biologics, Inc., Roswell, GA, United States) is made of decellularized extracellular matrix derived from porcine intestinal submucosa (SIS-ECM) which is rehydrated in solution for 1–2 min prior to use, whereas the non-biologic envelope (TYRX™, Medtronic PLC, Mounds View, MN, United States) is made from an absorbable synthetic substrate mesh coated with a bioresorbable

polymer containing the drug substances rifampin and minocycline. Both envelopes have been reported to release antibiotics over a period of seven days in separate studies[10-13].

Although both envelopes have similar indications and antibiotic elution abilities, the material each envelope is created from may affect the biologic response upon implantation into the patient. Synthetic (non-biologic) absorbable and non-absorbable materials have been reported to initiate a strong foreign body reaction, resulting in chronic inflammation leading to hypovascular fibrotic tissue surrounding the implanted material[14-18], which a previously-marketed non-absorbable synthetic envelope leveraged to stabilize the electronic device upon implantation[19]. Conversely, ECM (the material that the biologic envelope is made from) has been shown to promote constructive remodeling and healthy tissue restoration[20-23]. Both biologic and non-biologic envelopes have been reported to support clinical infection prevention strategies[12,24-26].

This is an analysis of a retrospective, real-world study which assessed the risk profiles and clinical outcomes of patients who underwent a CIED procedure and received an antibacterial envelope (biologic or non-biologic), or no envelope (CARE Plus, NCT04351269). To our best knowledge, this study contains the first reporting of biologic and non-biologic antibacterial envelopes reported together in the clinical setting.

MATERIALS AND METHODS

Records of consecutive patients undergoing CIED procedures from a single center performed by a single physician between March 2017 and December 2019 were retrospectively reviewed for up to 12 mo of follow-up. The study protocol was reviewed and approved by an independent internal review board (IRB) [WIRB-Copernicus Group® (WCG)] prior to the chart review. A waiver of informed consent and HIPAA was obtained due to the retrospective nature of the study.

The study aimed to determine risk profiles and clinical outcomes of patients who were undergoing a CIED procedure and received either no envelope, a biologic envelope (CanGaroo®) hydrated by the implanting physician for 1 – 2 minutes with a vancomycin and gentamicin solution before implantation, or a non-biologic envelope (TYRX™) coated by the manufacturer with a bioresorbable polymer containing the drug substances rifampin and minocycline. The implanting physician made all decisions regarding device type, which envelope and envelope size was used, and biologic envelope hydration solution (if one was used). Aside from the pre-hydration of the biologic envelope, the implanting technique of both the biologic and non-biologic envelope was similar. The no envelope group's CIED implantation procedure was identical to the envelope CIED implantation procedure, just without the use of an envelope. The pre- and post-operative protocol was the same for all 3 groups.

Information was extracted in detail from medical records, including medical history, infection risk factors, surgical details, and adverse events from the initial procedural visit out to 12 mo post-op. Infection risk factors were defined by previous literature[4,27,28] which identified elements that were significantly associated with increased risk for CIED infection, including renal insufficiency, diabetes, obesity, peripheral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, malignancy, coronary artery disease, hypertension, chronic steroid use, oral systemic anticoagulants, malnutrition, smoking, the presence of two or more leads, pocket re-entry within 2 wk of the initial implant, prior device infection, and reoperative procedure. The number of risk factors was counted for each patient to examine the relative levels of infection risk between patient groups. Infection risk was categorized for each patient as lower risk (0–1 infection risk factors) or higher risk (2 or more risk factors), based on the quantity of established clinical risk factors present in each patient from above. An independent, biomedical statistician performed analyses between the 3 groups (CanGaroo, Tyrx, and no envelope), and also between the no envelope and any envelope groups by using means with standard deviations for continuous variables and counts with percentages for categorical variables. Continuous variables were checked for normality. Fisher's exact tests were used when ≥ 1 expected cell counts were < 5, and Pearson chi-square tests were used for categorical variable comparisons when cell counts were ≥ 5. Statistical significance was set to a $P < 0.05$. SPSS version 26 (IBM, Armonk, NY, United States) was used for statistical analyses.

RESULTS

Among 248 enrolled patients who underwent CIED procedures, 191 (77%) received an envelope. These included 89 (46.6%) biologic and 102 (53.4%) non-biologic envelopes (Table 1).

Surgical procedure details

Patients who received high-powered devices, including implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices, were more likely to receive an envelope (P = 0.001) (Table 1). Patients undergoing reoperative procedures (generator changes, upgrades, other

Table 1 Comparison across cohorts

	Total	Biologic envelope	Non-biologic envelope	No envelope	[1]*P* value	Any envelope	[2]*P* value
	(*N* = 248)	(*n* = 89)	(*n* = 102)	(*n* = 57)		(*n* = 191)	
Age (yr, mean ± SD)	71.6 ± 13.3	73.6 ± 13.3	68.2 ± 14.0	74.9 ± 10.6	**0.002**	70.7 ± 14.0	**0.017**
BMI, mean ± SD	29.9 ± 7.1	28.0 ± 6.2	31.0 ± 7.9	31.0 ± 6.3	**0.008**	29.6 ± 7.3	0.206
BMI category					**0.016**		0.080
Underweight (< 18.5)	5 (2.0%)	2 (2.2%)	2 (2.0%)	1 (1.8%)		4 (2.1%)	
Normal (18.5 - < 25.0)	54 (21.8%)	30 (33.7%)	19 (18.6%)	5 (8.8%)		49 (25.7%)	
Overweight (25.0 - < 30.0)	73 (29.4%)	20 (22.5%)	31 (30.4%)	22 (38.6%)		51 (26.7%)	
Obese (30.0 - < 40.0)	97 (39.1%)	34 (38.2%)	38 (37.3%)	25 (43.9%)		72 (37.7%)	
Morbidly obese (40.0 ±)	19 (7.7%)	3 (3.4%)	12 (11.8%)	4 (7.0%)		15 (7.9%)	
Medical history							
Heart failure	106 (42.7%)	41 (46.1%)	49 (48.0%)	16 (28.1%)	**0.037**	90 (47.1%)	**0.011**
Systemic antico-agulant use	99 (39.9%)	43 (48.3%)	40 (39.2%)	16 (28.1%)	0.050	83 (43.5%)	**0.037**
CIED device type					**0.004**		**0.001**
Pacemaker	152 (61.3%)	52 (58.4%)	52 (51.0%)	48 (84.2%)		104 (54.5%)	
CRT-P	12 (4.8%)	8 (9.0%)	4 (3.9%)	0 (0.0%)		12 (6.3%)	
ICD	54 (21.8%)	17 (9.1%)	30 (29.4%)	7 (12.3%)		47 (24.6%)	
S-ICD	2 (0.8%)	0 (0.0%)	52 (51.0%)	1 (1.8%)		1 (0.5%)	
CRT-D	24 (9.7%)	10 (11.2%)	13 (12.7%)	1 (1.8%)		23 (12.0%)	
N/A	4 (1.6%)	2 (2.2%)	2 (2.0%)	0 (0.0%)		0 (0.0%)	
CIED category					**0.006**		**0.004**
Low-powered	164 (66.1%)	60 (67.4%)	56 (54.9%)	48 (84.2%)		116 (60.7%)	
High-powered	80 (32.3%)	27 (30.3%)	44 (43.1%)	9 (5.8%)		71 (37.2%)	
N/A	4 (1.6%)	2 (2.2%)	2 (2.0%)	0 (0.0%)		4 (2.1%)	
Procedure type					**< 0.001**		**< 0.001**
De novo	158 (63.7%)	33 (20.9% de novo)	68 (43.0% de novo)	57 (36.1% de novo)		101 (63.9% de novo)	
Re-operative	90 (36.3%)	56 (62.2% re-op)	34 (37.8% re-op)	0 (0.0% re-op)		90 (100% re-op)	
Infection risk factors					**< 0.001**		**< 0.001**
0-1	65 (26.2%)	14 (15.7%)	22 (21.6%)	29 (50.9%)		36 (18.8%)	
≥ 2	183 (73.8%)	75 (84.3%)	80 (78.4%)	28 (49.1%)		155 (81.2%)	
Hematoma (total)	6 (2.4%)	5 (5.6%)	1 (1.0%)	0 (0.0%)	**0.046**	6 (3.0%)	0.176
Requiring intervention	6 (2.4%)	5 (5.6%)	1 (1.0%)	0 (0.0%)		6 (3.0%)	
Infection							
Pocket infection	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0.408	1 (0.5%)	0.584
Minor infection	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0.408	1 (0.5%)	0.584

[1]*P* value across 3 cohorts: Biologic, non-biologic, and no envelope.

[2]*P* value across 2 cohorts: Any envelope and no envelope.

Values are reported as: *n* (%) unless specified otherwise. BMI: Basal metabolic index; CIED: Cardiovascular implantable electronic device; CRT-D: Cardiac resynchronization therapy/defibrillator; CRT-P: Cardiac resynchronization therapy/pacemaker; ICD: Implantable cardioverter defibrillator; N/A: Not applicable; S-ICD: Subcutaneous implantable cardioverter defibrillator; SD: Standard deviation.

reoperative procedures such as lead or pocket revisions) received an envelope significantly more often than no envelope (100.0% *vs* 0.0%, $P < 0.001$) and tended to be more likely to receive a biologic than a non-biologic envelope ($n = 56$, 62.9% *vs* $n = 34$, 33.3%). Those with de novo implants tended to be more likely to receive a non-biologic envelope ($n = 68$, 66.6%) than a biologic envelope ($n = 33$, 37.1%).

Clinical characteristics and infection risk factors

Patients who received any envelope were younger on average (70.7 ± 14.0 *vs* 74.9 ± 10.6 years, $P = 0.017$) and had higher rates of comorbid risk factors such as heart failure (47.1% *vs* 28.1%, $P = 0.011$) and systemic anticoagulation (43.5% *vs* 28.1%, $P = 0.037$) than those who did not receive an envelope (Table 1). Patients with biologic envelopes tended to be somewhat older (mean 73.6 ± 13.3 *vs* 68.2 ± 14.0 years) and less overweight (22.5% *vs* 30.4%) than those with non-biologic envelopes. Differences in systemic anticoagulation among the 3 groups were statistically significant (biologic 48.3%, non-biologic 39.2%, no envelope 28.1%, $P = 0.050$). Patients who received any envelope had a significantly higher number of infection risk factors (≥ 2) than those with no envelope (81.2% *vs* 49.1%, $P < 0.001$), and biologic envelopes tended to be used more frequently for these higher risk patients (84.3% *vs* 78.4%).

Infection outcomes

Pocket infection rates were low (envelope 0.5%, no envelope 0.0%), with no significant difference between biologic and non-biologic envelopes (Table 1). Among the patients who received an envelope, one (0.5%) developed a major CIED infection (pocket infection), and one (0.5%) developed a minor CIED infection (superficial surgical site infection). However, the incidence of major or minor infection did not significantly differ between the 3 cohorts.

Other adverse events

Pocket hematoma (requiring surgical intervention) developed in 6 patients (2.4%): 5 patients (5.6%) with biologic envelopes, 1 patient (1.0%) with a non-biologic envelope, and 0 patients without an envelope (0.0%) ($P = 0.046$) (Table 1). However, there was no significant difference in hematoma between any envelope (3.0%) and no envelope (0.0%). There were no reported hematoma that led to infections in this study. Other adverse events included 3 Lead dislodgements (1 in the biologic group, 2 in the non-biologic group), 1 Lead revision (non-biologic group), 1 hemothorax (non-biologic group), and 1 site drainage (biologic group) in the envelope cohorts and erythema/fever in 1 patient in the no envelope cohort. Rates of adverse events other than pocket hematoma did not significantly differ among the 3 cohorts.

DISCUSSION

This retrospective study examined clinical profiles and outcomes of patients receiving CIEDs implanted with antibacterial biological envelopes hydrated with gentamicin and vancomycin (biologic envelopes), CIEDs implanted with synthetic (non-biologic) antibacterial envelopes, and CIEDs with no envelope. Non-biologic antibacterial envelopes have been previously shown in a large, randomized study to reduce infection risk in patients who are at increased risk for CIED infection[12]. To the best of our knowledge, this is the first reporting of clinical outcomes from using either biologic or non-biologic antibacterial envelopes, or no envelope within the same dataset.

Patient selection for envelope use

Patient selection by the implanting physician is reflected in the study findings. Envelopes were selected significantly more often for younger patients, patients undergoing device replacement procedures, high-powered device implantations, those on systemic anticoagulation, patients with heart failure, and patients with 2 or more risk factors for CIED infection. Treatment preferences can be observed by envelope usage for at-risk patients who may benefit most from the local delivery of antibiotics to their CIED implant site. Interestingly, there was no statistical difference in observed infection rates between the envelope and no envelope groups, even though the envelope group contained significantly more patients with ≥ 2 infection risk factors. Our results and those of other studies[9,12,24,26], support that the utilization of antibacterial envelopes (biologic or non-biologic) may reduce the potential risk burden of patients with multiple concurrent infection risk factors who are undergoing CIED procedures. However, further studies are needed to determine if there are specific patient types that could benefit the most from receiving an antibacterial envelope.

Complications

There were no significant differences in individual adverse event rates between groups, except that more patients with biologic envelopes were reported to have hematoma requiring intervention compared to the other two groups. However, this observation may have been due to the greater use of systemic anticoagulation and reoperative procedures in the biologic envelope group, which have both

been shown to be risk factors for hematoma formation in previous studies[29,30]. In fact, a recent analysis of hematoma from the 6800 patients included in the WRAP-IT trial reported a hematoma occurrence of 2.2%, which was significantly associated with an increased risk of infection for the no envelope (control) group and a significantly lower risk of major infection in the non-biologic envelope group (2.5% *vs* 13.1%, $P = 0.03$)[31]. No hematoma in our dataset led to subsequent infection, which further supports a potential benefit from using antibacterial envelopes (biologic or non-biologic) to reduce the risk of hematoma manifesting to CIED implant site infection.

Infections at the CIED implantation site have serious morbidity, mortality, and economic consequences[1,32]. The use of antibacterial envelopes may reduce the risk of infection and could potentially reduce these serious complications and healthcare costs[33]. In our dataset, antibacterial envelopes were used significantly more often to treat patients with multiple comorbid risk factors, and biologic envelopes tended to be used more often in higher risk patients than non-biologic envelopes. We observed a 0.4% overall rate of pocket infection, which is lower than previously-reported studies of 0.7% to 4.6% for de novo implantations and up to 7% for reoperative procedures[5-8]. No significant difference was found in major CIED (pocket) infection rates between the 3 groups. A previous study reported that infection rate can differ depending upon various patient- and procedure-related circumstances (such as device type, procedure type, antibacterial envelope use, or perioperative antibiotics)[7], thus along with the major infection rates reported for high risk patients in the WRAP-IT (0.7%)[12] and PADIT (0.7%)[34] studies, the low pocket infection rate observed in our preliminary results (0.4%) supports that high infection risk factors can be countered with infection prophylaxis techniques such as the use of antibacterial envelopes.

Antibacterial CIED envelope types

There are currently two commercially available CIED envelopes in the United States. The biologic envelope (CanGaroo®) is manufactured from two sheets of 4-ply SIS-ECM material which can be hydrated by the implanting physician with an antibiotic solution prior to implantation, and the non-biologic envelope (TYRX™) is fabricated from an absorbable synthetic substrate mesh coated with a bioresorbable polyarylate polymer containing the drug substances rifampin and minocycline. In separate studies, the release of antibiotics occurs similarly from both envelopes over a period of seven days[10-13]. Both envelopes are intended to stabilize the CIED post-implantation, yet the host response to these different materials may vary. All biomaterials (biologic and non-biologic) interact with the body upon implantation, and certain characteristics of these materials can influence the host response to the implant[35,36].

Extensive studies have shown that implanted biologic materials (such as non-crosslinked decellularized SIS-ECM) stimulate the production of site appropriate, functional tissue (termed "constructive remodeling"[37])[20-23,36]. The ability to elicit a remodeling response post-implantation is due to the natural degradation of the implanted ECM by proteases which release intrinsic bioactive peptides and growth factors such as FGF-2 and VEGF *in situ*[22,38-40]. When implanted, for example into a CIED pocket, these bioavailable signaling molecules can influence the healing milieu surrounding the implant site by directing cellular activities such as differentiation, chemotaxis, adhesion, and angiogenesis[22,41-43]. Non-biologic materials do not contain these bioactive components.

Limitations

Limitations to this study include non-randomization of patients to the treatment groups, a limited period of follow up, and all implantations performed by a single physician at one institution. The choice of patients receiving an envelope (and which envelope was used) creates selection bias observed in the differing patient factors between groups. However, the intent of this report was to evaluate and define physician practice patterns instead of assessing superiority between the three therapies. Longer-term (> 1 year) follow up may have captured late adverse events, which cannot be ruled out in this study.

CONCLUSION

In this real-world study, patients at higher risk for CIED infection received antibacterial envelopes and lower infection risk patients did not receive envelopes, yet the CIED pocket infection rate did not differ between groups. There was also no significant difference in observed pocket infection rates for patients receiving biologic *vs* non-biologic antibacterial envelopes. These findings support that use of an antibacterial envelope may benefit patients who are at higher risk for infection, however further work will continue to refine patient selection and clinical decision-making for optimal utilization of antibacterial envelopes during CIED implantation.

ARTICLE HIGHLIGHTS

Research background

An increase in cardiac implantable electronic device (CIED) implantation has led to an increase in observed complication rates, including infection. Antibacterial CIED envelopes have been shown to reduce the risk of infection complications, even in high-risk patient groups. There are currently two different CIED envelopes in clinical use which differ in the material from which they are made.

Research motivation

There is a paucity of data describing real-world physician practice patterns when using antibacterial CIED envelopes. Understanding clinical rationale and outcomes from the use of this prophylactic therapy could improve future patient outcomes.

Research objectives

Patient risk profiles and outcomes were compared from patients undergoing CIED procedures receiving either no envelope, or one of two antibacterial envelopes.

Research methods

In this retrospective analysis, the records of consecutive CIED procedure patients were reviewed at one center through a follow-up time of 12 mo.

Research results

Patients who were selected to receive an antibacterial CIED envelope were at significantly higher risk for infection than patients who did not receive an envelope (81.2% *vs* 49.1%, $P < 0.001$). Among the infection risks, envelope patients were undergoing more reoperative procedures (47.1% *vs* 0.0%, $P < 0.001$) and received more high-powered devices (37.2% *vs* 5.8%, $P = 0.004$) than patients who received no envelope. There was a propensity for the physician choosing a biologic envelope in patients who were higher risk than non-biologic patients (84.3% *vs* 78.4%), and those that were undergoing reoperative procedures (62.9% *vs* 33.3%). The rate of pocket infection was low (any envelope 0.5% *vs* no envelope 0.0%), with no significant difference between the two envelope groups.

Research conclusions

There is an apparent benefit for using antibacterial envelopes in patients who are at higher risk of implant site infection. When using antibacterial envelopes, there was no significant difference in infection rate for biologic and non-biologic envelopes.

Research perspectives

Future studies should further explore patient and procedural factors that play a role in antibacterial envelope usage for specific patient types to further improve patient outcomes.

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FOOTNOTES

Author contributions: Woodard D led the conception, design, data collection and analysis, and drafting of the manuscript; Nilsson K and Kim G contributed their expertise to the analysis/interpretation of data and editing of the manuscript; and all authors accept accountability for the accuracy of this work, and drafted, revised, and approved the final version of the manuscript to be published within this journal.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the WIRB-Copernicus Group®.

Informed consent statement: A waiver of informed consent and HIPAA due to the retrospective nature of this study was obtained. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki and conducted according to United States and international standards of Good Clinical Practice in accordance with applicable Federal regulations, International Council for Harmonization guidelines, and institutional research

policies and procedures.

Conflict-of-interest statement: Woodard D is a consultant for Aziyo Biologics, Inc. The other authors have no relevant financial relationships to disclose.

Data sharing statement: The dataset supporting the conclusions of this article is available upon reasonable request to the corresponding author.

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LETTER TO THE EDITOR

Electrocardiographic alterations in patients with chronic obstructive pulmonary disease

Mehmet Eyuboglu

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk for cardiovascular events, and electrocardiography has an important role in detecting cardiac side effects of COPD-related hypoxia.

Key Words: Electrocardiography; Chronic obstructive pulmonary disease; QT interval; QT dispersion; Frontal plane QRS-T angle; Fragmented QRS

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Core Tip: QT parameters and frontal plane QRS-T angle may provide useful information regarding subclinical left ventricular dysfunction in patients with chronic obstructive pulmonary disease. In addition to standard electrocardiography parameters, these parameters may also be useful in demonstrating cardiac side effects of chronic obstructive pulmonary disease.

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TO THE EDITOR

I have read with great interest the article by Gupta *et al*[1] in which the authors reported the important electrocardiography (ECG) changes in patients with chronic obstructive pulmonary disease (COPD). Patients with COPD are at increased risk for cardiovascular events and ECG may provide useful information in monitoring these

patients. In their article, Gupta *et al*[1] mentioned various important ECG alterations in patients with COPD. However, I would like to point out some other important ECG parameters which may be significantly associated with myocardial damage and should not be neglected in patients with COPD.

COPD causes alterations in the cardiac conduction system and is associated with increased risk for cardiac arrhythmias and cardiovascular events[2,3]. Importantly, repolarization parameters QT interval and QT dispersion are the most important ECG parameters in predicting future arrhythmic events, and these parameters seem to be significantly altered in patients with COPD[3,4]. Alterations in these repolarization parameters seem to be associated with COPD-related hypoxia and significantly predict arrhythmic events in patients with COPD. Hence, QT parameters may be useful in the monitoring of patients with COPD for adverse cardiovascular events.

Additionally, frontal plane QRS-T angle (fQRST angle) which could be easily measured from standard 12-lead ECG as the absolute difference between QRS axis and T wave axis, maybe a useful ECG parameter in the monitoring of patients with COPD. fQRST angle describes the angular difference between depolarization and repolarization directions and increased fQRST angle is significantly associated with adverse cardiovascular events[5,6]. Importantly, fQRST angle seems to be associated with subclinical myocardial damage even in the absence of overt cardiovascular disease[7-9]. Moreover, COPD seems to cause an increase in fQRST angle, and fQRST angle seems to be associated with the severity of COPD[10]. Therefore, as a sign of ventricular repolarization heterogeneity, fQRST angle may be a useful ECG parameter in the clinical evaluation of patients with COPD.

Another important ECG parameter that should be considered in patients with COPD may be QRS fragmentation. In addition to its predictive value for myocardial scar tissue, presence of a narrow fragmented QRS complex (fQRS) on ECG is significantly associated with subclinical myocardial fibrosis even in the absence of manifest cardiovascular disease[11-14]. Importantly, fQRS also seems to be a sign of hypoxia-related subclinical left ventricular dysfunction in patients with the pulmonary disease[15]. Although its clinical importance in patients with COPD has not been demonstrated yet, QRS fragmentation patterns may be useful in detecting subclinical left ventricular dysfunction in patients with COPD.

In conclusion, various ECG changes may be seen in patients with COPD, and these ECG alterations seem to be associated with adverse cardiovascular events in these patients. However, besides the other ECG parameters, QT interval, QT dispersion and fQRST angle should be considered to demonstrate COPD's cardiac side effects. Also, evaluation of QRS fragmentation patterns may provide useful information in detecting subclinical myocardial dysfunction in patients with COPD.

FOOTNOTES

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REVIEW

Role of cardiac magnetic resonance imaging in troponinemia syndromes

Nhung Nguyen Nguyen, Joseph George Assad, Giuseppe Femia, Andreas Schuster, James Otton, Tuan Le Nguyen

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Abstract

Cardiac magnetic resonance imaging (MRI) is an evolving technology, proving to be a highly accurate tool for quantitative assessment. Most recently, it has been increasingly used in the diagnostic and prognostic evaluation of conditions involving an elevation in troponin or troponinemia. Although an elevation in troponin is a nonspecific marker of myocardial tissue damage, it is a frequently ordered investigation leaving many patients without a specific diagnosis. Fortunately, the advent of newer cardiac MRI protocols can provide additional information. In this review, we discuss several conditions associated with an elevation in troponin such as myocardial infarction, myocarditis, Takotsubo cardiomyopathy, coronavirus disease 2019 related cardiac dysfunction and athlete's heart syndrome.

Key Words: Cardiac magnetic resonance imaging; Troponin; Myocardial infarction; Myocarditis; Takotsubo cardiomyopathy; COVID-19; Athlete's heart

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Core tip: Cardiac magnetic resonance has excellent spatial resolution to assess ventricular volumes and function. It is also continuing to evolve to provide key diagnostic and prognostic information particularly through the use of gadolinium contrast agent for the conditions presented in this review.

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INTRODUCTION

Troponinemia describes an elevation in serum troponin levels that can result from a myriad of conditions such as acute myocardial infarction (AMI), takotsubo cardiomyopathy (TTS), myocarditis and athlete's heart syndrome (AHS). More recently, severe acute respiratory syndrome coronavirus 2 has been linked to cardiac disease and elevated troponin levels. Given that troponinemia is nonspecific, establishing a definitive diagnosis can be difficult. Fortunately, cardiac magnetic resonance imaging (CMRI) has the ability to characterise myocardial tissue and identify unique pathological features of cardiac disease. As a diagnostic tool for these conditions, CMRI imaging may be promising.

This narrative review gives an overview of the diagnostic features and potential role of CMRI in conditions associated with troponinemia such as myocardial infarction (MI), TTS, myocarditis, coronavirus disease 2019 (COVID-19) related cardiovascular disease and AHS (Table 1).

MI

AMI is one of the most common causes of elevated troponin levels. It is defined by the presence of acute myocardial injury in conjunction with dynamic changes in troponin levels, and evidence of myocardial ischaemia[1]. Electrocardiography (ECG), transthoracic echocardiography (TTE) and invasive coronary angiography are the standard of care in the evaluation of MI. Adjunctive use of CMRI can be useful to confirm the diagnosis, assess chronicity, guide management and aid prognosis. It can be utilised to distinguish the changes seen between an acute and an established, or also called chronic MI. CMRI is also highly accurate at assessing ventricular volumes and function with superior spatial resolution, contrast-to-noise ratio and tissue characterisation compared to TTE.

On CMRI, AMI can demonstrate ventricular regional wall motion abnormalities (RWMAs) corresponding with the affected vascular territory on cine images. Intramyocardial haemorrhage may occur, and is represented by a hypointense zone in the infarcted area on T2-imaging or mapping[2]. Following ischaemic insult from coronary artery obstruction, myocardial cellular injury begins in the subendocardial region, and continues to extend towards the subepicardium if there is ongoing oxygen deprivation. This process is known as the "wavefront phenomenon of myocardial death", named by Reimer *et al*[3]. Late gadolinium enhancement images characteristically demonstrate a hypodense core surrounded by an area of hyperenhancement (Figure 1), and is found in a subendocardial or transmural distribution depending on the extent of the MI[4-6]. In chronic MI (CMI), cine images will typically show wall thinning, RWMA, and a lack of oedema on T2-weighted images[7]. In a study by Rehwald *et al*[8], the authors used rabbit models to demonstrate that gadolinium contrast agent uptake was greater in infarcted myocardial tissue. In another study, Kim *et al*[9] demonstrated that the extent of transmural hyperenhancement reflected the degree of irreversible injury. Native T1-sequences have also been explored by Kali *et al*[10], who demonstrated CMRI may be useful in diagnosing CMI, and determining likely irreversible injury. It is particularly useful in some situations, such as in renal failure patients, where gadolinium contrast is contraindicated.

Besides determining left ventricular ejection fraction (LVEF) on cine imaging, a detailed assessment of LV deformation measurements can also take place using CMRI[11]. Left ventricular global radial strain, circumferential strain and global longitudinal strain (GLS) have all shown association with increased major adverse cardiac events (MACEs)[12], and GLS has been demonstrated to be an independent predictor of post-MI clinical outcome. Impairment of left atrial strain on CMRI post-MI has also been demonstrated to be an independent predictor for increase in MACEs, as well as improving prognostic value when combined with LVEF[13,14].

It has been demonstrated that in patients with coronary artery disease, those treated with revascularisation have a significantly lower annual mortality rate compared to those treated with medical therapy [15,16]. In these patients, CMRI can be used to assess the viability of a coronary artery territory. The most important parameters are LV end-diastolic wall thickness, quantitative LV systolic or diastolic performance during low-dose dobutamine stress testing, and late gadolinium enhancement (LGE)[17].

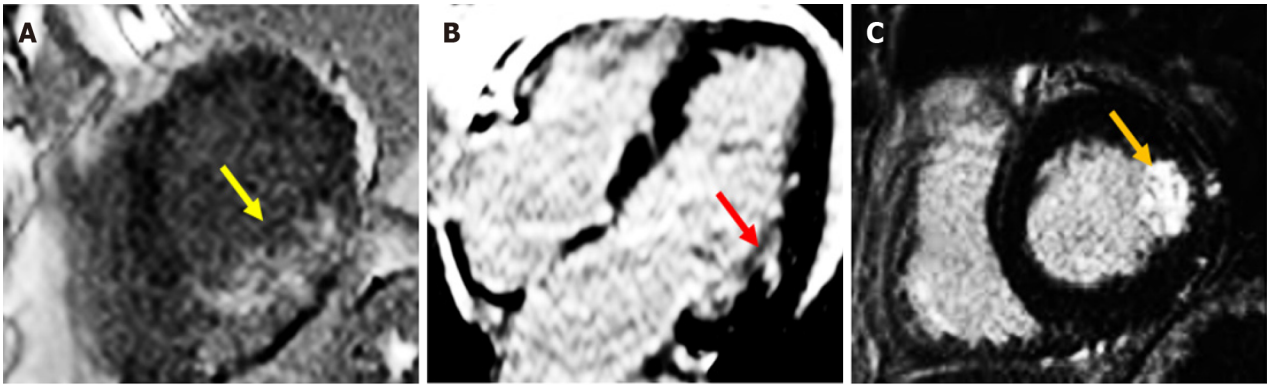
Table 1 Cardiac magnetic resonance imaging features

Condition	Cardiac magnetic resonance imaging features
Myocardial infarction	**< 1 mo**
	Myocardial oedema present on T2-weighted images, T2 mapping and T1 mapping
	Microvascular obstruction revealed as a hypointense core within hyperintense infarct zone in area of LGE
	Infarct size can be calculated using pre and post-contrast T1-weighted mapping and ECV assessment
	Myocardial necrosis/scar by LGE in a subendocardial or full-thickness pattern within a coronary artery territory
	Additionally at < 6 mo
	T2-weighted hyperintensity on double inversion recovery turbo spin echo
Takotsubo syndrome	Can help distinguish coexisting CAD or acute myocarditis LGE typically absent
	Myocardial oedema present on T2-weighted images, T2 mapping and T1 mapping
	Accurate assessment of WMAs on cine imaging
	Can be useful to identify ventricular thrombus
Myocarditis	Inflammatory hyperaemia demonstrated on T1-weighted images
	Myocardial oedema on T2-weighted images
	Myocardial necrosis/scar by LGE in a subepicardial or mid-wall pattern
	Greater T1 and T2 increases with acute inflammation
	Pericardial effusion
COVID-19 related cardiac dysfunction	Features similar to that of acute myocarditis
	Myocardial oedema on T2-weighted images
	Myocardial necrosis/scar by LGE in a subepicardial or mid-wall pattern
	Myocardial fibrosis using T1-weighted mapping and ECV assessment
	Can be useful to identify ventricular thrombus and pericardial effusion
Athlete's heart	LVH typically < 12 mm
	Lower ECV with LVH compared to HCM
	RV dilatation seen on cine imaging
	LGE focal and generally at the RV insertion points

LGE: Late gadolinium enhancement; ECV: Extra-cellular volume; CAD: Coronary artery disease; WMAs: Wall motion abnormalities; LVH: Left ventricular hypertrophy; HCM: Hypertrophic cardiomyopathy; RV: Right ventricular; COVID-19: Coronavirus disease 2019.

For example, in a LV segment with ≤ 50% transmural LGE, a normal dobutamine response is correlated with greater functional recovery after revascularisation[18,19]. In contrast, the presence of ≥ 50% transmural LGE indicates nonviable infarcted tissue[20,21]. This technique is comparable to fluorodeoxyglucose positron emission tomography, which is considered the gold standard in the assessment of myocardial viability[22]. Unfortunately, the role of CMRI can be limited in many healthcare settings, considering factors including machine access, availability of imaging experts, cost and time.

The use of CMRI in assessing prognosis following MI has shown promising results. Assessment for microvascular obstruction (MVO) through the use of first pass perfusion studies during and following gadolinium contrast administration is one of the prognostic features that has been studied. It is implicated in adverse ventricular remodelling, larger infarct size (IS) and poorer clinical outcome[23-25]. van Kranenburg *et al*[26] have also demonstrated that MVO is an independent predictor for major adverse clinical outcomes at 2 years. Infarct size on CMRI has also been shown to be strongly associated with heart failure hospitalisation and all-cause mortality[27]. More recently, postcontrast T1 mapping has been shown to accurately quantify IS in a small study[28]. CMRI has also demonstrated some correlation between IS and peak troponin I[29], however this has not been a consistent or reliable finding. Intramyocardial haemorrhage has been linked to adverse LV remodelling and increased MACEs, but heterogeneity in imaging techniques mean further study is required[23]. The presence of



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Figure 1 Cardiac magnetic resonance imaging of acute myocardial infarction. A: Short axis mid-ventricular image demonstrating almost full-thickness transmural late gadolinium enhancement (LGE) in posterolateral wall (yellow arrow); B: Four-chamber image demonstrating focal LGE in lateral wall (red arrow); C: Short axis image demonstrating > 75% transmural LGE in lateral wall (orange arrow).

LGE in patients with symptoms suggestive of MI conferred worse MACEs compared to those without LGE[30]. The prognostic importance of LVEF has been demonstrated in a number of studies[31,32]. Study delay for at least 1 wk following AMI should be considered, to allow for myocardial functional recovery as found by Mather *et al*[33], and further imaging at up to 6 mo may be required to assess stabilised LVEF[34]. LVEF ≤ 35% and LGE were independently associated with MACEs, with better predictive value than TTE[35]. The extent of LV scarring has also been clearly associated with risk of spontaneous ventricular arrhythmias[36-38]. Assessment of the peri-infarct, or "grey-zone", surrounding the infarcted core may also play a role in risk stratifying post-MI patients, with increased size posing potential heightened ventricular arrhythmic risk[39]. Yan *et al*[40] used a semiautomatic software detection system to quantify percentage of abnormal myocardial delayed enhancement of tissue surrounding the infarct core, and noted that it was an independent predictor of post-MI all-cause and cardiovascular mortality.

Incorporation of artificial intelligence-based analyses will likely have a role to play in the future in cardiac outcome and prognosis prediction. It has already been demonstrated that fully automated volumetric and myocardial segmentation assessment are equally effective as manual efforts in predicting MACEs[41].

As it stands, without the availability of randomised controlled data or larger studies, the actions to be taken if high risk CMRI features are seen are not completely clear[42,43].

TTS

TTS, which is also known as Takotsubo cardiomyopathy, transient apical ballooning syndrome, broken heart syndrome and stress-induced cardiomyopathy, is a condition of transient LV dysfunction that is typically triggered by physical or emotional stress[44]. TTS mimics MI with often indistinguishable clinical presentation, ECG changes and cardiac enzyme elevation, but without angiographic evidence of acute obstructive coronary artery disease or plaque rupture[44,45]. Given the transient nature of TTS, traditionally it was thought of as a benign condition however more recent data suggests this is misguided, with complications comparable to those seen in patients with the acute coronary syndrome [46,47]. CMRI is increasingly used to diagnose and evaluate complications of TTS in both the acute and subacute setting, particularly in those with atypical features, or bystander coronary artery disease[48].

In the acute setting, CMRI can define TTS by excluding other aetiologies such as MI and myocarditis and identifying RWMAs that extend beyond a single coronary artery distribution[49] (Figure 2). One of the hallmarks is reversible myocardial inflammation corresponding to RWMA[31,44]. CMRI can assess myocardial inflammation and oedema with T2-weighted images[44,50-52].

In the subacute phase, its strength in identifying subtle RWMA makes it the ideal modality to accurately assess for resolution of regional dysfunction, with full recovery being a criteria confirmation of diagnosis[44].

Late gadolinium-enhanced imaging is a valuable adjunct in confirming a diagnosis of TTS when there is coexisting coronary artery disease or suspicion for myocarditis. It is widely believed that in TTS, there is an absence of LGE on CMRI[31], however, there are studies challenging this notion, having demonstrated LGE in patients with TTS in the acute phase[52-54]. It should be noted that LGE in this setting is transient, resolving on serial imaging to confirm the diagnosis of TTS, and has been associated with increased incidence cardiogenic shock and a longer timeframe for resolution of wall motion abnormalities[55,56]. In contrast, patients with myocardial infarction will have focal subendocardial or

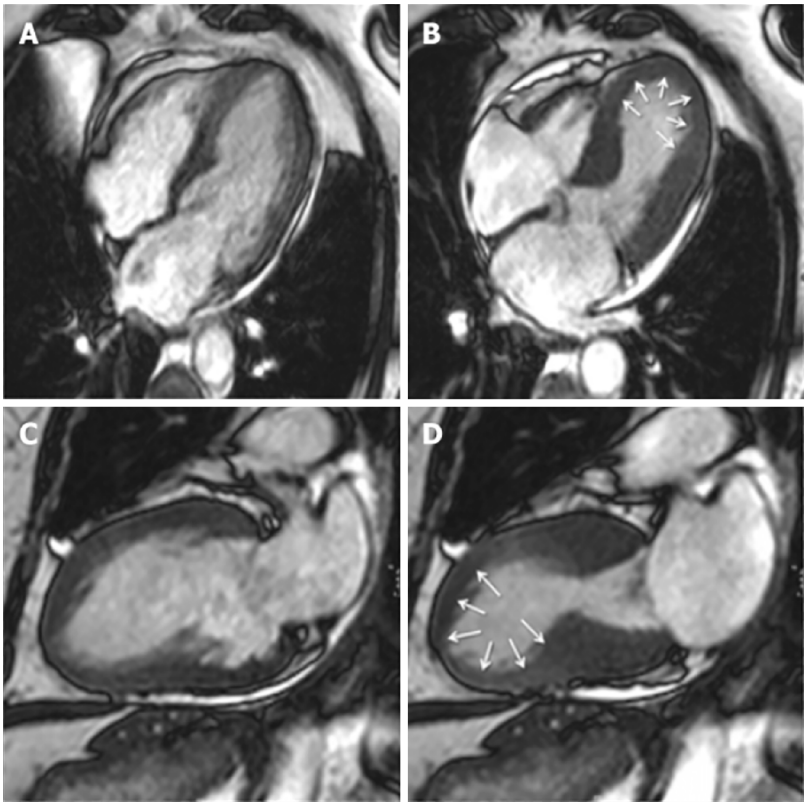


Figure 2 Cardiac magnetic resonance imaging of Takotsubo cardiomyopathy. Typical apical ballooning seen in takotsubo syndrome. A, B: Cine four-chamber in late diastole and systole respectively; C, D: Two-chamber view in late diastole and systole respectively. Modified from Plácido *et al*[123] and licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

transmural LGE evident, while those with myocarditis typically will have a mid-wall distribution of LGE[57].

In addition to confirming the diagnosis of TTS, CMRI is useful in identifying complications such as mitral regurgitation and LV outflow tract obstruction seen on blood flow imaging, pericardial effusion seen on black blood T1-weighted sequences, and ventricular (including apical) thrombi not visualised on TTE, during early gadolinium (EGE) sequences. Thrombi will appear as a low signal intensity without gadolinium uptake, in comparison to the high intensity signal from the blood pool[50,52].

It has been hypothesised that the elevated catecholamines observed in TTS have a role in the microvascular dysfunction noted in patients with TTS, correlating with improvement in myocardial function[58]. While not established in TTS, there is emerging evidence in the utility of quantitative perfusion CMRI to more objectively assess the role that microvascular dysfunction plays in this syndrome, and is subject to further research[59].

ACUTE MYOCARDITIS

Acute myocarditis is an inflammatory cardiomyopathy secondary to infectious and noninfectious conditions, sometimes associated with symptoms of heart failure developing over ≤ 3 mo. The clinical presentation can be nonspecific and may include chest pain, heart failure, cardiogenic shock, arrhythmias and/or sudden cardiac death. Early investigations may demonstrate elevated troponin levels, elevated acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate and eosinophil count. An ECG may be normal, show nonspecific abnormalities or be similar to the pattern of acute pericarditis and AMI. Most importantly, it is important to exclude alternative causes such as MI. Due to the variable clinical presentation, the gold standard for diagnosis remains an endomyocardial biopsy (EMB), which is an invasive procedure that carries risk of life-threatening complications. CMRI may provide a noninvasive alternative for the assessment of myocarditis[60].

CMRI has become an important tool in the assessment of myocardial inflammation in patients with suspected myocarditis. Assessment of gross abnormalities includes changes in ventricular size and geometry, regional and global wall motion abnormalities and identification of pericardial effusion. In addition, there are techniques to assess microscopic markers of myocardial inflammation such as T1-weighted sequences for detection of myocardial hyperaemia, LGE for myocardial necrosis, fibrosis or scars and T2-weighted imaging to identify oedema[61-63]. Following early CMRI data, consensus

diagnostic criteria were released and incorporated into the Lake Louise criteria[60] (LLC) (Table 2). The use of newer mapping techniques such as for native T1 and T2, and quantification of extracellular volume (ECV), in comparison to the LLC, appear superior in the diagnosis of acute myocarditis, with positive predictive value of 90% *versus* 71%[64].

LGE has been shown to be highly accurate in the diagnosis of myocarditis with a high correlation with EMB[65]. Acute myocarditis is associated with subepicardial or mid-wall late gadolinium enhancement most commonly in the lateral, inferolateral or inferior wall[66-68] (Figure 3). In particular, small studies have suggested specific patterns for certain viruses: parvovirus B19 is associated with the lateral wall while human herpes virus 6 is linked to the septal wall[69]. The presence of LGE on follow-up studies denotes areas of irreversible myocardial injury[62,65].

CMRI diagnostic accuracy in the workup for chronic myocarditis (> 14 d) is not as well established compared to acute myocarditis, with T2-mapping providing the only discernible additional diagnostic benefit together with the LLC[66,70].

Although CMRI has demonstrated prognostic guidance in acute myocarditis, cardiac enzyme markers do not reflect the degree of myocardial injury or permanent scarring as demonstrated on CMRI LGE[70]. There are insufficient data available to relate CMRI features to independent risk of ventricular arrhythmias, although this is clearly raised in the context of impaired LV function[67,71]. In a meta-analysis, the presence of LGE, particularly anteroseptal location, has been found to be an independent risk factors for adverse cardiac outcomes, including all-cause mortality, cardiac mortality including sudden cardiac death, and MACEs[72].

COVID-19 RELATED CARDIAC DYSFUNCTION

COVID-19 infection has variable presentations, most commonly involving respiratory symptoms. However, since the declaration of the pandemic in March 2020, there have been increasing reports of cardiovascular disease. The incidence has been reported to be ≥ 40%, depending on the definition or population sampled[73-76]. Postmortem studies of confirmed COVID-19 cases have demonstrated the presence of the virus in the myocardium, but not necessarily with consistent expression of cardiac sequelae[77]. There are numerous mechanisms involved in myocardial injury, which include direct viral invasion and host innate immunity response, hypoxia, micro- and macrovascular thrombosis, inflammatory injury and stress-induced cardiomyopathy[78].

Considering the multifaceted components of COVID-19-induced myocardial injury, it should not be expected that the imaging findings of this infection would duplicate that of a viral myocarditis syndrome alone. Cardiac involvement in COVID-19 infection may not be present with clinically severe cardiac symptoms[75,79], and even though echocardiography is a sensitive tool to identify gross cardiac dysfunction, LVEF may be normal[77]. There have been reports of primary cardiac involvement in COVID-19[80], where CMRI can be useful in identifying acute viral myocarditis features, as well as evidence of thrombosis such as LV apical thrombus.

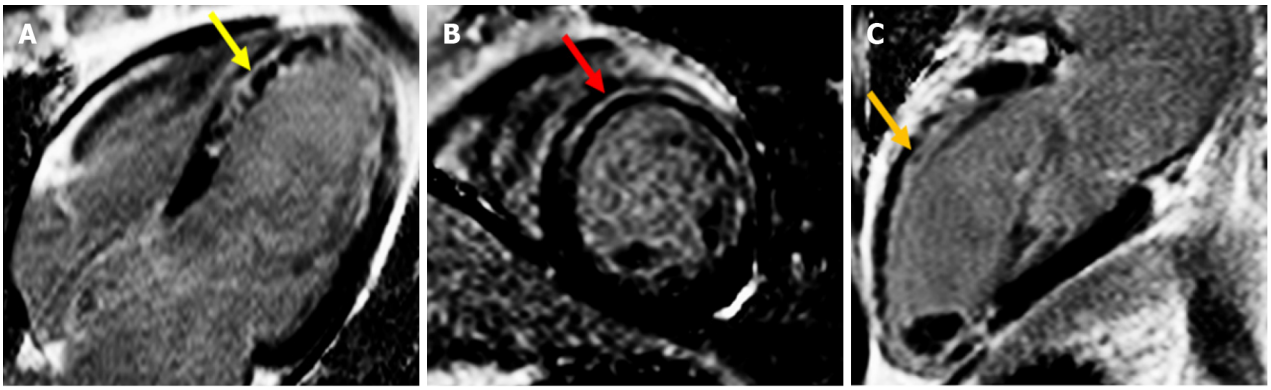
Studies using CMRI have demonstrated the severity of cardiovascular involvement following acute infection. In a report by Huang *et al*[81], the authors noted that 57% of patients had myocardial oedema or LGE on CMRI performed > 1 mo after development of infection (Figure 4). This suggests an ongoing pathological process affecting the myocardium. Historically, the LGE distribution in acute viral myocarditis involved the lateral and inferior walls. However with COVID-19, LGE patterns have been reported as subepicardial, mid-wall or subendocardial mimicking AMI[75]. Of note, there are no studies available where participants have baseline cardiac MRI data prior to COVID-19 infection. In addition, T2-signal hyperintensity tended to favour the interventricular septum, anterior and anterolateral walls, as well as basal inferior and mid-chamber. T1-mapping and ECV also demonstrated increased values, suggestive of myocardial fibrosis[75,81].

A developing use for CMRI is in the diagnosis suspected COVID-19-vaccine-associated myocarditis. These events tend to occur more frequently in young male patients after the second dose of mRNA vaccine[82,83]. Patients typically present with chest pain, troponin elevations, and abnormal CMRI findings[84]. CMRI abnormalities include myocardial oedema, hyperaemia and LGE, which are expected findings in acute myocarditis[85-89]. To date, there are no specific features for COVID-19-vaccine-associated myocarditis.

Evidence for the outcome of COVID-19-induced myocardial injury continues to evolve. Studies have found that elevation in troponin T levels confer significantly increased risk of mortality[73,90,91]. However, whether this and other markers of myocardial injury are byproducts of disease severity, or directly contribute to morbidity and mortality, remains to be elucidated. Currently, there is no long-term data on COVID-19 effects on the cardiovascular system, but considering its global impact, the identification, monitoring and study of outcomes is critical, with CMRI likely to play an essential role [92,93].

Table 2 Lake Louise consensus criteria for myocarditis on cardiac magnetic resonance imaging

Two out of three criteria must be met to be consistent with myocardial inflammation:
Regional or global myocardial signal intensity increase in T2-weighted images
Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
At least one focal lesion with nonischaemic regional distribution in inversion recovery-prepared gadolinium enhanced T1-weighted images (late gadolinium enhancement)



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Figure 3 Cardiac magnetic resonance imaging of acute myocarditis. A: Four-chamber image demonstrating LGE in septal wall in a mid-wall pattern (yellow arrow); B: Short axis mid-left ventricular image demonstrating LGE in anteroseptal wall in a mid-wall pattern (red arrow); C: Two-chamber image demonstrating LGE in the anterior wall in a mid-wall pattern (orange yellow).

HIGH-ENDURANCE ATHLETES AND AHS

Competitive sports level training can lead to a condition known as AHS, defined by complex cardiac chamber remodelling, ventricular systolic impairment and abnormalities involving the electrical conduction system. Electrocardiogram changes can include first-degree atrioventricular block, incomplete right bundle branch block, early repolarisation and isolated increased QRS voltages that may meet criteria for LV hypertrophy (LVH)[94]. Transient troponin elevation occurs with moderate-to-high intensity exercise[95,96]. The role of CMRI is also continuing to evolve in helping distinguish AHS from conditions such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM), which can have similar ECG and TTE features.

Although ventricular hypertrophy and dilatation can occur in both ventricles, impairment of systolic function following prolonged exercise tends to observed more frequently in the right ventricle (Figure 5A). In early forms of the disease, diastolic dysfunction is often observed, first defined by a reduction in mitral E:A ratio on echocardiographic Doppler imaging[97-100]. A hallmark of AHS is increased LV mass[101]. Unfortunately, this is not a discriminating feature and can overlap with other conditions such as HCM and ACM[102]. In particular, differentiating AHS from mild HCM, with LV wall thickness range 13–15 mm, is critical in preventing adverse outcomes for athletes. Despite early reports suggesting that different cardiac conditions can lead to particular patterns of LVH, this has not been demonstrated in subsequent studies[103,104]. Cessation of training usually leads to LVH regression and improvement in clinical outcomes.

The advancement of CMRI technology may help shed light on the potential long-term effects of competitive level exercise and help differentiate different cardiac conditions. LV cavity size (LV end-diastolic and end-systolic diameter) in AHS is usually larger than HCM, particularly if the end-diastolic diameter exceeds 54 mm[100]. CMRI can also provide accurate morphology assessment for excessive trabeculation and noncompaction cardiomyopathy, if it cannot be clearly delineated on echocardiography[105]. The use of more advanced CMRI tissue characterisation techniques such as T1 mapping and ECV assessment is also helpful. Athletes have been demonstrated to have lower ECV, likely as a result of myocyte enlargement, compared to nonathletes. Conversely, in HCM, there is increased ECV [106,107]. The role of LGE to distinguish AHS compared to HCM is not yet certain. Domenech-Ximenos *et al*[106] found that focal LGE was more prevalent in intensive endurance athletes compared to healthy subjects (37.6% *vs* 2.8%), with a typical pattern at the right ventricular (RV) insertion points. This may overlap with the LGE distribution in HCM[107].

Ventricular dilatation has been noted in athletes compared to healthy nonathletic individuals[108, 109]. LV dilatation is less severe as compared to the RV dilatation. Stress echocardiography observation

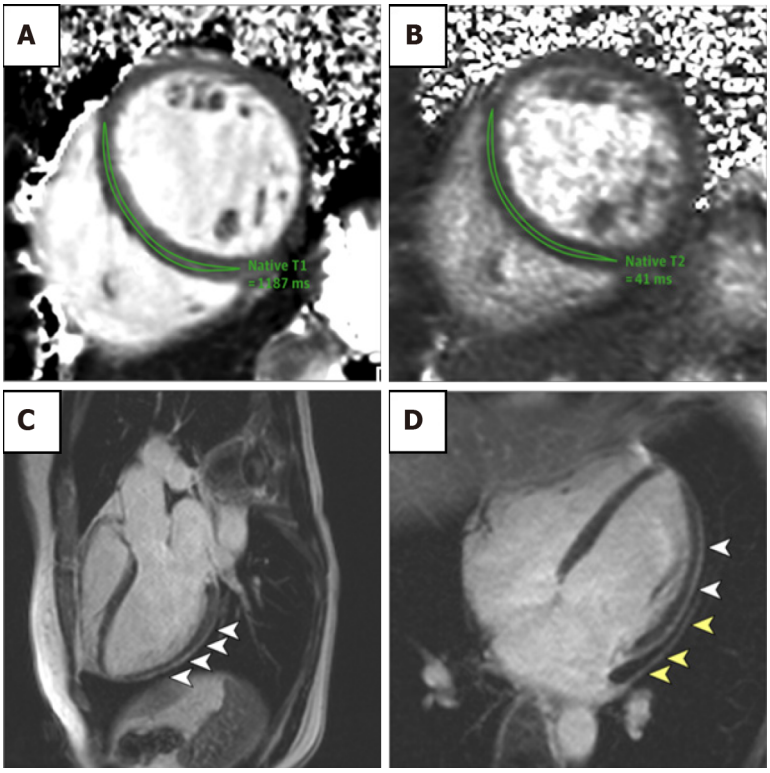


Figure 4 COVID-19 related cardiac dysfunction on cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging of an adult woman with COVID-19-related perimyocarditis. A, B: Significantly raised native T1 and native T2 in myocardial mapping acquisitions; C, D: Pericardial effusion and enhancement (yellow arrowheads) and epicardial and intramyocardial enhancement (white arrowheads) using LGE acquisition. Modified from Puntmann *et al*[75] and licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

of improvement in LVEF by > 11%, and presence of mid-wall LGE may help to discriminate between AHS and pathological dilated cardiomyopathy[95,96,110,111] but this has not yet been investigated in large studies. In a meta-analysis performed by D'Ascenzi *et al*[102], in high-performance athletes, RV end-diastolic volume (EDV) and end-systolic volume (ESV) exhibited the greatest relative increase in ventricular remodelling, compared to baseline parameters. This may be in response to increased venous return and other hemodynamic changes. The increase in RV size in athletes has led to situations where the dimensions meet part of the ACM criteria[112]. CMRI can be useful to improve spatial resolution in cases with poor echocardiographic windows. It can quantify function, identify RWMAs, and determine the presence of myocardial fibrosis and fibrofatty infiltration, to evaluate ACM versus AHS. In one study, Zaidi *et al*[113] found that the presence of RV ejection fraction < 45%, the ratio of RV EDV to LV EDV > 1.1/1, RV RWMA and LGE found together in athletes was highly indicative of ACM.

Exercise CMRI may provide addition diagnostic information by comparing the difference between adaptive responses and ventricular pathology in AHS, as well as potential prognostic information. The development of in-scanner CMRI exercise protocols with excellent reproducibility has been important in facilitating studies on the difference in physiological and pathological responses of athletes[114,115]. During exercise, elite athletes with evidence of ventricular arrhythmias had an increase in RV EDV, decrease in RV ESV, and, as a result, had reduced RV ejection fraction compared to athletes with no evidence of ventricular arrhythmia and healthy controls[116]. Of note, stress TTE yielded similar sensitivity in identifying exercise induced RV dysfunction.

The use of CMRI has been explored in AHS adverse outcome prognostication. In the context of excellent spatial and temporal resolution of CMRI, there appears to be no difference in resting in cardiac volumes of elite athletes with and without evidence of ventricular arrhythmias[116]. LGE at the junction of the right ventricle and interventricular septum has previously been noted in athletes, but is not related to any clinical sequelae. A pattern of myocardial wall fibrosis in AHS has otherwise not consistently been demonstrated, or has been affected by confounding factors such as veteran athletes with coronary artery atherosclerotic plaques[112,117-119] (Figure 5B–5D). Zorzi *et al*[120] did note that in athletes who presented with a history of ventricular arrhythmias and subsequently found to have LV LGE, a striae subepicardial – midmyocardial lateral LV wall distribution pattern was more prevalent. There are no long-term data on outcome of incidental finding of myocardial LGE[114,121-123]. The definitive role of CMRI for prognostication in AHS remains to be defined outside of its roles in excluding other important diagnoses such as HCM and ARC.



Figure 5 Cardiac magnetic resonance imaging of athlete's heart syndrome. A: Cardiac magnetic resonance imaging of an endurance athlete. Increased right and left ventricular volumes. Overall muscle mass may be increased although wall thickness remains within standard reference range[102]; B: A 51-year-old athlete training 7 h/wk in the last 30 years. The short-axis view shows subepicardial late gadolinium enhancement (LGE) in the inferior apical wall; C: A 55-year-old athlete training 8 h/wk in the last 30 years. Mild intramyocardial LGE is the lateral wall is shown in the four-chamber view; D: A 55-year-old athlete training 10 h/wk in the last 28 years. Mesocardial LGE in the apical-septal wall shown in three-chamber view image. Reproduced from Pujadas *et al*[122] and licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

COMMENTS AND LIMITATIONS

Traditionally, gross morphological cine scanning and determination of LGE location in the myocardial wall has formed key diagnostic features in the use of CMRI for many conditions. The advent of more advanced techniques such as T1 and T2 mapping has allowed a deeper understanding of the pathophysiological process involved.

The limitations for the use of CMRI include: (1) Access to CMR facilities with trained staff to perform the scan and process the images; (2) Standardised protocols; (3) Duration of procedure; (4) High cost; and (5) Lack of superiority to cheaper, faster and more accessible imaging modalities.

Moving forward, improving access to CMRI, increasing the number of skilled personnel and developing clear scanning guidelines are needed. Further research including large randomised trials are necessary to further define the role of CMRI in the assessment of MI, TTS, myocarditis, AHS and COVID-19-related cardiac conditions.

CONCLUSION

Troponinemia or an elevation in serum troponin levels can result from several different conditions making the diagnosis difficult. CMRI provides a powerful insight into the pathological mechanisms of disease, diagnostic features, as well as potential prognosis. With advancement in technology and research, this will only continue to improve.

FOOTNOTES

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provided the approval of the final version of the article to be published.

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REVIEW

Cardiac myxomas: A narrative review

A K M Monwarul Islam

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Abstract

Cardiac myxomas are common primary neoplasms of the heart. They are biologically benign but "functionally malignant" because of the potential for embolization. They arise most commonly from the left atrium, but no chambers of the heart are immune. They may be sporadic in the majority but also familial as a part of the Carney complex. Two morphological forms exist: polypoid and papillary. Polypoid myxomas often present with obstructive features, while the papillary forms are more prone to embolization. Histogenesis is still controversial; the current view centres around origin from the primitive pluripotent mesenchymal cells. They may be of giant proportion, be calcified or get infected. Clinical presentation typically involves the triad of intracardiac obstruction, embolic events and constitutional symptoms. Precordial examination findings may simulate those of mitral or tricuspid stenosis. The presence of tumour plop and change of the physical findings with changing position may help differentiation between the two. Echocardiography is the investigation of choice. Echogenic polypoid or papillary mobile mass within the atrial cavity remaining attached to the interatrial septum through a stalk are the tell-tale echocardiographic features. Cardiac magnetic resonance and computed tomographic scanning may have incremental diagnostic value. Histopathological examination reveals abundant loose myxoid stroma with scattered round, polygonal or stellate cells with dense irregular nuclei. Genetic testing may detect mutations in the *PRKAR1A* gene in the familial form of cardiac myxoma, *i.e.* the Carney complex. Surgical excision is the mainstay of treatment with low operative mortality, excellent postoperative survival and low recurrence rate. The current trend favours minimal-access surgery with or without robotic assistance. Physicians should have appropriate preparedness to make a timely diagnosis and enthusiastic treatment to avoid potentially fatal complications.

Key Words: Myxoma; Cardiac; Neoplasm; Carney Complex; Echocardiography; Embolism

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Core Tip: Cardiac myxomas are biologically benign but "functionally malignant". They can cause life-threatening embolic events. Associated constitutional symptoms may mimic those of inflammatory or connective tissue disorders. Timely diagnosis is of utmost importance because it offers a scope for definitive treatment, *i.e.* surgical excision. Cardiac myxoma is a relatively rare diagnosis, so physicians should have appropriate preparedness to deal with this entity. This review article has summarised the available information, offered practical tips and highlighted the recent advances.

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INTRODUCTION

Cardiac myxomas are primary neoplasms of the heart. Despite a preference for the left atrium, it can involve any of the cardiac chambers. The unusual feature of cardiac myxoma is that it has the biological potential to embolise and grow at the site of embolization[1], causing organ infarction. Timely diagnosis and treatment are essential for the prevention of sometimes life-threatening complications. Though a well-known entity, some aspects of cardiac myxoma are still evolving.

Epidemiology

Cardiac myxoma is a rare disease; however, the exact prevalence is unknown. The reported prevalence is 0.03% in the general population[2]. Annual incidence of cardiac myxoma may be 0.5 to 1 case per million individuals[3,4]. A recently published Spanish study revealed a higher incidence; age-adjusted incidence was 1.6 per million population adjusting to the world population as a reference and 2.1 per million adjusting to the European population[5]. Myxomas are the commonest primary cardiac tumour constituting 50% to 85% of benign ones[6-8]. Middle-aged persons are commonly affected, but no age is immune. The tumour has a female preponderance with a female-to-male ratio of approximately 3:1[3, 4]. Two epidemiological forms of cardiac myxoma exist: sporadic and familial. The former is far more common than the latter, constituting about 95% of cases[6].

Anatomy

Cardiac myxomas can affect any chamber of the heart, but the left atrium is most commonly affected. Sites affected include the following: left atrium (75%); right atrium (15%-20%); left ventricle (3%-4%); and right ventricle (3%-4%)[9-12]. Regarding origin, myxoma has a predilection for limbus fossa ovalis of the interatrial septum. However, it can arise from the posterior atrial wall, anterior atrial wall and atrial appendage (Figure 1). The sporadic myxomas are usually single and bear these characteristics. On the other hand, familial myxomas may be multiple, multicentric and arising from atypical sites[13]. Less commonly, myxomas may be bi-atrial or multi-chamber; the latter may be part of the Carney complex [14-18] (Figures 2 and 3). Only rarely, myxomas affect the heart valves[7,19-21].

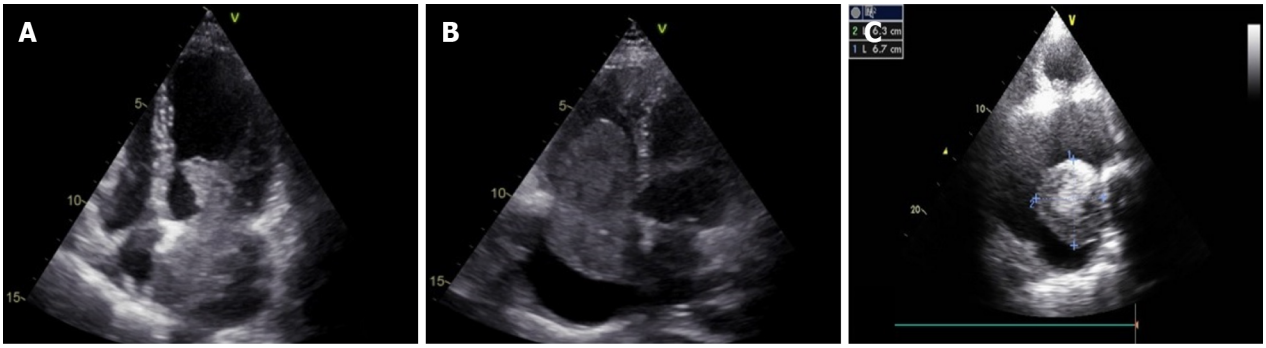
Myxomas may be 'more solid' polypoid in approximately two-thirds of cases or 'softer' papillary in one-third of cases[22] (Figure 4). The polypoid myxomas are generally pedunculated, more compact and have less tendency to undergo fragmentation and consequent embolisation[6]. On the other hand, papillary or villous myxomas are gelatinous, less compact, fragile and have a high potential for spontaneous fragmentation and embolisation to the central nervous system, kidney, spleen, extremities and coronary vessels (Figure 5).

Myxomas are considered biologically benign but "functionally malignant" tumours. They usually remain localised to the site of origin. They have a well-documented potential for fragmentation and embolisation. Besides this, metastasis to different locations, including the brain, sternum, spine and pelvis, has been described[23-29].

Myxomas may be enormous, occupying significant parts of the concerned cavity, sometimes termed "giant myxoma" (Figure 6). Rarely, they undergo calcification or osseous metaplasia[30-32] (Figure 7). Occasionally, they get infected[33-35] (Figure 8).

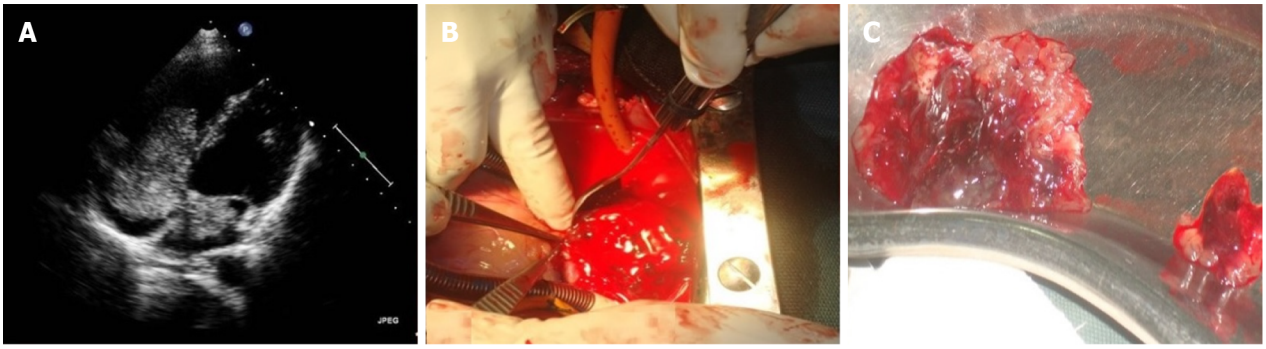
Histology

Histologically cardiac myxomas are mainly composed of stellated fusiform and polygonal cells immersed in an amorphous myxoid stroma[36] (Figure 9). Multinucleated cells are also observed. The cells are shaped and structured in chained rings or nests around the capillaries[37]. The surface of the tumour is often layered by flattened endothelium, while the tumour mass is infused liberally by thin-walled vessels lacking pericytes.



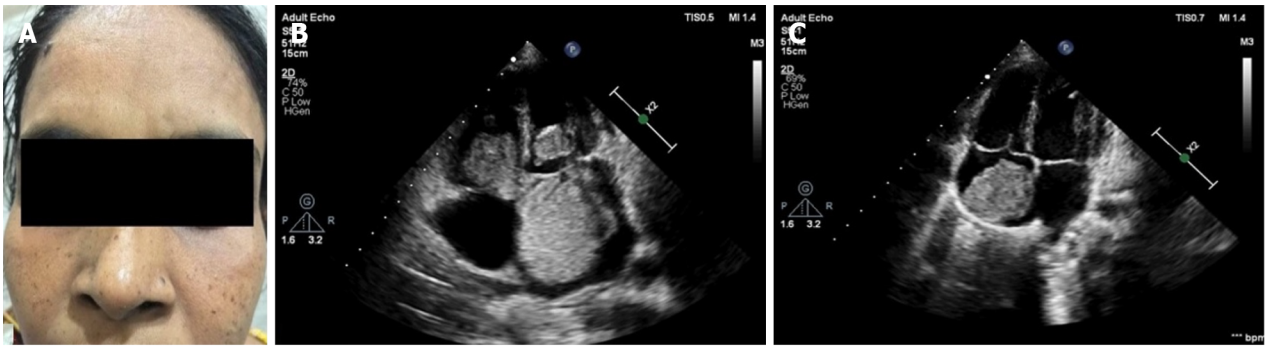
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Figure 1 Different locations of myxoma. A-C: Cardiac myxoma involving the left atrium (A and C) and the right atrium (B); A, B: The myxoma mass is attached to the atrial septum; C: The tumour is related to the lateral wall of left atrium.



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Figure 2 Biatrial myxoma in a 22-yr-old Bangladeshi male. A: 2-D transthoracic echocardiography shows biatrial myxoma arising from the midinteratrial septum; B, C: Tumour mass during and after surgery.

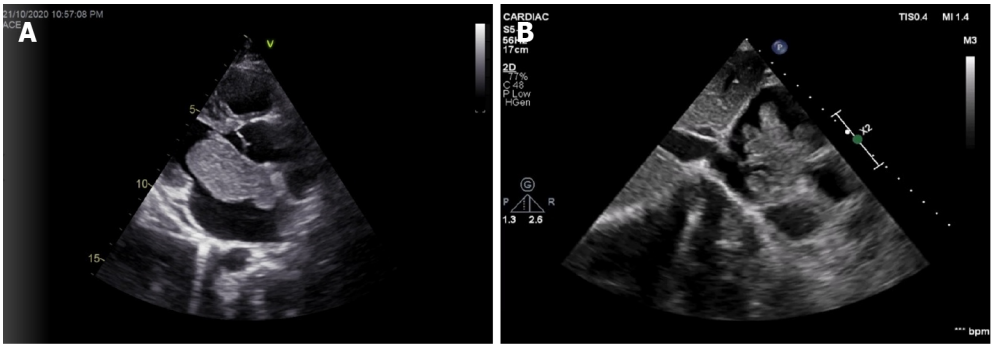


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Figure 3 Carney complex in a middle-aged Bangladeshi female. A: Multiple pigmented lentigines distributed symmetrically on the face of the patient; B: 2-D transthoracic echocardiography shows multichamber myxoma involving the left atrium, left ventricle and the right atrium; C: 2-D transthoracic echocardiography of the son of the lady shows myxoma in the right atrium.

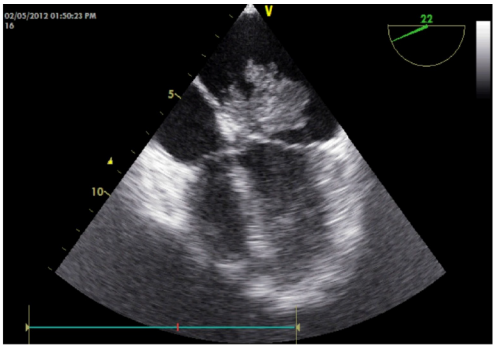
Immunohistochemically, a wide array of biological molecules has been found to be related to the cardiac myxomas, including CD31, CD34, CD56, FVIIIAg, S-100 protein, calretinin, vimentin, desmin, smooth muscle myosin, α1 antitrypsin and alpha 1-antichymotrypsin[38].

The histogenesis of myxoma is poorly understood; however, the current opinion favours origin from primitive pluripotent mesenchymal cells. Genes encoding heart precursor markers may get reactivated and expressed in cardiac myxoma cells leading to differentiation along endothelial/endocardial lines [39]. Previously, myxomas were thought to arise from Prichard structures, the microscopic endocardial/endothelial structures lined by plump endothelial cells, located in the fossa ovalis[40,41]. Origin from neuroendocrine tissue was also proposed.



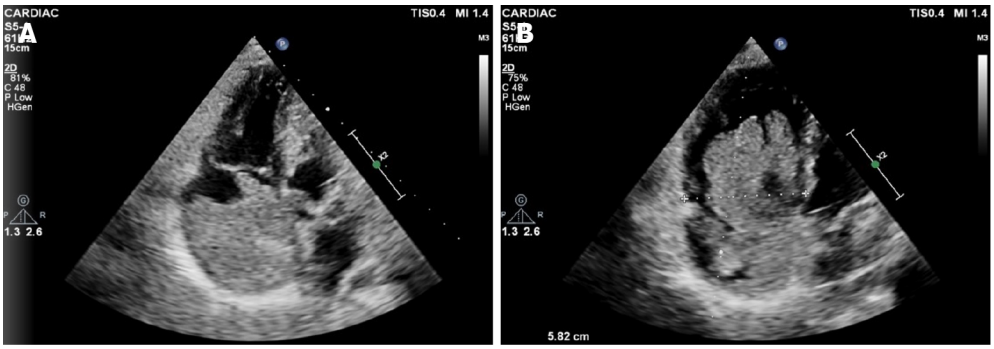
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Figure 4 Polypoid and papillary myxoma in 2D echocardiography. A: Parasternal long axis view shows a polypoid left atrial myxoma; B: Subcostal view shows a papillary right atrial myxoma with multiple projections.



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Figure 5 Papillary myxoma presenting with ischemic stroke. Transesophageal echocardiography shows a fragile papillary myxoma. The young patient presented with acute ischemic stroke.



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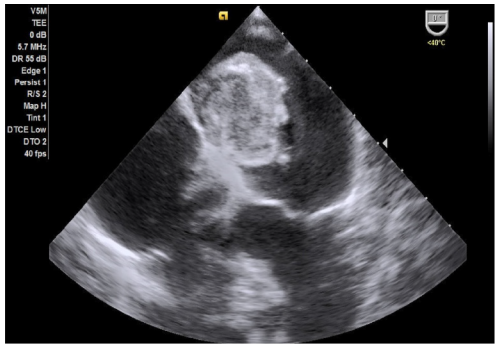
Figure 6 Giant myxoma in right atrium. A, B: 2D transthoracic echocardiography shows a giant myxoma occupying the major parts of the right atrial cavity. Note the multiple papillary projections evident in (B).

Clinical presentation

The clinical presentation of cardiac myxoma depends on their location, size and mobility and is typified by the triad of intracardiac obstruction, embolisation and constitutional symptoms[6]. In a French series of 112 cases of cardiac myxoma, intracardiac obstruction in the form of mitral valve obstruction was the commonest manifestation (67%), followed by embolisation (29%) and constitutional symptoms (34%) [22].

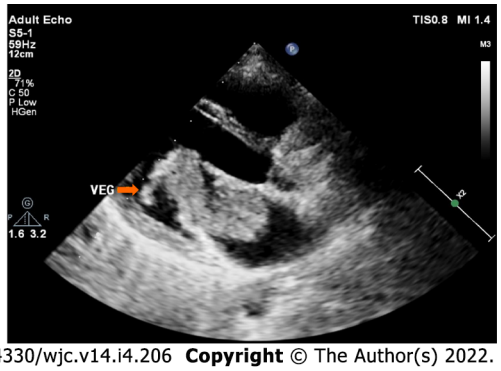
Intracardiac obstruction: Intracardiac obstruction is common in polypoid myxoma. Because of preferential location, mitral valve pseudo-obstruction is the typical presentation[42-48]. Pulmonary hypertension may be present[43,47]. Valvular obstruction may even lead to syncope[46,49].

Right atrial myxomas may obstruct the tricuspid valve, the manifestation of which may be heart failure[50,51] or even collapse[52].



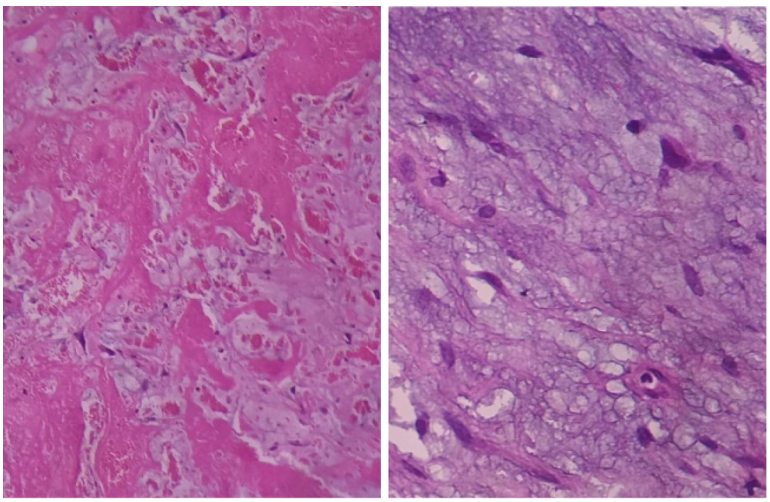
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Figure 7 Calcified myxoma in the left atrium. Transesophageal echocardiography shows a large calcified myxoma occupying the left atrial cavity.



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Figure 8 Infected myxoma in the left atrium. Transthoracic echocardiography shows a large left atrial myxoma protruding into the left ventricular cavity across the mitral valve. A vegetation with independent mobility is attached to the tumour. The patient presented with prolonged fever with positive blood culture.



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Figure 9 Histopathology of myxoma. Histopathological examination shows abundant loose myxoid stroma with scattered round, polygonal or stellate cells with dense irregular nuclei.

Embolisation: Embolisation is typically a feature of papillary-type myxomas because of their loose consistency and fragility. Overall, embolism occurs in 30% to 40% of patients with myxomas[6]. The site of embolisation depends on the location of the tumours. Left atrial myxomas commonly embolise to the brain, causing ischaemic stroke and occasionally visual loss. Coronary, renal and limb arteries may also be affected. In a retrospective study of 162 patients with cardiac myxomas surgically treated between 1998 and 2014 in China, the embolic event was observed in 33 patients (20.4%), in the brain (15.43%), limb (3.70%), pulmonary (0.62%) and coronary (0.62%)[53]. Tumour location (atypical), macroscopic

appearance (irregular surface), mean platelet volume and high platelet count were strong risk factors for embolic events in patients with cardiac myxomas in this study. Cerebral embolisation is relatively common, leading to ischaemic stroke[54,55] and cerebral aneurysm formation[56]. Retinal artery occlusion and consequent visual loss have also been reported[57-60]. Coronary embolisation is a rare but well-documented and potentially fatal complication of cardiac myxomas[61-64]. Systemic embolisation may affect multiple sites, *e.g.*, coronaries, viscera and limbs[65-67]. Right-sided myxomas are less prone to embolisation. However, right atrial myxoma, when present, may cause a pulmonary embolism[68-73].

Cardiac myxomas may even embolise peroperatively, leading to complications. Right atrial myxoma was reported to embolise during surgical excision, causing pulmonary embolism and cardiogenic shock and subsequent recovery after removal of the tumour embolus from the pulmonary artery[74].

Constitutional symptoms: Cardiac myxomas are commonly associated with constitutional symptoms mimicking inflammatory or connective tissue disorders[75-77]. These symptoms are more common in women than in men, in right-sided myxomas than in left-sided ones and in large and multicentric myxomas[78]. Malaise, anorexia, fever, arthralgia and weight loss are common. The underlying pathophysiology may be releasing cytokines from the tumour, especially interleukin-6 (IL-6)[79]. In fact, IL-6 may be a more sensitive biomarker than C-reactive protein in predicting the inflammatory status of patients with cardiac myxomas. Sessile, irregular and voluminous tumours tend to be associated with higher circulating IL-6 levels[80]. Myxomas occasionally present with pyrexia of unknown origin[79, 81]. They may mimic bronchial asthma[82] or pulmonary tuberculosis[14]. Rarely, myxomas are associated with pleural effusion[14,83,84].

Infected myxoma: Occasionally, myxomas get infected, presenting with high fever and multiple embolic events[85-88] (Figure 8).

Cardiac myxoma in pregnancy: Occasionally, cardiac myxomas are diagnosed for the first time in pregnancy, mostly by echocardiography. Favourable maternal and foeto-neonatal outcomes with surgical management of cardiac myxoma in the pregnant patients have been reported in a recent review of 44 articles with 51 patients[89].

PHYSICAL EXAMINATION

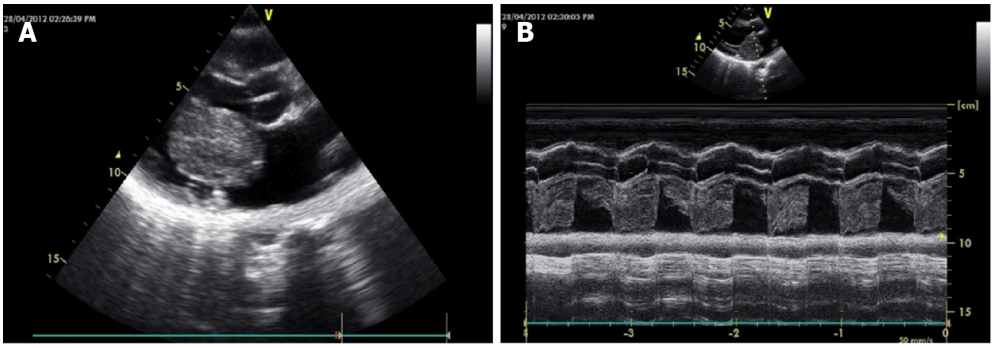
Cardiac myxomas are typified by the triad of intracardiac obstruction, embolic manifestations and constitutional symptoms. However, because of heterogeneity in location, size, morphology and histopathology, they may remain entirely asymptomatic, present with classical manifestations or produce life-threatening emergency of systemic embolisation or even sudden cardiac death[90]. As little as 10% to as high as 50% of the myxomas may be diagnosed incidentally during clinical evaluation[91, 92]. General examination may reveal cachexia, fever, cyanosis, clubbing or rash. Neck veins may be engorged, and there may be a prominent A wave in the jugular venous pulse. Precordial findings may mimic mitral stenosis. The first heart sound (S1) may be loud and widely split because of the delay in the closure of the mitral valve due to the prolapse of the tumour into the mitral valve orifice. The pulmonary component of the second heart sound (P2) may be normal or loud depending on the presence of pulmonary hypertension. The characteristic "tumour plop" is a low-pitched early diastolic sound just after the S2. It may be confused with the opening snap of rheumatic mitral stenosis; however, the latter is high-pitched. It may be followed by a low-pitched diastolic murmur. The tumour plop is produced by the impact of the myxoma against the endocardial wall or when its excursion is halted. Also, a third heart sound (S3), fourth heart sound (S4) or a diastolic murmur of functional mitral or tricuspid stenosis may be audible. Occasionally, a systolic murmur of mitral or tricuspid regurgitation may be present. The auscultatory findings of cardiac myxomas characteristically change with changes in the position of the patient.

INVESTIGATIONS

Echocardiography is the critical investigation for the diagnosis of cardiac myxomas. Other imaging modalities like computed tomography (CT) scanning and magnetic resonance imaging play an ancillary role. Chest X-ray and electrocardiography are of limited value. Haematological investigations are also routinely done. Histopathology confirms the diagnosis. Genetic testing plays a vital role in familial cases of myxomas.

Echocardiography

Transthoracic echocardiography is the most practical investigation and often yields adequate information necessary for surgical resection. It makes the diagnosis and determines the location, size



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Figure 10 Echocardiographic features of myxoma. A, B: Transthoracic echocardiography 2D (A) and M-mode (B) shows a large polypoid mass in the left atrial cavity attached to the interatrial septum by means of a stalk (not visualized here) and protruding into the left ventricular cavity across the mitral valve in diastole.

and shape of the tumour and its connections. Transesophageal echocardiography has a higher sensitivity and specificity and can detect small tumours, tumours located at atypical locations and possible multichamber myxomas[93-97].

Three-dimensional transthoracic echocardiography and transoesophageal echocardiography have also been used[98]. In a European study, transoesophageal echocardiography was superior to transthoracic echocardiography for myxoma detection (100% *vs* 95%) and attachment point identification (95.2% *vs* 64.5%)[99].

The classical features of an atrial myxoma in echocardiography include polypoid or papillary mass attached to the interatrial septum through a stalk and moving to and fro into the cavity, sometimes protruding into the corresponding ventricular cavity across the atrioventricular valve (Figure 10). Occasionally, the tumour mass may get areas of liquefaction or calcification. Doppler echocardiography shows the hemodynamic consequences of atrial myxoma.

During echocardiography, differentiation between myxoma and thrombus is of crucial importance. Myxomas typically have a stalk, a preference for limbus fossa ovalis of the atrial septum for stalk attachment and characteristic mobility. On the other hand, the thrombus is usually situated in the posterior portion of the atrium, has a preference for the atrial appendage, has a layered appearance and is most commonly seen in the presence of valvular mitral stenosis, atrial fibrillation and spontaneous echo contrast.

Contrast echocardiography can aid in the differential diagnosis of intracardiac masses based on perfusion of the mass. Malignant tumours are frequently highly vascular and present greater contrast enhancement than the adjacent myocardium, whereas myxomas demonstrate partial perfusion with lesser contrast enhancement than the adjoining myocardium. Thrombi, being avascular, show a complete absence of perfusion[100-102].

Despite the invaluable role of echocardiography and other imaging modalities, histopathological examination is the gold standard test for confirmation of the diagnosis of cardiac myxomas. A recently published study from Korea shows that out of 265 cases with an echocardiographic diagnosis of cardiac myxomas, 174 (65.7%) were surgically confirmed as myxomas. Compared with cardiac myxomas, other tumours were smaller and more frequently found in non-atrial sites[103].

ECG

ECG findings are nonspecific. Atrial enlargement or ventricular hypertrophy may be present. In contrast to the findings in mitral valve disease, atrial fibrillation is uncommon[6].

Other imaging modalities

Chest skiagram has a limited role. Occasionally, it can present features of mitral stenosis, *e.g.*, straightening of the left cardiac border and double contour of the right cardiac border and only rarely tumour calcification. Signs of pulmonary hypertension may be present.

Magnetic resonance imaging provides helpful information about the myxoma size, shape, surface characteristics and even its mobility on cine magnetic resonance gradient echo. The most frequent presentation is a mass isointense at T1-weighted and hyperintense at T2-weighted imaging with foci of hypointensity at one or two of these sequences[104]. Also, tissue characteristics can be used to differentiate a tumour from a thrombus.

CT scanning, generally, is not useful for the diagnosis of cardiac myxomas because it cannot reliably differentiate between myxomas and thrombi[105]. Typically, myxomas appear homogenous and isodense or as a slightly hypodense mass on non-contrast CT scanning, which does not show enhancement after iodinated contrast injection[106]. However, CT is the preferred technique to detect calcification, which is encountered in 10%–30% of cases[106,107].

Fluorodeoxyglucose positron emission tomography scanning is not typically indicated in the evaluation for myxoma[108].

Angiocardiography

Angiocardiography is seldom used for diagnosis of cardiac myxomas because of availability of non-invasive investigation modalities especially echocardiography. Also, manipulation of a catheter during angiocardiography carries a high risk of embolisation of tumour fragments[109,110]. In angiocardiography, cardiac myxomas typically appear as filling defects. In cases of left atrial myxoma, the levophase of a pulmonary angiogram may outline a radiolucent mass within the left atrium.

Genetic testing

Genetic testing for mutations in the *PRKAR1A* gene is increasingly used for diagnostic certainty of Carney complex.

Haematological tests

Erythrocyte sedimentation rate and C-reactive protein are generally elevated. Anaemia may be present. IL-6 rises especially when constitutional symptoms dominate.

TREATMENT

Cardiac myxoma needs surgical excision often on an emergency basis. This is to reduce the risk of embolisation of the tumour. Surgery is otherwise simple. The root of the stalk and the full thickness of the adjacent interatrial septum is excised, and the consequent atrial septal defect is closed accordingly. Data published over the past decades show excellent overall outcomes in operative mortality, short- and long-term survival and tumour recurrence[4,101-118]. Surgical excision of 23 myxomas in Turkey between 2010 and 2017 showed excellent outcomes with no early or late mortality[112]. A 16-year single centre study from China reported no need for secondary surgery in 97.4% ± 2.5% of cases after 10 years. Overall, the actuarial survival was 98.4% ± 1.6% at 5 years and 96.0% ± 2.8% at 10 years[113].

A similar encouraging outcome was observed in Italy; surgical excision of 98 cardiac myxomas between 1990 and 2007 showed 3% operative mortality. Actuarial survival was 98%, 98% and 89% at 5, 10 and 15 years, respectively. There was only one recurrence 68 mo after the first surgery[115].

In a smaller series of 18 patients treated surgically over 5 years in the United Kingdom, no death occurred within 30 d post-procedure[116]. Follow-up of surgical treatment of cardiac myxomas in Germany showed no in-hospital deaths. Out of 57 patients, 52 were alive at a median follow-up of 7.5 years[117]. Between 2002 and 2008, 34 cardiac myxomas were operated on in a single centre in Pakistan; 32 patients survived the surgery, 2 patients died over a median follow-up of 34 mo, and 1 patient had recurrence after 27 mo[118]. Twenty-four years of experience in 49 patients from Austria revealed relatively low early mortality of 2.0% and late mortality of 6.1%. The long-term prognosis was excellent, with an actuarial survival rate of 0.74. The rate of reoperations was low, with 2.0% after 24 years[4]. In a recently published small study from Bangladesh, all 20 patients with cardiac myxoma survived the surgery, and 1 patient presented with recurrence 28 mo after the surgery[111]. In recent years, cardiac myxomas have been excised successfully by minimally invasive surgery with or without robotic assistance[119-122]. Robotic surgery has been associated with early restoration of normal quality of life and early return to employment[121].

Utmost caution is warranted during surgical excision of cardiac myxomas because of their potential for embolisation peroperatively[74].

FAMILIAL CARDIAC MYXOMAS

Familial cardiac myxoma is rare and tend to form a syndrome, *e.g.*, Carney complex. They can usually be distinguished from the sporadic forms by the presentation at a younger age, the unusual location and multicentricity of the lesions and the presence of rare pathological conditions. In addition, a higher rate of recurrent lesions is usually associated with the familial forms of this disease. Carney complex is a rare multiple neoplasia syndrome, characterised by pigmented lesions of the skin and mucosa, cardiac and extra-cardiac myxomatous tumours and multiple endocrine and non-endocrine neoplasms (Figure 3) [123,124]. It is inherited as an autosomal-dominant disorder in three-fourths of the cases. In the remaining one-fourth, it occurs sporadically as a result of a de novo genetic mutation[125]. The disease is caused by inactivating mutations or large deletions of the *PRKAR1A* gene located at 17q22–24 coding for the regulatory subunit type I alpha of protein kinase A (*PKA*) gene[126]. Myxomatous tumours also occur in the skin and breast. Lentigines, blue nevus and cutaneous myxoma are the common skin manifestations (Figure 3). Primary pigmented nodular adrenocortical disease and thyroid nodules are examples of endocrinopathies[127,128].

Table 1 Diagnostic criteria for Carney complex

Diagnostic criteria
Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
Myxoma (cutaneous and mucosal)[1]
Cardiac myxoma[1]
Breast myxomatosis[1] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
Primary pigmented nodular adrenocortical disease[1] or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test
Acromegaly due to growth hormone-producing adenoma[1]
Large cell calcifying Sertoli cell tumour[1] or characteristic calcification on testicular ultrasonography
Thyroid carcinoma[1] or multiple, hypoechoic nodules on thyroid ultrasonography, in a young patient
Psammomatous melanotic schwannoma[1]
Blue nevus, epithelioid blue nevus (multiple)[1]
Breast ductal adenoma (multiple)[1]
Osteochondromyxoma[1]
Supplemental criteria:
Affected first-degree relative
Inactivating mutation of the*PRKAR1A* gene

[1]With histologic confirmation.

The Carney complex is diagnosed by the diagnostic criteria defined by Stratakis *et al*[124] (Table 1). Making the diagnosis, required either: (1) Two of the twelve manifestations of the disease listed; or (2) One of the twelve manifestations and one of the supplemental criteria. Genetic testing for mutations in the *PRKAR1A* gene confirms the diagnosis. For management, cardiac myxoma needs surgical excision. Primary pigmented nodular adrenocortical disease and pituitary adenomas are managed surgically, or the latter can be managed with somatostatin analogues[129,130]. Prognosis is good at present; however, lifelong follow-up is indicated[126].

CONCLUSION

Cardiac myxomas are the commonest neoplasm of the heart. They are primarily sporadic but may be familial as Carney complex. Though histologically benign, myxomas are prone to cause intracardiac obstruction and embolisation. Associated constitutional features may mimic inflammatory and connective tissue disorders creating diagnostic dilemmas. Echocardiography is a versatile tool for making the diagnosis and choosing the optimum management strategy. Surgery is the mainstay of treatment with an excellent prognosis. Long-term follow-up is often needed to look for recurrence. Physicians should have appropriate preparedness to diagnose this uncommon entity. Only timely diagnosis and prompt surgery can reduce the morbidity and mortality of cardiac myxoma patients.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

GRK5 is an essential co-repressor of the cardiac mineralocorticoid receptor and is selectively induced by finerenone

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Abstract

BACKGROUND

In the heart, aldosterone (Aldo) binds the mineralocorticoid receptor (MR) to exert damaging, adverse remodeling-promoting effects. We recently showed that G protein-coupled receptor-kinase (GRK)-5 blocks the cardiac MR by directly phosphorylating it, thereby repressing its transcriptional activity. MR antagonist (MRA) drugs block the cardiac MR reducing morbidity and mortality of advanced human heart failure. Non-steroidal MRAs, such as finerenone, may provide better cardio-protection against Aldo than classic, steroidal MRAs, like spironolactone and eplerenone.

AIM

To investigate potential differences between finerenone and eplerenone at engaging GRK5-dependent cardiac MR phosphorylation and subsequent blockade.

METHODS

We used H9c2 cardiomyocytes, which endogenously express the MR and GRK5.

RESULTS

GRK5 phosphorylates the MR in H9c2 cardiomyocytes in response to finerenone but not to eplerenone. Unlike eplerenone, finerenone alone potently and efficiently suppresses cardiac MR transcriptional activity, thus displaying inverse agonism. GRK5 is necessary for finerenone's inverse agonism, since GRK5 genetic deletion renders finerenone incapable of blocking cardiac MR transcriptional activity. Eplerenone alone does not fully suppress cardiac MR basal activity regardless of GRK5 expression levels. Finally, GRK5 is necessary for the anti-

apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against Aldo, as well as for the higher efficacy and potency of finerenone at blocking Aldo-induced apoptosis, oxidative stress, and fibrosis.

CONCLUSION

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR inhibition, which underlies, at least in part, its higher potency and efficacy, compared to eplerenone, as an MRA in the heart. GRK5 acts as a co-repressor of the cardiac MR and is essential for efficient MR antagonism in the myocardium

Key Words: Aldosterone; Cardiac myocyte; Finerenone; G protein-coupled receptor kinase-5; Mineralocorticoid receptor antagonist; Signal transduction

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Core Tip: G protein-coupled receptor-kinase (GRK)-5 blocks the cardiac actions of aldosterone *via* phosphorylation of the mineralocorticoid receptor (MR). We show here that the non-steroidal MR antagonist (MRA) finerenone may provide better cardio-protection against aldosterone than classic, steroidal MRAs, like eplerenone, thanks to induction of GRK5's phosphorylation and subsequent blockade of cardiac MR. GRK5 is necessary for the anti-apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against aldosterone but also for the higher efficacy/potency of the former drug at producing all these effects in cardiomyocytes. Thus, GRK5 acts as a co-repressor of the cardiac MR and is essential for efficient MR antagonism in the myocardium.

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INTRODUCTION

Aldosterone (Aldo) is one of several cardio-toxic hormones, whose elevated circulating levels significantly confound and aggravate heart disease, including hypertension and chronic heart failure (CHF)[1-4]. The mineralocorticoid receptor (MR), a cytosolic transcription factor that, upon activation, translocates to the nucleus to activate gene transcription, is the main receptor mediating Aldo's adverse remodeling effects in the failing heart[1-5]. GRK2 and GRK5 are the most abundant cardiac G protein-coupled receptor (GPCR)-kinase (GRK) isoforms. Both phosphorylate GPCRs but also non-GPCR substrates[6-10]. We recently showed that GRK5 blocks the cardio-toxic MR-dependent effects of aldosterone in the heart by directly phosphorylating the cardiac MR and inhibiting its transcriptional activity[11].

MR antagonist (MRA) drugs are beneficial in human advanced CHF thanks to their blockade of the MR in various cardiovascular tissues, including in cardiomyocytes and cardiac fibroblasts[3,12]. Novel, non-steroidal MRAs, such as finerenone, may provide better cardio-protection against aldosterone's cardio-toxic actions than the classic steroidal MRAs, such as sprironolactone and eplerenone[13,14]. Indeed, finerenone was recently shown to be a more potent and efficacious inverse agonist at the MR, compared to eplerenone, in terms of cardiac fibrosis/adverse remodeling attenuation[15]. This prompted us to investigate the effects of these two MRAs on GRK5-dependent cardiac MR phosphorylation and subsequent suppression, in an effort to delineate potential molecular mechanisms underlying their differences in cardiac MR blocking efficacy. Indeed, we found that finerenone, but not eplerenone, promotes the inhibitory action of GRK5 on cardiac MR, which may underlie finerenone's significantly greater efficacy/potency as an inverse agonist at this receptor. Moreover, GRK5 is necessary for both MRA drugs' cardioprotective actions against Aldo in cardiac myocytes.

MATERIALS AND METHODS

All methods were carried out in accordance with the relevant guidelines and regulations.

Materials

All drugs/chemicals were from Sigma-Aldrich (St. Louis, MO, United States), except for finerenone (BAY94-8862) which was purchased from MedKoo Biosciences, Inc. (Cat. #319698, Morrisville, NC, United States).

Cell culture, viruses, and transfections

The H9c2 rat cardiomyoblast cell line was purchased from American Type Culture Collection (Manassas, VA, United States) and cultured as previously described[11,16-18]. Recombinant lentiviruses encoding for wild-type full-length GRK5 or for empty vector (control) (OriGene Technologies, Rockville, MD, United States) were propagated and purified *via* CsCl density gradient ultracentrifugation, as described previously[11,19]. For CRISPR/Cas9-mediated *GRK5* gene deletion, a gRNA sequence was custom-synthesized by Sigma-Aldrich (target ID: RN0000391809, target sequence: 5′-GTGGTT-TGAATTTATGCGG-3′) and incorporated into a lentiviral vector (Sigma-Aldrich). Along with negative control CRISPR lentiviral particles (CNCV, Cat #CRISPR12V-1EA, Sigma-Aldrich), this lentivirus was also propagated and purified through cesium chloride density gradient ultracentrifugation.

Immunoprecipitation/western blotting

Cell extracts were prepared, as described previously[11,20], in a 20-mmol/L Tris pH 7.4 buffer containing 137 mmol/L NaCl, 1% Nonidet P-40, 20% glycerol, 10 mmol/L phenylmethylsulfonyl-fluoride (PMSF), 1 mmol/L Na_3VO_4, 10 mmol/L NaF, 2.5 μg/mL aprotinin, and 2.5 μg/mL leupeptin. Protein concentration was determined (Pierce BCA Protein Assay Kit, Thermo Scientific, Waltham, MA, United States), and equal amounts of protein per sample were used for Immunoprecipitation (IP) or western blotting. MR was immunoprecipitated by overnight incubation of extracts with an anti-MR antibody (#ab62532; Abcam, Cambridge, MA, United States), attached to Protein A/G-Sepharose beads (Sigma-Aldrich). The IPs were then subjected to immunoblotting for GRK5 (#sc-565; Santa Cruz Biotechnology, Santa Cruz, CA, United States) or for phosphoserine (#AB1603; Millipore-Sigma, Burlington, MA, United States) to measure the pSer content of the immunoprecipitated MR. Finally, an anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH) antibody (#sc-25778; Santa Cruz Biotechnology) was used to control for protein loading. All immunoblots were revealed by enhanced chemiluminescence (ECL, Life Technologies, Grand Island, NY, United States) and visualized in the FluorChem E Digital Darkroom (Protein Simple, San Jose, CA, United States), as described previously[21].

Luciferase reporter activity assay

Luciferase reporter activity assay was performed, as described previously, by transfecting the cells with the LightSwitch™ luciferase reporter gene vector under the influence of the MR promoter (Active Motif, Inc., Carlsbad, CA, United States)[11]. The measurements were done the next day with the manufacturer's assay kit and according to the manufacturer's instructions.

TUNEL

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay to measure apoptotic cell death was done as described[22]. Briefly, cells were fixed with 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5-μm thickness. DNA fragmentation was detected in situ in deparaffinized sections using the ApopTag peroxidase *in situ* apoptosis detection Kit (Millipore-Sigma) and according to the manufacturer's instructions. The total number of nuclei was determined by manual counting of 4′,6′-diamidino-2-phenylindole (DAPI)-stained nuclei in six random fields per section. All terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL)-positive nuclei were counted in each section.

Real-time PCR

Real-time PCR for rat plasminogen activator inhibitor (PAI)-1 and rat fibronectin mRNA levels in total RNA isolated from cells was done as described previously[16]. Briefly, quantitative real-time PCR was performed using a MyIQ Single-Color Real-Time PCR detection system (Bio-Rad Laboratories, Hercules, CA, United States) using SYBR Green Supermix (Bio-Rad) and 100 nmol/L of gene-specific oligonucleotides. Quantification of mRNA included normalization to 18s rRNA levels. No bands were seen in control reactions in the absence of reverse transcriptase. Primer pairs used were: 5′-TTCCTCCACAGC-CATTCTAGTCT-3′ and 5′-GAAAGGATCGGTCTAAAACCATCTC-3′ for PAI-1; 5′-CGAGGTGACA-GAGACCACAA-3′ and 5′-CTGGAGTCAAGCCAGACACA-3′ for fibronectin; and 5′-TCGATGCTCT-TAGCTGAGTG-3′ and 5′-TGATCGTCTTCGAACCTCC-3′ for 18S rRNA.

Oxidative stress assay

To determine reactive oxygen species (ROS) production, the 2′,7′-dichlorofluorescein diacetate (DCFDA) dye-based assay kit from Molecular Probes (Cat. #C13293; Eugene, OR, United States) was used and the measurements were done according to manufacturer's instructions and as previously described[11]. Briefly, cell extracts were incubated with 2 μmol/L DCFDA for 20 min and ROS production was

monitored by determining the fluorescence intensity using a fluorescent plate reader in which excitation and emission wavelengths were set at 495 and 520 nm, respectively. The fluorescence OD values obtained were normalized with protein determination and expressed as % of the values obtained upon 100 nmol/L Aldo treatment (1 mmol/L DMSO was used as vehicle treatment).

Statistical analysis

Student's *t* test and one- or two-way ANOVA with Bonferroni test were used for statistical comparisons, unless otherwise indicated. For multiple group analyses, Dunnett's test with SAS version 9 software (Cary, NC, United States) was also used. A P value of < 0.05 indicated statistical significance.

RESULTS

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR phosphorylation

We recently reported that GRK5 selectively phosphorylates and inhibits the cardiac MR[11]. Based also on recent evidence suggesting greater potency for finerenone, compared to eplerenone, at inhibiting the cardiac MR and its downstream fibrosis[15], we hypothesized, in the present study, that the higher efficacy/potency of finerenone over eplerenone might be due (at least in part) to differences in modulation of the GRK5 inhibitory action on the cardiac MR. Thus, in a first series of experiments, we overexpressed or knocked out (*via* CRISPR) GRK5 in H9c2 cardiac myocytes (Figure 1A), which endogenously express both GRK5 and MR[11,23], and checked for the effects of the two MRA drugs on MR serine phosphorylation. GRK5, being a Ser/Thr kinase, likely phosphorylates multiple Ser and Thr residues of the MR protein, with phosphorylations of Ser601 and Ser843 (in the human orthologue sequence), in particular, resulting in significant functional inhibition of the MR, courtesy of cytosolic retention and transcriptional activity suppression, respectively[24,25]. After preliminary concentration-response experiments (not shown), and based on the associated literature, we chose a 10 mmol/L concentration for both drugs throughout the experiments of our study, as this concentration (10 mmol/L) is quite close to both drugs' effective IC_{50} values[12,15]. As shown in Figure 1B and C, finerenone led to much higher phosphorylation (pSer content) of the MR than eplerenone did in control H9c2 cardiomyocytes (mock virus-EV lanes). This finerenone-induced MR phosphorylation was significantly enhanced upon GRK5 overexpression but essentially abrogated in GRK5-depleted H9c2 cardiomyocytes (Figure 1B and C). Notably, eplerenone essentially failed to elicit any appreciable MR Ser phosphorylation in H9c2 cardiomyocytes (Figure 1B and C), irrespective of GRK5 expression levels [eplerenone-induced phosphorylation: 1.2 ± 0.25-fold of vehicle in EV cells; 1.23 ± 0.27-fold of vehicle in GRK5-OE cells; 0.6 ± 0.55-fold of vehicle in GRK5-KO cells; *i.e.*, non-significant *vs* vehicle, in all three clones at $P = 0.05$ ($n = 3$); Figure 1C]. Although we cannot account for the potential of some extent of Thr phosphorylation of the MR induced by the two drugs, these results strongly suggest that only finerenone (not eplerenone) induces GRK5-mediated phosphorylation of the MR in H9c2 cardiac myocytes.

GRK5 is essential for finerenone's inverse agonism at the cardiac MR

Since GRK5-induced phosphorylation translates into transcriptional repression of the cardiac MR[11], we next examined the impact of the finerenone-induced, GRK5-mediated MR phosphorylation on the transcriptional activity of the receptor. In contrast with eplerenone, finerenone lacks agonist activity at the MR in control (CNCV) H9c2 cardiomyocytes, *i.e.*, no increase in MR basal transcriptional activity (in the absence of Aldo) is observed with finerenone (Figure 2). In the absence of GRK5 however, finerenone loses the ability to keep the MR transcriptionally inactive, *i.e.*, the MR displays significant basal activity in GRK5-KO H9c2 cardiomyocytes (Figure 2). Upon GRK5 overexpression, this picture is reversed, *i.e.*, finerenone acts as potent inverse agonist at the MR, markedly suppressing MR basal transcriptional activity in GRK5-overexpressing (GRK5-OE) cardiomyocytes (Figure 2). In contrast, eplerenone allows for substantial MR basal transcriptional activity, regardless of GRK5 expression levels (Figure 2). Taken together, these results indicate that GRK5 is essential for finerenone's inverse agonism at the cardiac MR, while eplerenone is essentially a partial agonist (mixed agonist/antagonist) at this receptor in the heart, a finding consistent with the literature[12,15]. GRK5 is unable to affect eplerenone's actions on the cardiac MR, probably because this MRA agent cannot induce the inhibitory phosphorylation of this receptor by GRK5 in cardiac myocytes (see above, Figure 1).

GRK5 is essential for MRA-dependent antagonism of Aldo-induced cardiac apoptosis and oxidative stress and underlies finerenone's advantage over eplerenone toward these effects

Next, we compared the cardio-protective efficacies of the two MRA drugs against the deleterious actions of Aldo. Finerenone was much more effective than eplerenone at suppressing Aldo-induced apoptosis (Figure 3A) and oxidative stress (Figure 3B), in control myocytes. However, upon GRK5 genetic deletion, both MRAs failed completely to block these two cardiac adverse remodeling-promoting Aldo effects (Figures 3A and B). This strongly suggests that GRK5 is essential for the anti-

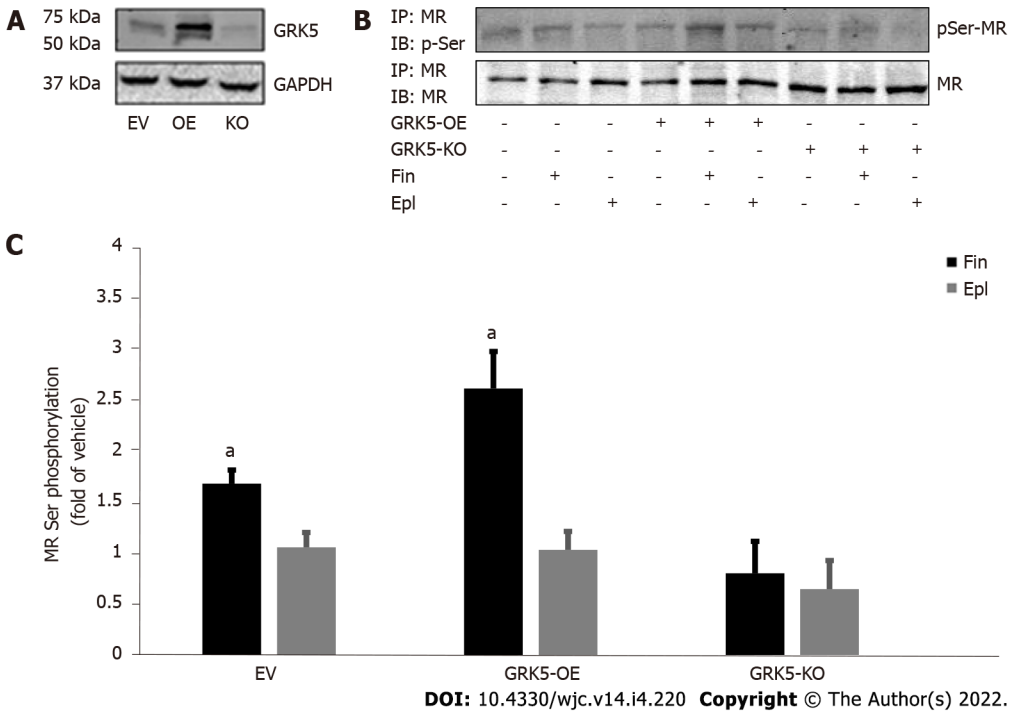


Figure 1 G protein-coupled receptor-kinase 5 phosphorylates the cardiac mineralocorticoid receptor in response to finerenone but not to eplerenone. A: Western blotting to confirm G protein-coupled receptor-kinase (GRK)-5 overexpression (OE) with a wild type GRK5-encoding lentivirus or deletion (KO) *via* a GRK5-targeting CRISPR lentivirus in H9c2 cardiomyocytes. GAPDH blotting is also shown as loading control; B, C: Western blotting for the phosphoserine content of the mineralocorticoid receptor in response to 10 mmol/L finerenone (Fin) or 10 mmol/L eplerenone (Epl) in GRK5-overexpressing (GRK5-OE) or in GRK5-KO or in control, empty virus (EV)-infected H9c2 cells. Representative blots are shown in (B) and the densitometric quantitation of three independent experiments in (C). $^{a}P < 0.05$, *vs* Epl; $n = 3$ independent experiments performed in duplicate per cell clone/treatment. EV: Empty vector mock virus-transfected (control) cells; IP: Immunoprecipitation; IB: Immunoblotting.

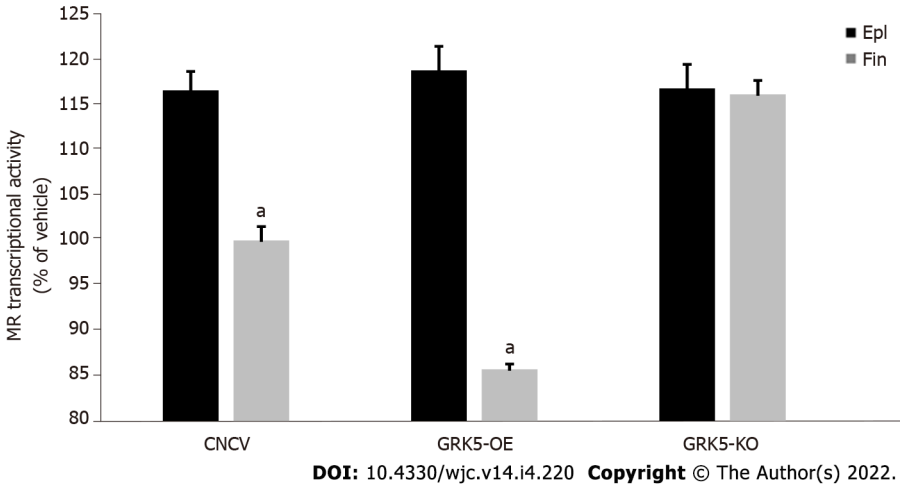
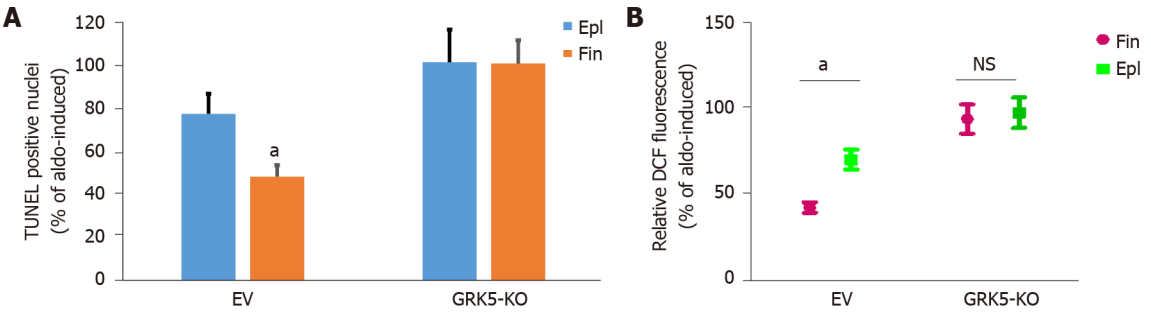


Figure 2 G protein-coupled receptor-kinase 5 inhibits the cardiac mineralocorticoid receptor in response to finerenone but not to eplerenone. Transcriptional activity of the mineralocorticoid receptor (MR) in response to either 10 mmol/L eplerenone or 10 mmol/L finerenone in H9c2 cardiomyocytes overexpressing G protein-coupled receptor-kinase (GRK)-5 or having GRK5 genetically deleted *via* CRISPR (GRK5-KO). Neither agent was able to suppress MR basal transcriptional activity in GRK5-KO cells. $^{a}P < 0.05$, *vs* eplerenone; $n = 5$ independent measurements per cell clone/treatment performed in triplicate. CNCV: CRISPR negative control virus-infected control cells; GRK5-OE: G protein-coupled receptor-kinase 5-overexpressing.

apoptotic and anti-oxidative effects of MRAs against Aldo in the heart, as well as for the better cardioprotective efficacy of finerenone *vs* eplerenone against Aldo.

GRK5 is essential for MRA-dependent anti-fibrotic effects in the heart and for finerenone's advantage over eplerenone towards this effect

In addition to apoptosis and oxidative stress, we compared the two MRAs in terms of Aldo-induced



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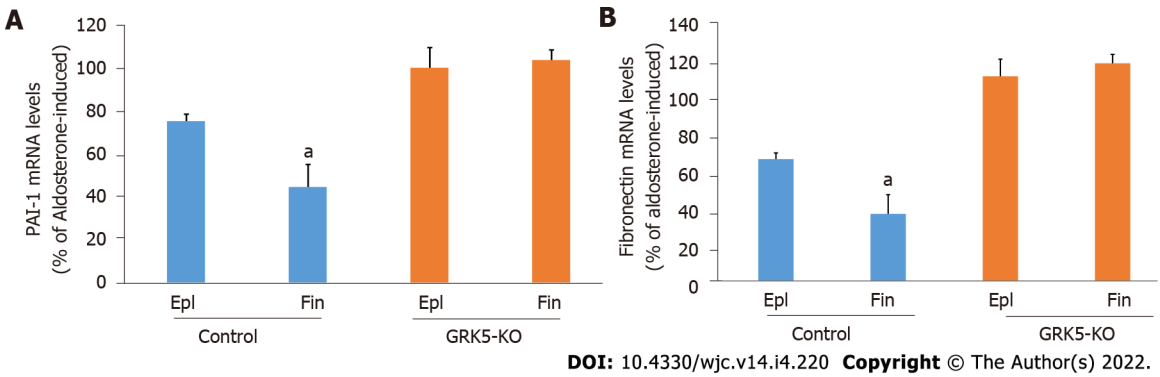
Figure 3 Comparison of anti-apoptotic and anti-oxidative efficacies of finerenone *vs* eplerenone in aldosterone-treated cardiomyocytes in the presence or absence of G protein-coupled receptor-kinase 5. A: Apoptotic cell death in control, empty vector (mock) virus-infected (EV) cells or in cells having G protein-coupled receptor-kinase (GRK)-5 genetically (CRISPR lentivirus-mediated) deleted (GRK5-KO) and treated with 100 nmol/L aldosterone (Aldo) alone or in the presence of 10 mmol/L eplerenone (Epl) or 10 mmol/L finerenone for 24 h. $^{a}P < 0.05$, *vs* Epl; $n = 4$ independent experiments per transfection/treatment. Essentially no inhibition of Aldo-induced apoptosis could be detected with either drug in GRK5-KO cells; B: ROS generation in these cells, as measured *via* the DCF assay. $^{a}P < 0.05$. Not significant at $P = 0.05$; $n = 4$ independent experiments per transfection/treatment. EV: Empty virus; Epl: Eplerenone; Fin: Finerenone; NS: Not significant.

fibrosis inhibition in cardiac myocytes. Assessment of Aldo-dependent mRNA induction of two major pro-fibrotic stimuli, PAI-1 and fibronectin, both of which are immediate/early MR-responsive genes[1,3,16], revealed that finerenone was more effective than eplerenone at suppressing both PAI-1 (Figure 4A) and fibronectin (Figure 4B) mRNA inductions by Aldo in control cells. Again however, neither drug was effective at all when GRK5 was absent (Figure 4A and B, compare with GRK5-KO bars). Thus, GRK5 is essential also for the anti-fibrotic effects of MRAs in cardiac myocytes.

The MR has long been established as an important molecular culprit in heart disease progression[1-5], including a recent study in transgenic mice showing that, unlike its closely related glucocorticoid receptor, the MR promotes cardiac dysfunction even in the absence of a cardiac insult or injury[26]. Indeed, the well-documented deleterious effects of the cardiac MR have provided the pharmacological basis for the use of MRA drugs in advanced stage human CHF and other heart diseases[1-5,27,28]. The MRA drug class, which began with the approval and marketing of spironolactone more than 60 years ago, now encompasses several agents, with some already in clinical use and some in clinical trials. The MRAs are broadly divided to traditional, steroidal MRAs, like spironolactone and eplerenone currently in clinical use, and later generation, non-steroidal agents. Among the latter is finerenone (formerly BAY 94-8862), a third generation, non-steroidal, dihydropyridine-derived MRA currently in phase III clinical trials[3,12].

Despite being very potent and effective aldosterone antagonists with salutary effects in the heart and kidneys, the currently available steroidal MRAs are hampered by several limiting side effects, most prominent of which are hyperkalemia, renal function deterioration, and gynecomastia. These are generally thought to be due to their binding to other types of steroid receptors (*e.g.*, estrogen receptor, glucocorticoid receptor, *etc.*) exactly because of their steroidal structure[3,12,29]. Thus, non-steroidal MRAs have been developed, currently headlined by finerenone. Finerenone has shown advantageous pharmacological and therapeutic profiles, compared to the steroidal MRAs. It has demonstrated improved therapeutic properties in heart failure animal models in head-to-head comparisons with eplerenone[12,15] and leads to bigger improvements in HFrEF (heart failure with reduced ejection fraction) confounded by diabetes or chronic kidney disease[12,14]. In addition to its much higher selectivity for the MR over other steroid receptors, finerenone is also at least one log scale more potent at MR antagonism than eplerenone and spironolactone, both of which are competitive MR antagonists[3]. Furthermore, finerenone displays inverse agonist activity at the MR, whereas the steroidal MRAs are only partial MR antagonists[3,12]. This means that, depending on the activity status of the MR, spironolactone and eplerenone may actually promote the activity of the MR rather than inhibiting it[12,14,15]. In other words, eplerenone inhibits the MR when the receptor is activated by Aldo but it may actually promote the activity of the MR when bound alone to the receptor (in the absence of Aldo). Finerenone, thanks to the non-steroidal nature of its structure, appears to be devoid of any agonist activity at the MR and thus, has strong potential to provide better cardiovascular and renal outcomes, especially in diseases severely affected by hyperaldosteronism.

One of the most important parameters affecting the selectivity of a particular MRA for the MR *vs* other steroid receptors, as well as tissue specificity for MR antagonism (inhibition of the cardiac MR *vs* inhibition of the MR in other tissues), is the identity/identities of the receptor's co-factors activated or repressed by the MRA agent, which ultimately affects the MRA drug's potency and efficacy[1,3,15,25]. In other words, how good a particular MRA is at blocking the cardiac MR depends strongly on which co-activators of the MR the drug inhibits and/or which co-repressors of the MR it activates inside the cardiac myocyte[3]. Indeed, a recent study in mice reported much higher potency and inverse agonism



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Figure 4 Comparison of the anti-fibrotic efficacies of finerenone *vs* eplerenone in aldosterone-treated cardiomyocytes in the presence or absence of G protein-coupled receptor-kinase 5. mRNA levels of PAI-1 (A) and fibronectin (B), in response to a 2-h-long treatment of 100 nmol/L aldosterone in the presence of either 10 mmol/L eplerenone (Epl) or 10 mmol/L finerenone in control (mock, empty vector CRISPR lentivirus-infected) or in G protein-coupled receptor-kinase (GRK)-5-KO (rat GRK5-targeting CRISPR lentivirus-infected) cells. 18S rRNA levels were used for normalization of the results. [a]$P < 0.05$, *vs* Epl; $n = 3$ independent measurements per cell clone/treatment performed in triplicate. Epl: Eplerenone; Fin: Finerenone.

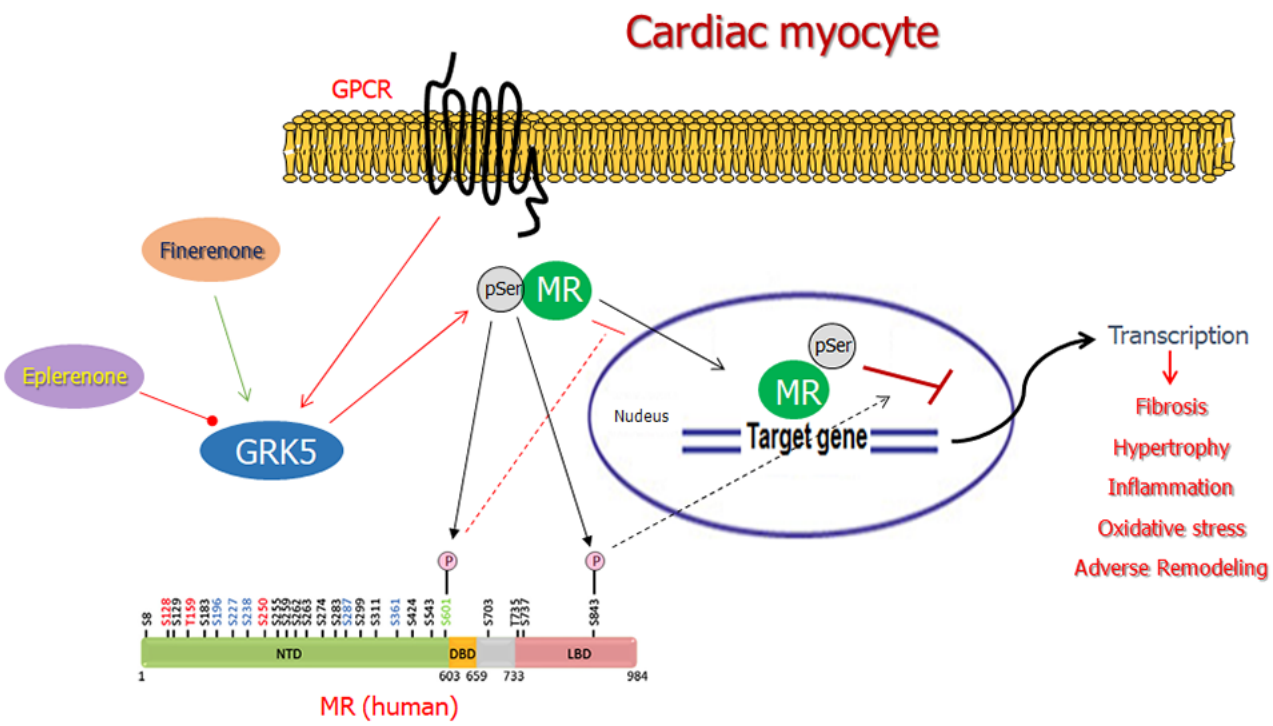
of finerenone, relative to eplerenone, in terms of cardiac fibrosis suppression and suggested that the pharmacological difference between these two MRAs was probably due to differential cardiac MR co-factor regulation/engagement[15]. We recently uncovered that GRK5 is an important co-repressor of the cardiac MR, *via* its direct binding to, and phosphorylation of the MR that results in cytosolic retention of the phosphorylated receptor and thus, MR transcriptional repression[11]. Our present data strongly suggest that finerenone selectively activates this kinase in cardiac myocytes to potently inhibit/repress the cardiac MR. In contrast, eplerenone is incapable of this action (GRK5 activation) and thus, is a much weaker MR antagonist in the myocardium.

There are a few very important questions emanating from our present work that await delineation in future studies. First, does finerenone activate GRK5 to suppress MR activity only in the heart or in other tissues, as well (*e.g.*, kidneys)? Another critical question is whether this property is shared by other non-steroidal MRAs or it is specific to finerenone. Finally, there is also the obvious mechanistic question of how exactly finerenone, not known to be a GPCR agonist, induces GRK5, normally activated by a GPCR, such as the b_2-adrenergic receptor (Figure 5)[8,11], to phosphorylate and inhibit the MR in the cytosol of a cardiac myocyte. Nevertheless, these salient questions will be the focus of our future investigations, along with our already ongoing efforts to map the specific phosphorylation sites of GRK5 on the human MR protein and to characterize the functional impact for the receptor of each one of them.

In summary, our present study reinforces the emerging and therapeutically very intriguing notion that GRK5, acting as a cardiac MR co-repressor in this instance, may actually be beneficial in the myocardium[11,31-33], contrary to its counterpart GRK2 that is generally considered deleterious in the heart[7,10]. Importantly, we have identified GRK5 as a potential co-factor of the cardiac MR that is differentially regulated by finerenone and eplerenone, which may underlie the higher potency/efficacy (and inverse agonism) of finerenone at the MR. To our knowledge, cardiac GRK5 is the first such MR co-factor to be shown as differentially modulated/stimulated among different individual MRA drugs. Finally, from the therapeutic standpoint, we provide evidence that GRK5 is indispensable for MRAs' cardioprotective actions against Aldo (*e.g.*, anti-apoptosis, anti-oxidant action, anti-fibrosis) and, importantly, this applies to both steroidal (eplerenone) and non-steroidal (finerenone) MRA agents alike.

DISCUSSION

In the present study, we report that finerenone is a more potent and efficacious cardiac MR blocker than eplerenone, thanks, at least in part, to stimulation of GRK5-dependent cardiac MR phosphorylation, which eplerenone is incapable of inducing (Figure 5). This non-canonical effect of GRK5 on the cardiac MR is essential for efficient blockade of Aldo's deleterious actions in the heart, such as apoptosis, oxidative stress, fibrosis, and probably other adverse remodeling-associated effects (Figure 5). Therefore, GRK5-dependent inhibitory phosphorylation is a key molecular mechanism for cardiac MR inverse agonism and needs to be considered in the design and development of novel, more effective MRA drugs for heart disease (*e.g.*, CHF, hypertension, renal insufficiency, *etc.*) treatment.



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Figure 5 Schematic illustration of the differential effects of finerenone *vs* eplerenone on G protein-coupled receptor-kinase 5-dependent repression of the cardiac mineralocorticoid receptor. Finerenone, unlike eplerenone, stimulates G protein-coupled receptor-kinase (GRK)-5 to phosphorylate the mineralocorticoid receptor (MR). The two main (putative) GRK5 phosphorylation sites on the human MR protein, Ser601 and Ser843, are highlighted, along with their functional impacts for the MR (pSer601 blocks nuclear translocation; pSer843 suppresses Aldo-induced transcriptional activity)[24,30]. GPCR: G protein-coupled receptor; NTD: N-terminal domain; DBD: DNA-binding domain; LBD: Ligand-binding domain; pSer: Phosphoserine. See text for more details and for all other molecular acronyms' descriptions.

CONCLUSION

Cardiac GRK5 is an essential mediator of the general cardio-protection afforded by MRA drugs against the cardio-toxic effects of excess Aldo, *e.g.*, during CHF and other chronic cardiac diseases. This is due to the inhibitory phosphorylation GRK5 performs on the cardiac MR. This non-canonical (given the substrate is not a GPCR), co-repressor effect of GRK5 on cardiac MR is also (at least partly) responsible for the inverse agonism properties of finerenone at this receptor that bestow this non-steroidal MRA with superior potency and efficacy, compared to eplerenone, at protecting the heart against the damaging effects of Aldo. Finally, since GRK5 is a co-repressor of the MR, at least in the myocardium, its stimulation (or potentiation) should be a desired property of every novel MRA drug designed and developed for improved cardiovascular pharmacotherapy.

ARTICLE HIGHLIGHTS

Research background

Different mineralocorticoid receptor (MR) antagonists (MRAs) have different potencies at the cardiac MR blockade. G protein-coupled receptor kinase (GRK)-5 phosphorylates the MR in the heart and inhibits its transcriptional activity.

Research motivation

The authors wanted to compare two different MRAs, eplerenone and finerenone, in their ability to stimulate GRK5-dependent MR inhibition in cardiac myocytes.

Research objectives

The authors sought to identify a mechanism for the increased effectiveness of finerenone over eplerenone at blocking cardiac MR.

Research methods

The authors studied MR phosphorylation and activity in cardiomyocytes in response to eplerenone or finerenone treatments.

Research results

GRK5 is necessary for the anti-apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against Aldo, as well as for the higher efficacy and potency of finerenone at blocking Aldo-induced apoptosis, oxidative stress, and fibrosis.

Research conclusions

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR inhibition, which underlies, at least in part, its higher potency and efficacy, compared to eplerenone, as an MRA in the heart.

Research perspectives

GRK5 is an essential mediator of finerenone's effects on cardiac aldosterone antagonism.

FOOTNOTES

Author contributions: Pollard CM, Suster MS, Cora N, and Carbone AM performed all experiments and assisted with data analysis; Lymperopoulos A supervised the project, performed data analysis, provided funding for the study, and wrote the manuscript; and All authors have read and approved the manuscript.

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Conflict-of-interest statement: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Observational Study

Association of dissected ascending aorta diameter with preoperative adverse events in patients with acute type A aortic dissection

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Abstract

BACKGROUND

Acute type A aortic dissection (ATAAD) is a life-threatening disease associated with high morbidity and mortality.

AIM

To evaluate the diameter of dissected ascending aorta in patients diagnosed with ATAAD and whether the aortic diameter is associated with preoperative adverse events.

METHODS

A total of 108 patients diagnosed with ATAAD who underwent emergency operation under hypothermic circulatory arrest were enrolled in this study. Demographic characteristics and perioperative data were recorded. In all patients, preoperative chest and abdomen computed tomography (CT) scans were performed.

RESULTS

Median age of the patients was 61.5 (52.5-70.5) years and median body mass index (BMI) was 28.2 (25.1-32.6) cm^2. The number of female patients was 37 (25%). Median diameter of the ascending aorta was 5.0 (4.5-6) cm and 53.8% of the patients had an aortic diameter < 5.0 cm, while 32.3% of the patients had an aortic diameter of 4.5cm and 72.0% had an ascending aorta diameter < 5.5 cm. The diameter of the ascending aorta did not differ in patients with *vs* without preoperative adverse events: Preoperative neurological dysfunction (P = 0.53) and hemodynamic instability (P = 0.43). Median age of patients with preoperative hemodynamic instability was 65 (57.5-74) years, while it was 60 (51-68) years in patients without (P = 0.04)

CONCLUSION
Although current guidelines suggest replacing the ascending aorta with a diameter > 5.5 cm, most of the patients with ATAAD had an aortic diameter of less than 5.5 cm. The diameter of the ascending aorta in patients diagnose with ATAAD is not associated with preoperative adverse events.

Key Words: Acute; Aortic dissection; Type A; Ascending aorta; Diameter

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Core Tip: Do patients with an ascending aorta diameter < 5.5 cm undergo more aggressive surgery for prevention of acute type A aortic dissection (ATAAD)? Most of the patients (72.0%) with ATAAD had an ascending aorta diameter < 5.5 cm. An international taskforce should adapt the new data extracted from the most recent scientific evidence in the surgical treatment of the ascending aortic aneurysm.

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INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening condition with excessive mortality and morbidity if not operated, reaching approximately 50% during the first 24 h and 70%-90% days and weeks after diagnosis[1-3]. Emergency surgical correction with replacement of the ascending aorta with or without aortic arch, despite being the treatment of choice, also carries a significant mortality and morbidity burden. Nowadays, emergency surgical correction of ATAAD under hypothermic circulatory arrest remains the treatment of choice[4-6]. On the other hand, the mortality rate of patients who underwent ATAAD repair is high at approximately 15%-25%[7-9].

The most common clinical manifestation of thoracic aorta dissection is acute chest pain. Due to the much commoner incidence of acute coronary syndrome (ACS), pulmonary embolism (PE), and other thoracic pathology, accurate diagnosis is frequently hindered or delayed. The sudden and insidious onset of symptoms, the delay in diagnosis, and the time required to transport of patients to cardiac surgery centers for treatment negatively affect the outcomes of these patients[10-12]. Replacement of the ascending aorta in patients with an enlarged aortic diameter is considered as an option for preventing acute aortic dissection. Existing and current guidelines recommend replacing the ascending aorta if the size reaches 5.5 cm in patients without Marfan syndrome[6,13]. On the other hand, the exact threshold of aortic size (< 5.5 cm) for early (preventive) operation remains a grey zone in current indications and guidelines, because in most patients with acute aortic dissection, the maximum aortic diameter is approximately 5 cm or less[14-17].

The present study evaluated the diameter of dissected ascending aorta in patients diagnosed with ATAAD and whether the aortic diameter is associated with preoperative adverse events.

MATERIALS AND METHODS

Study population

The study period was 2010-2017. This retrospective study included 108 patients with ATAAD who underwent an emergency operation under hypothermic circulatory arrest with antegrade or retrograde cerebral perfusion. Patients with a known diagnosis of connective tissue disorder or Marfan syndrome or iatrogenic dissection were excluded. All demographic characteristics and perioperative data were recorded. In all patients, preoperative chest and abdomen computed tomography (CT) scans were performed. The ascending aorta diameter was calculated based on preoperative chest CT or CT angiography. The maximum diameter of the ascending aorta was defined as the diameter which included the true and false lumen of the ascending aorta. The method for measuring the maximum aortic diameter was double oblique short axis. All preoperative neurological dysfunctions (including temporary and permanent neurological dysfunctions) on admission were included in our database. Temporary neurological dysfunctions (TND) were defined if the patients had transient ischemic attack (TIA) or delirium or disorientation, while permanent neurological dysfunctions (PND) if the patients

were admitted to hospital with hemiplegia or paraplegia or coma. Preoperative hemodynamic instability was defined as preoperative cardiac arrest or systolic blood pressure (< 80 mmHg) despite inotropic support or preoperatively diagnosed cardiac tamponade with hemodynamic consequences. The study was approved by the hospital's institutional review board (546/30-04-2015).

Statistical analysis

Continuous variables are presented as the median (interquartile range), while categorical variables are presented as *n* (%). Normality of continuous variables was examined by Shapiro-Wilk test and Q-Q plot. Continuous variables were compared by Student's *t*-test for the normally distributed, while Mann-Whitney and Kruskal-Wallis tests for the non-normally distributed variables. Chi-square or Fisher's exact test was implemented for the rest variables (categorical variables). Correlation of ascending aorta diameter with continuous variables was evaluated by Spearman (r_s) or Pearson (r) correlation coefficient. Univariable linear regression model was used to identify the association of demographics and other factors with diameter of the ascending aorta. The effect size was expressed by linear regression coefficient ''β''. Binary univariable and multivariable logistic regression modeling was used to estimate the association of ascending aorta diameter with preoperative adverse events (neurological dysfunction and hemodynamic instability). Predictive ability is presented as odds ratio (OR). The Hosmer-Lemeshow goodness of fit test was performed for logistic regression analysis model. Confidence interval (CI) was set at 95% in all tests. Statistical significance was considered at $P < 0.05$. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, United States) was used in analysis.

RESULTS

Median age of the patients was 61.5 (52.5-70.5) years and median body mass index (BMI) was 28.2 (25.1-32.6) cm^2. Thirty-seven (25%) were female patients. Median diameter of the ascending aorta was 5.0 (4.5-6) cm and 53.8% of patients had an aortic diameter < 5.0 cm, while 32.3% of the patients had an aortic diameter of 4.5 cm. In addition, 72.0% of the patients had an ascending aorta diameter < 5.5 cm. Coexisting aortic regurgitation was recorded in 26.8% of the patients, while history of hypertension was observed in 86.1%. Other demographic characteristics and preoperative details are listed in Table 1.

We tested the correlation of aortic diameter with age, BMI, LVEF, D-dimer, and NT-proBNP. No correlation was detected between aortic diameter and age ($r = 0.13$, $P = 0.20$), BMI ($r = 0.05$, $P = 0.67$), LVEF ($r = 0.08$, $P = 0.47$), D-dimer ($r_s = -0.14$, $P = 0.31$), or NT-proBNP ($r_s = 0.19$, $P = 0.14$). No difference in ascending aorta diameters was observed between males *vs* females ($P = 0.83$), as well as between patients with *vs* without history of hypertension ($P = 0.87$) and smoking *vs* no smoking ($P = 0.90$). The BMI did not predict the diameter of the ascending aorta [β = 0.01, 95%CI: -0.05 to 0.08, $P = 0.68$]. Preoperative plasma creatinine was not associated with the diameter of the ascending aorta (β = 0.09, 95%CI: -0.19-0.36, $P = 0.53$).

The diameter of the ascending aorta did not differ in patients with *vs* without preoperative adverse events: Preoperative neurological dysfunction ($P = 0.53$) and hemodynamic instability ($P = 0.43$). In addition, univariable logistic regression analysis showed that aortic diameter did not predict the preoperative hemodynamic instability (OR = 1.2, 95%CI: 0.87-1.60, $P = 0.29$) or preoperative neurological dysfunction (OR = 1.0, 95%CI: 0.72-1.51, $P = 0.81$). Multivariable logistic regression analysis (adjusted for age, gender, and BMI) showed that aortic diameter did not predict preoperative neurological dysfunction (OR = 1.1, 95%CI: 0.68-1.74, $P = 0.70$) (Table 2). Furthermore, multivariable logistic regression analysis (adjusted for age, gender, BMI, and aortic diameter) revealed that only age predicted the preoperative hemodynamic instability (OR = 1.05, 95%CI: 1.01-1.11, $P = 0.02$), while diameter of the aorta did not (OR=1.1, 95%CI: 0.68-1.57, $P = 0.86$) (Table 3). Median age of the patients with preoperative hemodynamic instability was 65 (57.5-74) years, while it was 60 (51-68) years in those without ($P = 0.04$) (Figure 1). In conclusion, our analysis showed that no difference in dissected ascending aorta diameter was observed between patients who died in hospital *vs* who did not ($P = 0.75$). In addition, the diameter of dissected ascending aorta was not correlated with postoperative ICU or hospital stay ($r_s = -0.08$, $P = 0.45$ and $r_s = -0.02$, $P = 0.85$, respectively).

DISCUSSION

Currently, American and European guidelines are in agreement regarding the main criterion for elective surgical aneurysm resection in the thoracic aorta: The size of the aortic diameter[6,13]. For non-syndromic, asymptomatic aortic aneurysmal disease, the indicative diameter threshold for elective replacement of the ascending aorta is 5.5 cm. However, these guidelines are relying on post-dissection diameter measurements, which are much larger than diameter size prior to dissection[6,13].

Table 1 Demographic characteristics and preoperative details of patients

Variable	Total number of patients (*N* = 108)
Age, yr, median (IQR)	61.5 (52.5-70.5)
Body mass index, cm^2, median (IQR)	28.2 (25.1-32.6)
Female, *n* (%)	37 (25)
History of hypertension, *n* (%)	93 (86.1)
History of smoking, *n* (%)	65 (60.2)
Aortic regurgitation, *n* (%)	29 (26.8)
Left ventricle ejection fraction, %, median (IQR)	45 (40-50)
Diabetes mellitus, *n* (%)	11 (10.2)
Preoperative neurological dysfunction, *n* (%)	22 (16.1)
Temporary neurological dysfunction	14 (13.0)
Permanent neurological dysfunction	3 (2.7)
Preoperative hemodynamic instability, *n* (%)	35 (32.4)
Maximum diameter of ascending aorta, cm, median (IQR)	5.0 (4.5-6)
NT-proBNP, pg/mL, median (IQR)	377.5 (180-928)
D-Dimers, μg/L, median (IQR)	5256.5 (2477-10000)

NT-proBNP: N-terminal pro-brain natriuretic peptide; IQR: Interquartile range.

Table 2 Multivariable logistic regression analysis of risk factors for preoperative neurological dysfunction

Variable	*P* value	OR	95%CI
Age	0.28	1.1	0.97-1.09
Gender	0.46	1.7	0.38-8.12
Body mass index	0.42	1.1	0.92-1.19
Diameter of ascending aorta	0.70	1.1	0.68-1.74

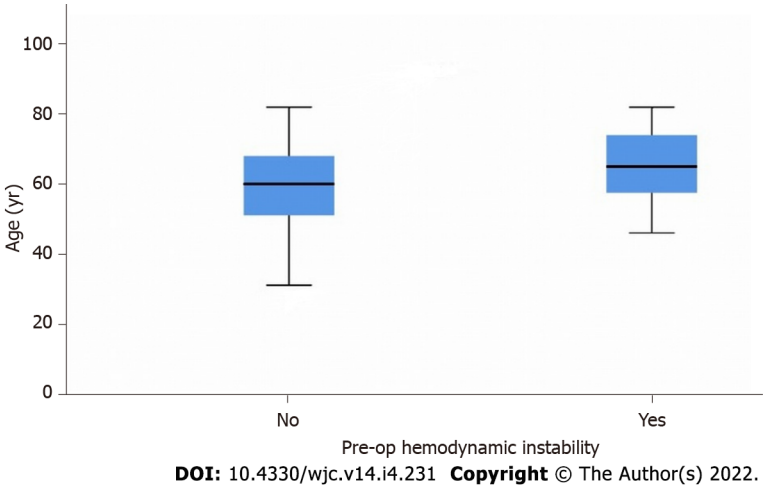
OR: Odds ratio; CI: Confidence interval.

Table 3 Multivariable logistic regression analysis of risk factors for preoperative hemodynamic instability

Variable	*P* value	OR	95%CI
Age	0.02[1]	1.05	1.01-1.11
Gender	0.76	0.81	0.21-3.11
Body mass index	0.56	0.97	0.86-1.08
Diameter of ascending aorta	0.86	1.1	0.68-1.57

[1]Statistical significance ($P < 0.05$).
OR: Odds ratio; CI: Confidence interval.

There is evidence to suggest that the size of the aorta significantly increases post-dissection[18]. Mansour *et al*[18] from the Aortic Institute at Yale-New Haven Hospital demonstrated that the mean aortic diameter at ATAAD was 54.2 mm, whereas the mean aortic diameter prior to dissection was only 45.1 mm[18]. Wu *et al*[19] described an 18% increase in aortic diameter after an ATAAD. Therefore, the pre-dissection aortic diameter falls in several studies well below the current threshold for elective surgical replacement of the ascending aorta. Saade *et al*[20] introduced the term aortic size index in order to stratify patients into risk groups. It was calculated by dividing the aortic diameter by the body



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Figure 1 Boxplot graph for the age of patients with and without preoperative hemodynamic instability (*P* = 0.04).

surface area. However, 10 years later, researchers from the same institution argued against that theory and concluded that body surface area should not be taken into consideration[21]. The same researchers focused on the importance of aortic height index, which is calculated by dividing the aortic diameter by the patient's height. An increased index is associated with an increased annual risk of aortic aneurysm complications[21]. Eliathamby *et al*[22] concluded that the aortic length (distance between the aortic valve and the innominate artery) was strongly correlated with the diameter of the ascending aorta. Wu *et al*[19] suggested the length-height index, which is calculated by dividing the aortic length by the patient's height. An index > 7.5 cm/m was found to have an annual fivefold increased risk of aortic adverse events compared with patients with an index < 5.5 cm/m. However, genetic susceptibility should always be taken into account as it plays an important role in identifying high risk patients[19,23].

ATAAD continues to carry a high peri-operative mortality risk with rates reaching as high as 25%[23,24]. Many authors highlight the safety of preventive surgical replacement of the ascending aorta as published data on elective replacement of the ascending aorta is associated with mortality rates less than 3%[23,24]. For elective operations, postoperative stroke rates are also low with no more than 1.0% strokes noted when the operation takes place in a large volume aortic centre[25]. Moreover, emergency surgical operations show a 5-year survival rate of 37%, rather poorer than the rate (> 85%) related to elective surgical repair of the ascending aorta[25].

CONCLUSION

Although current guidelines suggest replacing the ascending aorta with a diameter ≥ 5.5 cm, many of the patients with ATAAD have an aortic diameter of less than 5.5 cm. The diameter of the ascending aorta in patients diagnosed with ATAAD is not associated with preoperative adverse events. An international taskforce should adapt the new data extracted from the most recent scientific evidence for the surgical treatment of the ascending aortic aneurysm.

ARTICLE HIGHLIGHTS

Research background

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular disease. Current guidelines recommend that ascending aortic replacement be performed when the ascending aorta is 5.5 cm in non-syndromic patients, while in syndormic patients, it should be replaced if the diameter reaches 4.5 cm in the sinus of Valsalva and 5.0 cm in the ascending aorta.

Research motivation

New approach for ascending aorta aneurysm management should be considered for prevention of ATAAD.

Research objectives

The objective of our study was to evaluate the correlation of the diameter of dissected ascending aorta in patients with ATAAD with preoperative adverse events, such as neurological dysfunctions and

hemodynamic instability.

Research methods
A retrospective analysis was performed on patients who were admitted to our hospital for ATAAD treatment. In all patients, the diameter of dissected ascending aorta was measured and its association with adverse events was analyzed.

Research results
The diameter of dissected ascending aorta was not associated with adverse events. Also, the diameter of the ascending aorta was not associated with 30-d mortality and ICU and hospital stay postoperatively.

Research conclusions
Maybe the threshold of ascending aorta aneurysm should be revised for lower limits regarding the risk for late acute dissection

Research perspectives
Randomized controlled studies including more patients should be performed to confirm our results and preventive ascending aorta replacement may be considered for prevention of ATAAD.

FOOTNOTES

Author contributions: All authors contributed equally in carrying out the research and writing the manuscript.

Institutional review board statement: The study was approved by our hospital's institutional review board (No. 546/30-04-2015).

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ORIGINAL ARTICLE

Retrospective Study

Global longitudinal strain is superior to ejection fraction for detecting myocardial dysfunction in end-stage renal disease with hyperparathyroidism

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Abstract

BACKGROUND

The estimation of left ventricular ejection fraction (LVEF) by 2D echocardiography (2D-ECHO) is the most used tool to assess LV systolic function (LVSF). Global longitudinal strain (GLS) has recently been suggested as a superior method for

several evaluations. This study explored the association and prevalence of LV systolic dysfunction (LVSD) by using these methods in patients with end-stage renal disease (ESRD) and severe hyperparathyroidism (SHPTH); both associated with cardiovascular events (CEs).

AIM

To evaluate the myocardial function in patients with ESRD and SHPTH by using the GLS and LVEF measured through conventional 2D-ECHO.

METHODS

In 62 patients with ESRD and SHPTH, asymptomatic, and without a history of CEs, LVSF was evaluated by 2D-ECHO, obtaining the EF, by the Simpson biplane method, and GLS by speckle tracking.

RESULTS

The total patients with ESRD had a preserved LVEF (> 50%) but abnormal GLS (< 13.55%). Additionally, multivariate analysis showed an independent association of GLS and serum parathyroid hormone (PTH), LV mass index, and hemoglobin. Also, PTH was independently associated with lateral e' wave and tricuspid regurgitation velocity.

CONCLUSION

In patients with SHPTH linked to ESRD, the use of GLS by 2D-ECHO is a more sensitive tool than LVEF for detecting LVSD.

Key Words: Left ventricular hypertrophy; Systolic dysfunction; Global longitudinal strain; End-stage renal disease; Parathormone

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Core Tip: This study compared global longitudinal strain (GLS) with the often-used left ventricular ejection fraction to estimate ventricular dysfunction in patients with end-stage renal disease. GLS had an advantage to detect dysfunction, but also, it was found that the parathyroid hormone levels were attractive as a complementary tool to predict patient status.

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INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Heart failure (HF) is a cardiovascular event (CE) that may occur simultaneously in these patients[1-3]. Chronic elevated pressure, volume overload and nonhemodynamic factors including inappropriate activation of the renin–angiotensin–aldosterone system (RAAS) and alterations in calcium–phosphorus mineral metabolism by an excess of parathyroid hormone[4,5] are involved in left ventricular hypertrophy (LVH)[6,7], then, in the myocardial dysfunction in ESRD[3,8].

LV ejection fraction (LVEF) calculated by 2D echocardiography (2D-ECHO) is the most widely used echocardiographic parameter that provides objective information on LV systolic function (LVSF), and it has been used as a prognostic and treatment indicator for CVD[9-11]. However, in some studies involving patients with ESRD, LVEF fails as a sensitive parameter for detecting subclinical data of LV systolic dysfunction (LVSD). In this sense, research groups have explored new variables and methods to increase the early and efficient diagnosis and prognosis of patients with LVSD[12]. Thus, for example, determination of left atrial volume[13], natriuretic peptides (NPs)[14] and catecholamines metabolites in serum (related to sympathetic overactivity)[15] have been proposed as advantageous tools.

Special attraction is on alternative 2D-ECHO methods, specifically, predialysis and peritoneal dialysis patients with preserved LVEF (> 50%) showed reduced GLS (15%), which was associated with an increased risk of HF hospitalization and increased mortality[3]. Thus, GLS may be a better tool to assess

subclinical changes in LVSD in particular cases, for example, where the LVEF is preserved as in those patients subject to volume or pressure overload, or both[3,16]. Additionally, studies have mentioned that the variables used to define a preserved LVEF and a reduced GLS are associated with differences between the characteristics of the population studied (race, stage of ESRD, risk factors, and comorbidities). However, despite this variability, GLS is an important echocardiographic tool that might be used in patients with ESRD to identify those with a high-risk prognosis for developing HF or other CEs.

In the present study, a comparison was made from echocardiographic changes in patients with ESRD and hyperparathyroidism, the degree of LV remodeling, LVSF using 2D-ECHO, EF (by Simpson's method), and GLS (by Speckle tracking). Additionally, plasma parathyroid hormone (PTH) concentration was considered to increase ability to detect LVSD in patients with ESRD and hyperparathyroidism (a common hormone elevated in ESRD, but poorly explored or linked to CEs in these patients).

MATERIALS AND METHODS

This study was done in patients with asymptomatic ESRD with renal replacement therapy (RRT; dialysis and hemodialysis) and with no history of CEs. The degree of LVDD (I, II or III) was assigned by applying the Nagueh SF, 2020 recommendations[17], and the measurement of plasma PTH in relation to the LVSF and LV diastolic function (LVDF) was explored.

This retrospective and observational study included a total of 77 individuals divided into three groups: healthy individuals with no known disease (Control; n = 15), age > 18 years, both genders; patients with ESRD on hemodialysis (ESRD-HD; n = 31) and patients with ESRD on peritoneal dialysis (ESRD-PD; n = 31). The ESRD groups came from the Nephrology service of Centro Médico SXXI, IMSS. This study was carried out from February 2019 to October 2020.

All patients with ESRD maintained their RRT and were supplemented with calcium and calcitriol following clinical practice guidelines[18]. Those individuals with hemodynamic alterations increasing risk on their physical integrity were excluded. A complete medical history was taken. Demographic, clinical and comorbid characteristics were collected. A blood sample was collected in the morning before the RRT, and 4 h later, echocardiography was performed.

Echocardiography

Transthoracic echocardiography images were obtained using a commercially available ultrasound system (Ecocardiograph iE33; Philips). Standard 2D Doppler, color, pulsed and continuous wave echocardiographic acquisitions were made. LV dimensions were obtained from images in a long axis parasternal view, and LV mass and body surface area-corrected indexed LV mass were calculated. In addition, the relative wall thickness was obtained as a ratio of (2 × RWTd) / LVIDd, where RWTd is the back-wall thickness, and LVIDd is the internal diameter of the LV at the end of diastole. The LV end-diastolic and systolic volumes were then measured from the apical views (two and four chambers) using the Simpson biplane method[19]. Mitral annulus early diastolic velocity (E') was identified by tissue Doppler imaging in a four-chamber view. Mitral inflow velocities, such as transmitral peak early passive filling velocity (E), late diastolic filling velocity caused by atrial contraction (A), and deceleration time, were determined using Pw-Doppler over the mitral valve in four-chamber views. The degree of diastolic dysfunction of each patient was assessed[17].

GLS was evaluated by obtaining LV grayscale scatter images from all three apical views. From the 2D images, the endocardial border was manually drawn during the end of the systole, and the thickness of the myocardial region of interest was adjusted to include the entire thickness of the myocardial wall. In each echocardiographic view, the myocardium was automatically divided into six segments. Therefore, the overall maximum systolic longitudinal pressure was calculated by averaging the maximum systolic values of all 18 segments, derived from the three apical views (six segments in each apical view) adjusted to the heart rate.

Biostatistics

Continuous variables are expressed as the mean ± SD. Continuous variables were compared between groups using ANOVA and then a χ^2 test. A multivariate logistic regression analysis was used, which included the clinical and echocardiographic parameters associated with the univariate analysis as independent variables. $P < 0.05$ was considered statistically significant. The statistical analysis was performed with SPSS version 20.

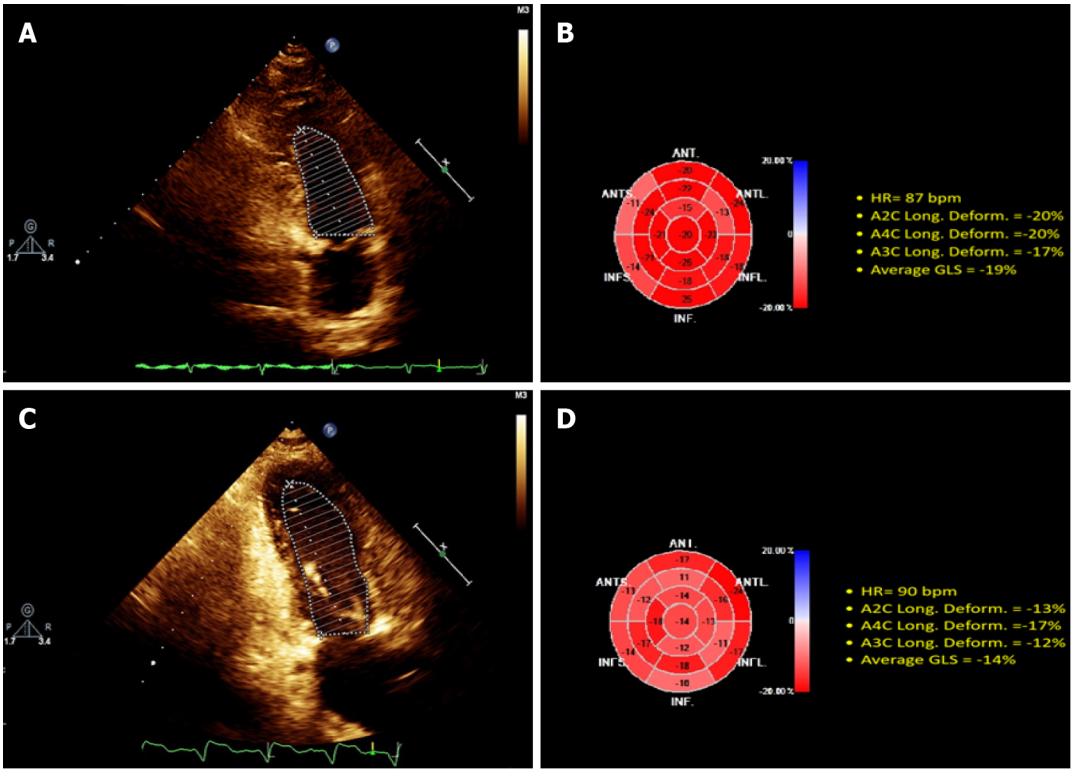
RESULTS

The characteristics were as follows from the total population: 48 participants were female (62%) and 29

Table 1 Demographic and clinical variables in the study groups

Demographic variables	Control, *n* = 15	ESRD-HD, *n* = 15	ESRD-PD, *n* = 15	Total, *n* = 15
Age (yr)	34 ± 13	36 ± 2	34 ± 10	34.6 ±
Gender, *n* (%)	F = 10 (67), M = 5 (33)	F = 26 (84), M = 5 (16)	F = 12 (39), M = 19 (61)	F = 48 (62), M = 29 (38)
BMI (kg/m^2)	23.4	23.3	22.4	23 ±
Hypertension, *n* (%)	N/A	28 (90)	31 (100)	59 (77)
DMT2, *n* (%)	N/A	2 (6.45)	5 (16)	7 (9.09)

ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; F: Female; M: Male; BMI: Body mass index; N/A: Not available.



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Figure 1 Illustrative 2D echocardiography. Top: control patient; Bottom: patient with end-stage renal disease (ESRD) and severe hyperparathyroidism (SHPTH). The ejection fraction (EF) by the Simpson method was calculated as a function of the endocardial borders at end-diastole and end-systole in the apical projection of two cavities. A and C (left): in the control patient, left ventricular EF (LVEF) was 56% (A), and 61% in the patient with ESRD and SHPTH (C). 2D ECHO ST real-time showed longitudinal deformation (B and D, right). The deformation pattern in the control patient (B) was normal, with global longitudinal strain (GLS) = 19%, and GLS was abnormal (14%) in the patient with ESRD and SHPTH (D).

(38%) male. According to the division, in the control group, the age was 34 ± 13 years, body mass index (BMI) 23.4 kg/m^2, 67% female and 33% male, without relevant comorbidities. The ESRD-HD group age was 36 ± 2 years, BMI 23.3 kg/m^2, 84% female and 16% male, 90% presented with hypertension and 6.45% with type 2 diabetes mellitus (T2DM). In the ESRD-PD group, age was 34 ± 10 years, BMI 22.4 kg/m^2, 39% female and 61% male, all presented with hypertension, and 16% with T2DM (Table 1).

Patients with ESRD had severe refractory hyperparathyroidism (PTH > 650 pg/mL), but calcium (Ca^{2+}), phosphorus (P), and calcium/phosphorus (Ca_{2+}/P) ratio levels were within normal ranges. There was no significant difference from the control group, suggesting an average plasma calcitriol level. All of our population with ESRD showed LVH. LV mass and LV mass index (LVMI) were substantially increased; LVH concentric type was predominant (ESRD-HD = 80.65% and ESRD-PD = 93.35%) (Table 2).

The 2D-ECHO variables of the population studied are shown (illustrative case in Figure 1), demonstrating that by Simpson's method, LVEF was preserved, while the GLS was substantially reduced compared to the control group (21% ± 0.58% *vs* 13.93% and 13.18%; $P < 0.0001$; control *vs* ESRD-HD and ESRD-PD). The average GLS was 13.55% in all populations with ESRD. This shows that LVEF

Table 2 Biochemical and left ventricular remodeling variables in the study groups: Control, end-stage renal disease on hemodialysis and end-stage renal disease on peritoneal dialysis

Variables	Control	ESRD-HD	ESRD-PD	*P* value
Biochemical				
PTH (pg/mL)	50 ± 4.55[a,c]	1188 ± 203.9	1188 ± 203.9	< 0.0001
Ca^{2+} (mg/dL)	8.55 ± 2.34	8.47 ± 0.14	8.38 ± 0.09	NS
P (mg/dL)	4.56 ± 2.28	4.75 ± 0.24	4.75 ± 0.28	NS
Ca^{2+}/P (mg^2/dL^2)	45.32 ± 1.05	42.31 ± 2.35	39.87 ± 2.5	NS
Albumin (mg/dL)	4.47 ± 0.10[a,c]	4.13 ± 0.12	3.94 ± 0.06	< 0.0284
Hemoglobin (g/dL)	15.3 ± 0.12[a,c]	8.73 ± 0.24	8.91 ± 0.22	< 0.0001
LV remodeling				
LV mass (g)	133.8 ± 3[a,c]	182.7 ± 12.2	186.6 ± 15	< 0.0001
LVMI (g/m^2)	70.65 ± 2.11[a,c]	130.2 ± 6.24	127.5 ± 6.55	< 0.0001
RWT	0.39 ± 0.016[a,c]	0.51 ± 0.01	0.51 ± 0.02	< 0.0001

[a]*P* < 0.05, control *vs* ESRD-HD.
[c]*P* < 0.05, control *vs* ESRD-PD.
The data represent the mean SD. ANOVA followed by a Tukey test was performed and was considered significant. ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; PTH: Plasma parathyroid hormone; LV: Left ventricular; LVMI: LV mass index; NS: Not significant.

Table 3 Echocardiographic population variables control, end-stage renal disease on hemodialysis and end-stage renal disease on peritoneal dialysis

Variables	Control	ESRD-HD	ESRD-PD	*P* value
LVEF	60.75 ± 1.30	63.5 ± 10.36	61.8 ± 11.19	NS
GLS (%)	21 ± 0.58[a,c]	13 ± 0.72	12 ± 1.83	< 0.0001
LAV (mL/m^2)	33.07 ± 0.22[a,c]	26.49 ± 1.4	25.73 ± 1.57	< 0.0001
E/A ratio	1.25 ± 0.03[a,c]	1.05 ± 0.06	0.91 ± 0.05	< 0.0001
E/é ratio	5.38 ± 0.18[a,c]	11.62 ± 0.96	12.22 ± 1.13	< 0.0001
E (cm/s)	60.39 ± 1.71[a,c]	80.19 ± 6.26	81.29 ± 6.97	< 0.0001
Lateral e' (cm/s)	13.44 ± 0.36[a,c]	8.33 ± 0.43	7.49 ± 0.16	< 0.0001
Septal é (cm/s)	10.85 ± 0.35[a,c]	6.18 ± 0.24	6.49 ± 0.23	< 0.0001
TRV (m/s)	2.21 ± 0.02[a,c]	2.94 ± 0.08	2.80 ± 0.07	< 0.0001
LVMI (g/m^2)	70.65 ± 2.11[a,c]	130.2 ± 6.24	127.5 ± 6.55	< 0.0001
RWT	0.39 ± 0.016[a,c]	0.51 ± 0.01	0.51 ± 0.02	< 0.0001

[a]*P* < 0.05, control *vs* ESRD-HD.
[c]*P* < 0.05, control *vs* ESRD-PD.
The data represents mean SD. ANOVA followed by Tukey test was performed and was considered significant. ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; LVEF: Left ventricular ejection fraction; GLS: Global longitudinal strain; LAV: Left atrial volume; TRV: Tricuspid regurgitation velocity; LVMI: LV mass index; NS: Not significant; RWT: Relative wall thickness.

does not establish systolic dysfunction in patients diagnosed with ESRD, even though they have systolic dysfunction by GLS evaluation (Table 3).

In the bivariate analysis, an association of GLS with hemoglobin, hypertension, PTH, LVH and LVMI was shown. In comparison, the multivariate analysis showed an independent association of GLS and hemoglobin, PTH and LVMI (Table 4).

This study analyzed the LVDF by obtaining the pattern of transmitral flow rates and their relationship with the tissue velocities at the mitral ring level. The above is related to the fact that the increase in LV filling pressures is the primary physiological consequence of LVDD. These variables

Table 4 Global longitudinal strain and variables association

Variables	Univariate					Multivariate using significant variables					Multivariate by step method				
	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value
			Lower limit	Upper limit				Lower limit	Upper limit				Lower limit	Upperlimit	
Association with GLS (%)															
Hemoglobin	-1.09	-0.61	-1.42	-0.77	0.00	-0.58	-0.32	-1.12	-0.05	0.03	-0.62	-0.35	-0.99	-0.26	0.00
Hypertension	5.60	0.54	3.58	7.61	0.00	1.52	0.15	-1.44	4.49	0.31					
PTH	0.00	0.50	0.00	0.00	0.00	0.00	0.27	0.00	0.00	0.01	0.00	0.29	0.00	0.00	0.00
LVEF	-0.04	-0.08	-0.15	0.07	0.50										
LVH	6.40	0.57	4.27	8.53	0.00	-1.82	-0.16	-7.75	4.12	0.54					
LVMI	0.06	0.51	0.04	0.08	0.00	0.03	0.28	0.01	0.05	0.01	0.03	0.29	0.01	0.05	0.00
RWT	11.36	0.25	1.27	21.46	0.03	-1.21	-0.03	-10.14	7.73	0.79					

95%CI: 95% confidence interval; GLS: Global longitudinal strain; PTH: Plasma parathormone; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; RWT: Relative wall thickness.

Table 5 Association between parathyroidism levels and left ventricular diastolic dysfunction variables

Variables	Univariate					Multivariate using significant variables					Multivariate by step method				
	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value
			Lower limit	Upper limit				Lower limit	Upper limit				Lower limit	Upper limit	
Association with PTH															
E/é ratio	54.22	0.33	18.34	90.09	0.00	28.19	0.17	-11.55	67.93	0.16					
é lateral	-124.,51	-0.36	-199.34	-49.69	0.00	-81.10	-0.23	-177.06	14.87	0.10	-89.72	-0.26	-169.01	-10.44	0.03
é septal	-121.78	-0.28	-215.64	-27.91	0.01	-0.63	0.00	-121.22	119.97	0.99					
TRV	698.98	0.35	276.86	1121.10	0.00	360.73	0.18	-141.53	862.99	0.16	500.88	0.25	53.87	947.89	0.03

95%CI: 95% confidence interval; PTH: Plasma parathormone; TRV: Tricuspid regurgitation velocity.

were significantly altered in the ESRD population compared to the controls (Table 3).

The tricuspid regurgitation velocity (TRV) and E/e' ratio associated with the decrease in the E/A ratio and the e' septal lateral waves reflect the pattern of altered relaxation and myocardial distensibility during the diastolic phase. Previously reported recommendations were applied[17], and it was found that among individuals with ESRD-HD, 67.74% (n = 21) had grade I, 22.58% (n = 7) grade II, and 9.67% (n = 3) grade III LVDD. Among individuals with ESRD-PD, 84.37% (n = 27) had grade I and 15.63% (n = 4) had grade II LVDD. The univariate and multivariate analyses (Table 5) showed the associations between the variables studied and PTH. An independent association of serum PTH and lateral e' wave and TRV was shown.

DISCUSSION

Despite the extended use of EF to evaluate myocardial dysfunction, recent proposals promise to improve detection of cardiovascular dysfunction. As an example, 2D-ECHO for measuring left atrial volume is useful to predict diastolic dysfunction in ESRD patients[13]. Measuring plasma biomarkers has been suggested to extend diagnostic advantages. Thus, plasma NP levels are reported to be linked to cardiac remodeling[18], survival[19] and volume expansion-related LV disorders[20] in patients with ESRD[14].

Currently, 2D-ECHO methods remain core in diagnosis and evaluation of patients with CEs. The identification of LV strain changes is crucial for early cardiac damage detection in ESRD[21-24]. This study showed that increased LVMI, low hemoglobin levels but high PTH are independent factors associated with GLS alterations. The overall average GLS was 13.55%, with LVEF > 50% in the patient population, which according to the literature, is related to poor prognosis[25-29]. In this case, it was suggested that in the population with ESRD, the determination of GLS by 2D-ECHO is highly recommended for the assessment of LVSF; being a more powerful tool than LVEF, which can identify systolic myocardial damage[3,18,19] during follow-up of patients[29].

In patients with ESRD, bone mineral disorder is correlated with adverse outcomes from cardiovascular causes[25,30,31]. Recently, the mineral disorders in the early stages of ESRD have been associated with myocardial remodeling, which is a crucial point for LVH development[31-33]. In our study population, the presence of LVH was 100%, with a predominance of the concentric type. In this regard, some studies have directly implicated hyperphosphatemia and hypercalcemia in developing LVH[7,30] by regulating several factors[31,34-36]. However, it must be considered that the kidney is an essential target organ for PTH, and the interaction with its receptor activates multiple signaling pathways[37-39], triggering numerous changes in the kidney and some other systems[40]. As strong evidence of the PTH role in cardioremodeling, studies have shown that patients undergoing parathyroidectomy (PTX) have a substantial reduction in LV mass[41]; in contrast, patients with severe hyperparathyroidism and PTX showed a significant decrease in the risk of death from all causes[42]. Patients in the current study were supplemented with calcium or analogs; plasma values of Ca, P and Ca/P ratio were within normal ranges, while PTH levels were higher than reference values (PTH > 650 pg/mL). Multivariate analysis showed an independent association of GLS and PTH, suggesting a putative role of PTH in LVSF by diverse mechanisms, including those related to remodeling of subendocardial fibers[43].

Additional research is required to elucidate the mechanisms involved in the PTH modulation of the structure and function of the cardiomyocytes, as the pleiotropic effects are attributed to the interaction of PTH with its receptor [33,40].

PTH serum levels showed an independent association with some diastolic function parameters (Table 5): Particularly e' lateral wave and TRV. The alterations in diastolic function primarily involve the mechanisms of myocardial relaxation and compliance. The signaling pathways involving remodeling and cardiac fibrosis in patients with ESRD are complex and multifactorial, involving alterations in the extracellular matrix proteins, type I collagen, elastin, fibroblasts, and myofibroblasts[9,44-46], which reduce myocardial compliance. These effector pathways involve PTH and 25-hydroxy vitamin D3 and several other factors[34-39,46-51]. Elevated levels of catecholamine by sympathetic overactivity are reported to be linked to LV disorders and volume excess in ESRD patients[15].

Finally, our results are in line with recent reports supporting that conventional speckle-tracking echocardiography[52-54] might help identify LVSD in patients with ESRD and preserved LVEF. Early detection of myocardial morphological and functional changes in the routine evaluation of patients with ESRD can tackle the early stages of disease-independent modifiable risk factors that are associated with adverse CEs.

CONCLUSION

An accurate diagnosis is increasingly important in this type of patient with ESRD with systolic and diastolic myocardial function evaluation, offering integrated, lower cost, and noninvasive information. The use of new diagnostic tools is essential to provide the population with new targeted therapies for

defined subsets of patients who may be at risk of developing potential complications. The use of GLS by 2D-ECHO is a more sensitive tool than LVEF to detect of LVSD. For individuals with ESRD and severe hyperparathyroidism refractory to hormone replacement but with normal Ca/P levels, it is essential to recommend the use of GLS as a diagnostic and prognostic tool for systolic myocardial dysfunction; albeit if patients have preserved LVEF.

ARTICLE HIGHLIGHTS

Research background

Echocardiography is the most-used tool for diagnosis of myocardial dysfunction. Among 2D-ecocardiography (2D-ECHO) methods, ejection fraction (EF) is the most used. In patients with myocardial dysfunction and end-stage renal disease (ESRD) parathyroid hormone (PTH) is often altered.

Research motivation

Recent echocardiography methods are being compared with ejection fraction. Global longitudinal strain (GLS) is among the most explored. Additional serum biomarkers could help to increase sensibility of tests.

Research objectives

To compare the EF and global strain methods for detecting myocardial dysfunction. To measure the potential role of some biomarkers as complementary tools in patient evaluation.

Research methods

Left ventricular systolic function (LVSF) was evaluated in 62 patients with ESRD with altered levels of PTH. LVSF was evaluated by performing 2D-ECHO, obtaining the EF, by the Simpson biplane method, and GLS by speckle tracking.

Research results

All patients with ESRD had preserved LVEF (> 50%) but abnormal GLS (< 13.55%). PTH was independently associated with lateral e' wave and tricuspid regurgitation velocity.

Research conclusions

In patients with elevated PTH and ESRD, the use of GLS by 2D-ECHO is a more-sensitive tool than LVEF for detecting myocardial dysfunction.

Research perspectives

GLS and serum PTH should be widely explored as potential sensitive tools to detect myocardial dysfunction in patients with ESRD. The mechanisms linked to this disrupted condition should be analyzed. Alternative echocardiography methods and biomarkers should be compared to select the most-sensitive and accurate tools.

FOOTNOTES

Author contributions: Carrasco-Ruiz MF, Ruiz-Rivera A, and Perez-Capistran T conceptualized the study; Ruiz-Rivera A, Martinez-Hernandez CM and Manuel-Apolinar L done data collection; Carrasco-Ruiz MF, Ruiz-Rivera A, Mejia-Ruiz A, Soriano-Ursúa MA and Martinez-Hernandez C carried out data analysis and interpretation; Carrasco-Ruiz MF, Soriano-Ursúa MA, and Perez-Capistran T drafting article; and All authors revised and approved the final version of this manuscript.

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META-ANALYSIS

Effect of preoperative renin-angiotensin system blockade on vasoplegia after cardiac surgery: A systematic review with meta-analysis

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Abstract

BACKGROUND

Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] is still debated.

AIM

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

METHODS

All published studies from MEDLINE, EMBASE, and Web of Science providing relevant data through January 13, 2021 were identified. A random-effects meta-analysis method was used to pool estimates, and post-cardiac surgery shock was differentiated from vasoplegia.

RESULTS

Ten studies reporting on a pooled population of 15672 patients (none looking at ARBs exclusively) were included in the meta-analysis. All were case-control studies. Use of ACEIs was associated with an increased risk of vasoplegia [pooled

adjusted odds ratio (Aor) of 2.06, 95%CI: 1.45-2.93] and increased inotropic/vasopressor support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29). Post-cardiac surgery shock was increased in the presence of left ventricular dysfunction (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) but not increased by the use of beta blockers (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%). Two randomized control trials (RCTs), not eligible for the meta-analysis, did not show an association between continuation of RAS blockers and vasoplegia.

CONCLUSION

Preoperative continuation of ACEIs is associated with an increased need for inotropic support postoperatively and with an increased risk of vasoplegia in observational studies but not in RCTs. The absence of a consensus definition of vasoplegia should lead to the use of perioperative cardiovascular monitoring when designing RCTs to better understand this discrepancy.

Key Words: Vasoplegia; Cardiac surgery; Coronary artery bypass graft; Angiotensin converting enzyme inhibitors

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Core Tip: Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system blockers, mainly angiotensin converting enzyme inhibitors (ACEIs), is still debated. The meta-analysis of observational studies suggests that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. However, these associations were not observed in two included randomized controlled trials with limited power. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. However, well-powered randomized controlled trials using a consensus definition of vasoplegia are still needed to properly assess management strategies of RAS blockers in the perioperative setting.

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INTRODUCTION

Shock is a frequent complication of major cardiac surgery, occurring in approximately a quarter of procedures, especially those with cardiopulmonary bypass (CPB)[1-3]. Vasoplegia is a form of distributive shock characterized by persistent hypotension, reduced systemic vascular resistance (SVR) with normal or elevated cardiac output[1]. It is due to reduced vascular smooth cell contraction resulting from several mechanisms including the alteration of the endothelial glycocalyx, impaired receptor signaling, changes in endothelial cell metabolism, and depletion and decreased response to endogenous vasopressors[1,4]. This impairment of vascular reactivity is worsened by a systemic inflammatory response to surgical trauma, ischemia-reperfusion syndrome, and exposure of blood to the foreign surfaces during extracorporeal circulation[1,4]. The use of some medications prior to surgery is also thought to contribute to inappropriate vasodilatation in vasoplegia[1,4].

The association of continuation of renin angiotensin system (RAS) blockers and vasoplegia following cardiac surgery is still a matter of debate[2,5-7]. Preoperative administration of ACEIs has been associated with poor outcomes including acute kidney injury and increased mortality[8]. This systematic review and meta-analysis aimed to comprehensively summarize data on the effect of preoperative use of RAS blockers on vasoplegia in patients undergoing cardiac surgery.

MATERIALS AND METHODS

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines[9]. It was registered with PROSPERO (CRD42017072923).

Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science were searched to identify all cohort studies, case-control studies or randomized controlled trials (RCTs) reporting primary data on the association between ACEIs or ARBs and the incidence of vasoplegia after cardiac surgery, published by January 13, 2021 (date of the last search), without language restriction. The search strategy used a combination of terms or their synonyms related to vasoplegia, a detailed list of cardiac surgical procedures, and names of ACEIs or ARBs (Supplementary Table 1). The reference lists of relevant research and review articles were also screened to identify potential additional data sources.

Study selection

We included: (1) Cohort studies, case-control studies or RCTs; (2) With 30 participants or more; and (3) Reporting on risk of vasoplegia associated with ACEIs or ARBs, or studies with enough data to compute these estimates. We excluded studies: (1) Which included patients undergoing non-cardiac surgery; (2) Lacking explicit description of the perioperative follow-up of patients; and (3) Not reporting primary data (reviews, commentaries, editorials). For duplicate publication of the same group/cohort of patients, we included the single most comprehensive report with the largest sample size. Two investigators (JJN and BN) independently selected records from bibliographic searches based on titles and abstracts screening. Full texts of articles deemed potentially eligible were retrieved and screened independently by the same investigators for final inclusion. Disagreements were resolved *via* discussion and consensus.

Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by a second investigator (BN). We collected data on study characteristics, type of cardiac surgery, definition of vasoplegia, sample size, mean or median age, sex proportion, proportion of patients with co-morbidities such as hypertension, diabetes, heart failure, or previous cardiac surgery, proportion of patients taking relevant medications (ACEIs, ARBs, beta blockers, calcium channel blockers, nitrates, number of participants with vasoplegia, and risk estimate [odds ratio (OR) or relative risk (RR)] with the 95% confidence interval (95%CI) for the association between vasoplegia and ACEIs or ARBs. We also extracted adjusted risk estimates (from multivariable regression analysis) for other risk factors for vasoplegia as complementary information. We assessed the risk of bias using the tools for case-control studies and randomized controlled trial developed by the CLARITY group at McMaster University[10,11]. We separated studies with or without perioperative cardiac index monitoring in an attempt to further differentiate post-cardiac surgery shock from vasoplegia.

Statistical analysis

Analyses were conducted with R statistical software (version 3.6.2, The R Foundation for statistical computing, Vienna, Austria). The generic inverse variance method was used to pool adjusted risk estimates (OR or RR) and their standard errors with the random-effects meta-analysis model using the *metagen* function. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic, which was quantified by I^2 values, assuming I^2 values of 25%, 50% and 75% respectively representing low, moderate and high heterogeneity[12]. We assessed the presence of publication bias related to small study effect by funnel plot inspection and by linear regression test of funnel plot asymmetry (Egger's test)[13]. All statistical tests were two-tailed and statistical significance defined as P value ≤ 0.05.

RESULTS

Study selection and characteristics

Bibliographic searches retrieved 8076 records and 12 articles were finally included[2,5-7,14-21]. Ten studies were included in the meta-analysis[2,5-7,14-19] and 2 were summarized narratively[20,21]. The study selection is summarized in Figure 1. The observational studies included in the meta-analysis reported data from a pooled sample of 15672 patients undergoing a cardiac surgery. Half of them focused on patients undergoing coronary artery bypass (CABG)[6,7,15,18,19], while the other studies included patients undergoing various procedures including CABG or valvular surgery[2,5,14,16,17]. All observational studies were case-control studies, with data collection done prospectively in most of them [5-7,14-17,19]. The two studies summarized narratively were RCTs[20,21]. The characteristics of the included studies are presented in the appendix (Supplementary Table 2). Most of the studies had a low risk of bias in the majority of assessment items (Supplementary Tables 3 and 4).

The definition of vasoplegia varied across studies (Table 1). Nine studies were considered having acceptable definitions of vasoplegia[2,5-7,14-17,20]. In the remaining three studies, the need for inotropic support was the outcome variable and the definition of vasoplegia seemed to encompass other causes of shock[18,19,21]. We therefore separated studies reporting on vasoplegia and those reporting on post-cardiac surgery shock. The proportions of patients who developed post-cardiac surgery shock

Table 1 General characteristics of included studies

Ref.	Design	Procedure	Definition of vasoplegia	Total sample	Vasoplegia (%)	ACEI (%)
Tuman *et al*[14]	Case-control	Coronary artery and/or valve surgery requiring CPB	Post-CPB ≥ 2 vasoconstrictors with adequate cardiac output	4301	4.5	12.1
Bruce *et al*[16]	Case-control	Cardiac surgery requiring CPB	MAP ≤ 50 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, cardiac index ≥ 2.2 L/min/m^2, requiring norepinephrine infusion	188	34.0	42.0
Carrel *et al*[17]	Case-control	CABG or AVR	SVR < 600 dynes s/cm^5 with adequate cardiac output	800	7.5	43.1
Mekontso-Dessap *et al*[7]	Case-control	CABG	MAP < 70 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, normal cardiac output, requiring vasoconstrictor	108	33.3	31.5
Sun *et al*[15]	Case-control	CABG	MAP ≤ 70 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, cardiac index ≥ 2.5 L/min/m^2, and central venous pressure ≥ 10 mmHg	696	4.7	38.5
Levin *et al*[2]	Case-control	Cardiac surgery	Epinephrine/norepinephrine (≥ 150 ng/kg/min), dopamine (≥ 10 μg/kg/min) or vasopressin (≥ 4 U/h)	2823	20.4	19.7
Shahzamani *et al*[6]	Case-control	CABG	MAP < 65 mmHg, normal cardiac output, requiring vasoconstrictor	300	17.0	64.0
Radaelli *et al*[19]	Case-control	Cardiac surgery	3 of these 4: MAP < 65 mmHg, indexed SVR ≤ 1600 dynes s/cm^5/m^2, cardiac index ≥ 2.5/min/m^2, and requirement of norepinephrine (> 0.03 μg/kg/min) or vasopressin	3139	32.5	52.1
Suga *et al*[5]	Case-control	CABG	Inotropic support post-CABG	562	11.7	9.1
Miceli *et al*[18]	Case-control	CABG	Inotropic support post-CABG	2655	43.5	51.0
Pigot *et al*[21]	RCT	CABG	Inotropic support post-CABG	40	15.0	100
van Diepen *et al*[20]	RCT	CABG or valve surgery	MAP < 60 mmHg requiring vasopressor administration for at least 4 h and a central venous pressure ≥ 8 mmHg	121	29.8	76.9

ACEI: Angiotensin; AVR: Aortic valve replacement; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass; MAP: Mean arterial blood pressure; RCT: Randomized controlled trial; SVR: Systematic vascular resistance.

varied from 4.5% to 34.0% (Table 1). The proportion of patients who used ACEIs preoperatively varied from 9.1% to 64.0% in observational studies. Data on the use of other medications such as ARBs, beta blockers, calcium channel blockers, and nitrates are reported in the appendix (Supplementary Table 2), along with the distribution of co-morbidities across study populations. One of the 2 RCTs reported on an aggregated use of ACEIs and ARBs[20].

Association between angiotensin converting enzyme inhibitors and vasoplegia

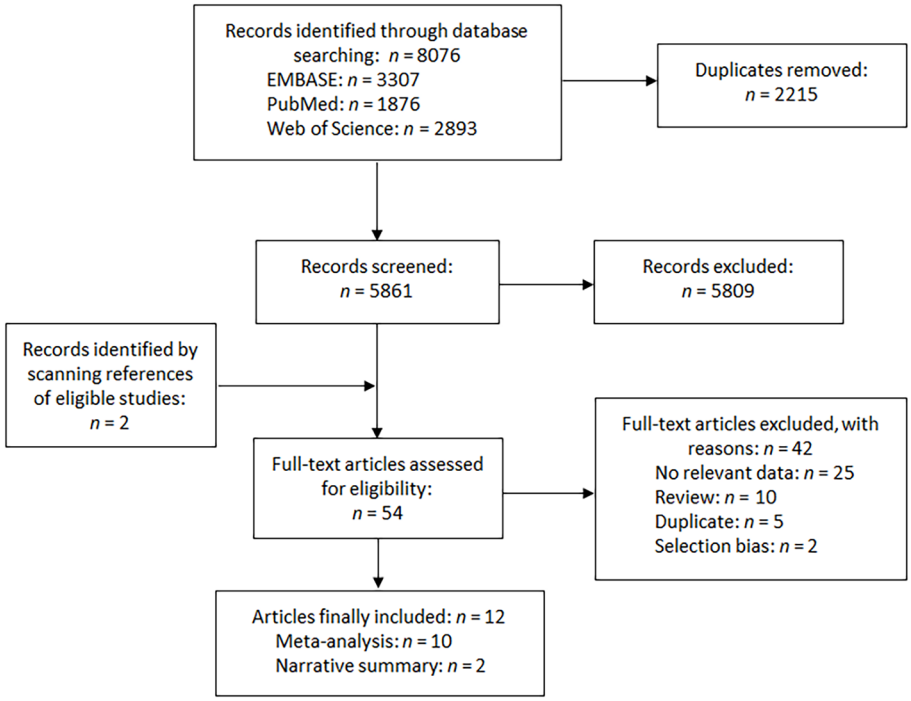
From the 10 observational studies selected, 1076 out of 9778 patients had post-cardiac surgery shock (Figure 2A). In the 6 studies with perioperative cardiac monitoring, 755 patients (12.0%) developed vasoplegia and the risk was increased by preoperative continuation of ACEIs [pooled adjusted odds ratio (aOR) 2.06, 95%CI: 1.45-2.93] (Figure 2B). Considering the high heterogeneity (I^2 = 80%), we performed influencer analysis using a leave-one-out approach. Omission of the study by Carrel *et al*[17] resulted in a pooled aOR that changed to 1.61 (95%CI: 1.41-1.85) (Supplementary Figure 1). There was no evidence of small study effect on funnel plot inspection (Supplementary Figure 2), and according to the Egger's test (P = 0.906).

Association between angiotensin converting enzyme inhibitors and inotropic support

Three studies reported data on the association of omitting ACEIs with the need of inotropic support (use of at least one inotropic drug). A total of 4226 (31.1%) patients required inotropic support from a pooled population of 13595 patients undergoing cardiac surgery. Preoperative continuation of ACEI was associated with an increased risk of inotropic support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29) (Figure 3). There was no heterogeneity (I^2 = 0), and no evidence of publication bias both on funnel plot inspection (Supplementary Figure 3) and based on the Egger's test (P = 0.2).

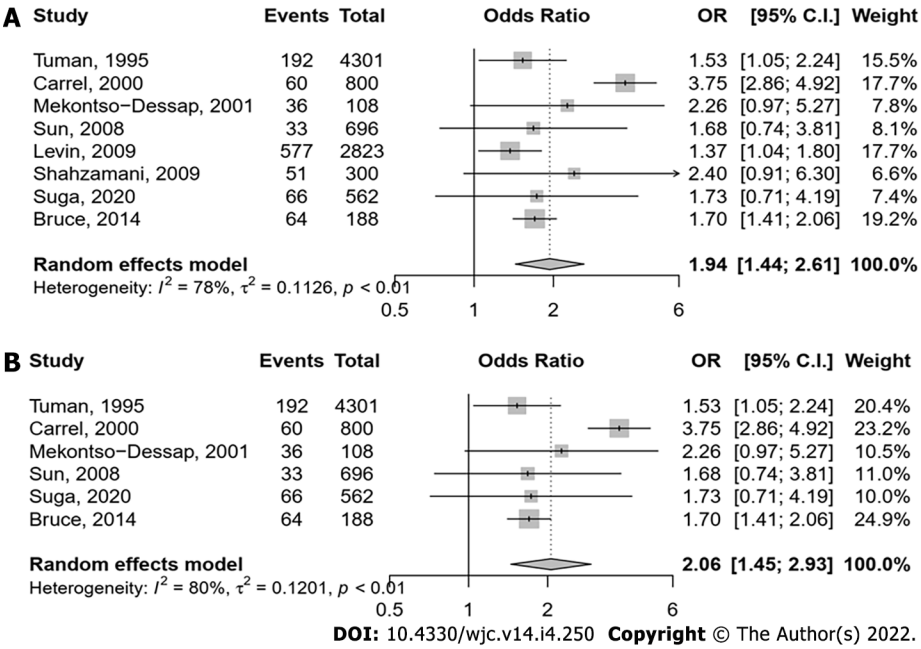
Risk factors for post-cardiac surgery shock

There was no association between beta-blockers and post-cardiac surgery shock (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%) (Figure 4A). The presence of left ventricular dysfunction (ejection fraction <



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Figure 1 PRISMA flow chart of study selection.



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Figure 2 Association between angiotensin converting enzyme inhibitors adverse vascular outcomes. A: Post cardiac surgery shock; B: Vasoplegia.

40%) increased the risk of post-cardiac surgery shock (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) (Figure 4B). The risk of post-cardiac surgery shock increased with CPB time (pooled aOR 1.012 per 1 min increase, 95%CI: 1.003-1.021, P = 0.008; I^2 0%) (Figure 4C). There was no significant association between age and post-cardiac surgery shock (pooled aOR 1.02 per 1 year increase, 95%CI: 1.00-1.04, P = 0.052; I^2 0%) (Supplementary Figure 4). There was no evidence of publication bias on funnel plot inspection (Supplementary Figures 5 and 6), and according to the Egger's test for studies reporting on the association between beta blockers and vasoplegia (P = 0.906), and between left ventricular dysfunction and vasoplegia (P = 0.193).

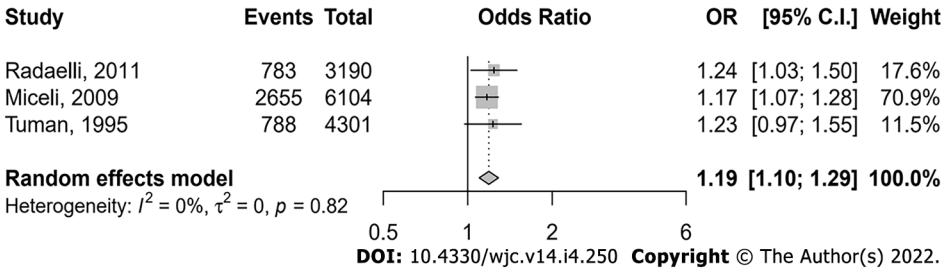


Figure 3 Association between angiotensin converting enzyme inhibitors and need for inotropic support.

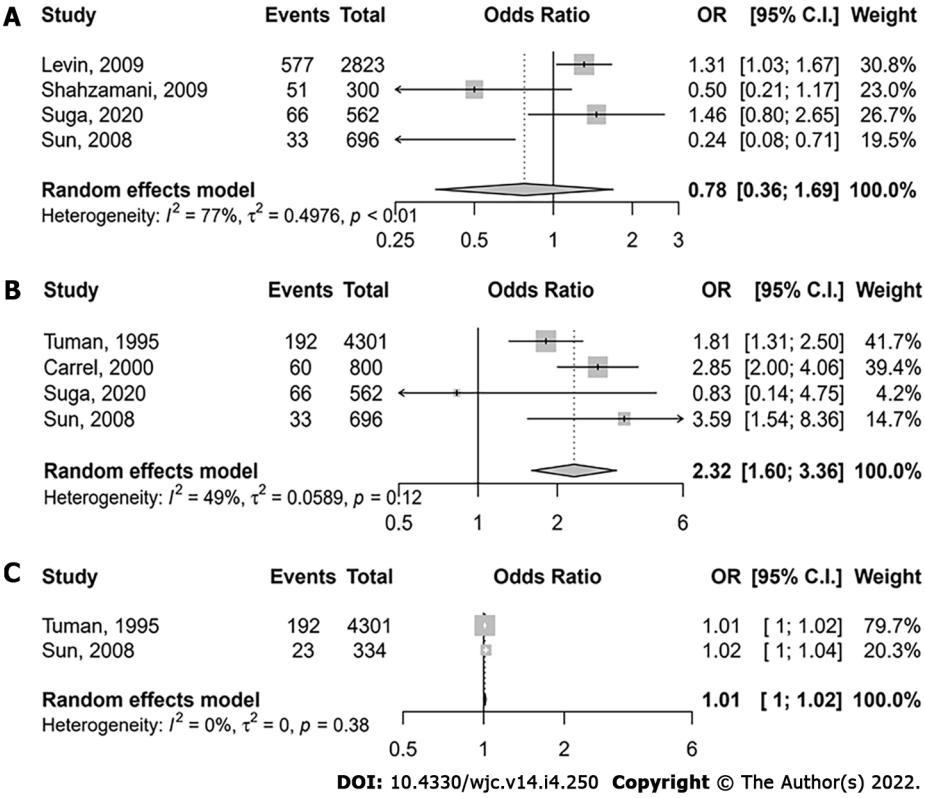


Figure 4 Association between other variables and post cardiac surgery shock. A: Beta blockers; B: Left ventricular dysfunction (EF < 40%); C: Cardiopulmonary bypass time (in minute).

Clinical trials on continuation of ACEIs and vasoplegia

Two RCTs reported on the risk of refractory hypotension with preoperative use of ACEIs[20,21]. The study by van Diepen *et al*[20] included perioperative cardiac monitoring in their definition of vasoplegia and had a larger sample size (61 patients taking RAS blockers)[21]. Incidence of post-cardiac surgery shock was 5%-15% in the study by Pigott *et al*[21] and in the RCT by van Diepen *et al*[20], vasoplegia was found in 29.8% of patients. Preoperative continuation of ACEIs (RAS blockers) was not associated with an increased risk of vasoplegia.

DISCUSSION

This study aimed to summarize data on the effect of preoperative use of ACEIs on incident vasoplegia in patients undergoing cardiac surgery using all relevant studies. Higher odds of vasoplegia (even when defined using perioperative cardiac monitoring) and more frequent use of inotropic support postoperatively were observed in patients who did not discontinue ACEIs. Other factors associated with the risk of post-cardiac surgery hypotension included left ventricular dysfunction and longer duration of CPB, whereas beta blockers use preoperatively was not. Interestingly, the 2 RCTs which evaluated the risk of vasoplegia and continuation of ACEIs (RAS blockers) before cardiac surgery did not show any association.

Hypotension is very common in cardiac surgery, especially with CPB. In response to reduced systemic blood pressure, the kidneys release renin that cleaves angiotensinogen to yield angiotensin I, further converted into angiotensin II by the angiotensin–converting enzyme which causes systemic vasoconstriction. It also increases the secretion of arginine vasopressin and aldosterone, and potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibers. The increased risk of vasoplegia attributable to preoperative ACEI use reported in our study is also consistent with the evidence supporting a hemodynamic benefit of treatment with angiotensin II in patients undergoing cardiac surgery. For instance, a post-hoc analysis of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) multinational, randomized, double-blind trial showed that patients with vasoplegia after cardiac surgery with CPB rapidly responded to angiotensin II, reducing significantly vasopressor use[22].

Whether RAS blockers and specifically ACEIs should be held or not before cardiac surgery has been a matter of debate for more than two decades. The benefits of ACEIs and ARBs in patients with cardiovascular disease are well-established[23]. These positive effects are particularly prominent in the long-term management of patients with ischemic heart disease, especially those undergoing CABG, as evidenced in the QUinapril On Vascular Ace and Determinants of Ischemia (QUO VADIS) RCT[24]. A meta-analysis of 29 studies, mostly retrospective, showed that preoperative use of RAS blockers was associated with increased odds of postoperative acute kidney injury and mortality in patients undergoing cardiovascular surgery[25]. Despite the theoretical favorable mechanisms for RAS blockers in reducing post-operative atrial fibrillation, an increased incidence of post-operative atrial fibrillation has been shown in patients on preoperative RAS blockers, with an adverse effect on survival[26]. These data have motivated the recommendation to omit ACEIs or ARBs before cardiac surgery as a rational strategy to reduce the risk of postoperative vasoplegia and other adverse outcomes[27]. The two RCTs included in this review did not confirm an increased risk of vasoplegia, increased inotropic use or acute kidney injury when ACEIs (RAS blockers) were not discontinued before cardiac surgery[20,21]. However, these trials were not well-powered to be conclusive. They highlight the importance of conducting large multicenter randomized trials to examine the impact of preoperative RAS blockers discontinuation and of its timing on postoperative hemodynamic and clinical outcomes. A previous review already mentioned the weakness of the association between ACEIs and post-cardiac surgery vasoplegia, but a causal relationship has been widely accepted in some cardiovascular anesthesiology communities[28].

This study has some limitations. The definition of vasoplegia was not exactly the same across studies, thereby introducing a potential bias. This is probably due to the fact that there is still no consensus definition of vasoplegia. To address this issue, we pooled together data from studies that used similar definitions and as a result, the level of heterogeneity was low in most analyses. Next, it is possible that the effect of RAS blockers on vasoplegia and inotrope use were confounded by LVEF. Patients receiving RAS blockers are more likely to have low LVEF as these drugs are guideline-recommended in this population. As patients with low LVEF are more likely to have a more complicated post-operative course, it is possible that it is the low LVEF that drove the results, rather than the use of RAS blockers. Unfortunately, stratified analyses by LVEF were not available in the included studies. Moreover, there was no standardized perioperative medication management across studies. It is unclear whether patients reportedly not on ACEI ever took one, or whether some of them were chronically on ACEI but stopped few days before surgery. Another limitation is the relatively low number of eligible studies, which makes some of our estimates less robust. Furthermore, the association between vasoplegia and other factors such as age, CPB time, left ventricular dysfunction or preoperative beta blockers were not preplanned. These variables were not specifically included in the search strategy. Therefore, it is possible that some studies reporting on their attributable risk of vasoplegia were missed. Our findings related to these variables should therefore be interpreted with caution. Despite these limitations, our study is the first to systematically present the discrepancy between observational studies and RCT's on the effect of preoperative RAS blockage and the risk of vasoplegia.

CONCLUSION

Our meta-analysis shows that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. A consensus definition of vasoplegia may help future RCTs properly assess management strategies of RAS blockers in the perioperative setting.

ARTICLE HIGHLIGHTS

Research background

Vasoplegia is a common complication of cardiac surgery. The use of some medications prior to surgery is thought to contribute to inappropriate vasodilatation in vasoplegia. The causal relationship between preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] between vasoplegia is unclear.

Research motivation

If perioperative use of RAS blockers is associated with vasoplegia, withholding these medications in patients undergoing cardiac surgery might help preventing vasoplegia after cardiac surgery.

Research objectives

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

Research methods

The authors performed a systematic review of the literature, and summarized available data using a random-effects meta-analysis.

Research results

Ten studies reported on a pooled population of 15672 patients were included in the meta-analysis. Use of ACEIs was associated with an increased risk of vasoplegia and increased inotropic/vasopressor support requirement. Left ventricular dysfunuction increased the risk of post-cardiac surgery shock. There was no association between continuation of RAS blockers and vasoplegia in the two included randomized control trials (RCTs) .

Research conclusions

Preoperative continuation of ACEIs is associated with an increased risk of the use of inotropic support postoperatively and vasoplegia in observational studies but not in RCTs.

Research perspectives

Further studies are needed to clarify the relationship between perioperative use of RAS blockers and vasoplegia after cardiac surgery. Such studies should use a consensus definition of vasoplegia and conduct appropriate perioperative cardiovascular monitoring.

FOOTNOTES

Author contributions: Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the conception and design; Nouthe B, Noubiap JJ, and Spaziano M contributed to the search strategy; Nouthe B and Noubiap JJ contributed to the studies selection, data analysis and synthesis, data interpretation; Noubiap JJ contributed to the manuscript drafting; Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the manuscript revision, and approval of the final manuscript.

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CASE REPORT

Uncommon post-infarction pseudoaneurysms: A case report

Hamid Jallal, Soufiane Belabes, Ali Khatouri

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Abstract

BACKGROUND

Mechanical complications are a rare presentation in chronic coronary syndromes, which have significantly decreased in the primary coronary intervention era. Incomplete rupture may occur, resulting in pseudoaneurysms (PANs). Early reperfusion decreases the risk of this complication. Echocardiography is the method of choice for diagnosis.

CASE SUMMARY

A 54-year-old female hypertensive patient, with a history of non-revascularized inferior and anterior ST-segment elevation myocardial infarction (MI) 4 years prior, was admitted to the cardiac unit of the hospital with complaints of abdominal pain and dyspnea lasting 2 mo. The patient was hemodynamically stable, and 12-lead electrocardiogram showed persistent ST elevation and Q wave in the inferior and apical regions. Transthoracic echocardiogram in the two-chamber view showed a narrow neck of a wide PAN in the distal apical left ventricular inferior wall. In addition, the apical four-chamber and subcostal views revealed a second bulky PAN of the apical wall separated from the first by a common organizing thrombus. Cardiac magnetic resonance imaging confirmed the coexistence of more than one PAN. The patient received conservative medical treatment, and surgery was scheduled for outside the country. The patient had worsening multiple organ failure and died 4 wk after presentation.

CONCLUSION

Multifocal PANs rarely occur in chronic MI. Attention should be paid to patients with pain and cardiovascular risk factors.

Key Words: Cardiac rupture; Myocardial infarction; Pseudoaneurysm; Echocardiogram;

Case report

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Core Tip: Multiple left ventricular pseudoaneurysms are a rare complication following myocardial infarction (MI), which can be diagnosed years after the infarction. This case highlights the ultimate importance of appropriate early reperfusion of MI and the role of echocardiography and multimodal imaging for the diagnostic assessment of this lethal condition.

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INTRODUCTION

Left ventricular (LV) pseudoaneurysms (PANs) are rare mechanical complications of acute myocardial infarction (MI). They are caused by rupture of the free wall, are composed of organizing thrombus due to hemorrhage into the pericardial space after cardiac rupture (CR), and involve various amounts of epicardium and parietal pericardium. As stated by Hung *et al*[1], "PAN following transmural infarction has a high mortality rate of up to 20%". There have been few reports of LV PAN during the chronic phase of MI, and among them all have had a single localization. Although surgical repair is the treatment of choice, transcatheter intervention for PAN repair is feasible in selected cases.

Herein, we present the first case of uncommon CR manifested as multiple adjacent LV PANs, which occurred in a female patient with a history of MI.

CASE PRESENTATION

Chief complaints

A 54-year-old female patient presented to the emergency department with complaints of abdominal pain and dyspnea.

History of present illness

The patient presented with recurrent episodes of epigastric pain and dyspnea, which began 2 mo prior and worsened 48 h before hospital admission.

History of past illness

The patient had a long history of untreated and advanced hypertension, as well as a history of inferior and anterior ST-segment elevation MI without revascularization, which had occurred 4 years prior.

Personal and family history

The patient had no relevant family history.

Physical examination

The patient presented with hemodynamic stability, a heart rate of 96 beats/min, respiratory rate of 16 breaths/min, blood pressure of 130/80 mmHg, and oxygen saturation in room air of 98%. Symptoms of acute heart failure were excluded by clinical cardiological examination. A painful and hard epigastric mass was detected upon abdominal examination.

Laboratory examinations

Blood analysis revealed mild leukocytosis (12 × 10^9/L), with neutrophil predominance (80%) and normal hematocrit and platelet levels. Prothrombin and partial thromboplastin times were normal, and troponin T was slightly increased at 1.2 ng/mL. Blood creatinine was increased at 435 mmol/L. The 12-lead electrocardiogram showed persistent ST elevation and Q wave in the inferior and apical territory. Chest X-ray revealed increased cardiothoracic ratio with rounded opacity along the left cardiac silhouette.

Imaging examinations

Echocardiography is the first test performed after admission because of its availability. In the four-chamber view, initial imaging evaluation with transthoracic echocardiogram (TTE) showed the narrow neck of a large PAN in the LV apical wall (arrow) (Figure 1A), in the apical two-chamber view (Figure 1B) and modified short axis view (Figure 2A). TTE revealed a second PAN of the distal apical inferior wall, separated from the first PAN by a common organizing fibrous tissue, as detected in the subcostal view (Figure 3A) and apex view (Figure 3B), without pericardial effusion. Color Doppler imaging in the four-chamber view (Figure 2B) demonstrated flow in and out of the pericardial cavity at the site of the tear, as well as abnormal flow into the PAN without any shunt through the organizing thrombus. The LV communicated with the PAN *via* a narrow neck formed by the ruptured apical and inferior myocardium. The dimensions of the cavity (68/15 mm; Figure 2A) and imaging findings were indicative of a PAN; however, it is of great clinical importance to differentiate PANs, which have a high likelihood of spontaneous rupture, from a true aneurysm, which seldom ruptures.

Further diagnostic work-up

The patient was further evaluated with transesophageal echocardiogram, despite the difficulty in assessing the apical wall by this approach; however, the left ventricle communicated with the PANs *via* a narrow neck formed by the ruptured apical and inferior myocardium (Figure 4). To better characterize this finding, a cardiac magnetic resonance (CMR) scan was performed since the severe chronic renal failure precluded evaluation by thoracic computed tomography angiography and to take advantage of the good non-invasive tissue characterization offered by CMR; the cine sequence images confirmed severe LV dysfunction and showed an apical PAN without an intracavitary thrombus in the two-chamber view (Figure 5A). Curiously, a larger and a small outpouching, separated by fibrous tissue, was revealed in the inferior apical wall (Figure 5B); the outpouchings were seen to be associated with disrupted myocardial wall, and they were surrounded only by pericardium.

FINAL DIAGNOSIS

Multiple adjacent LV PANs following chronic MI.

TREATMENT

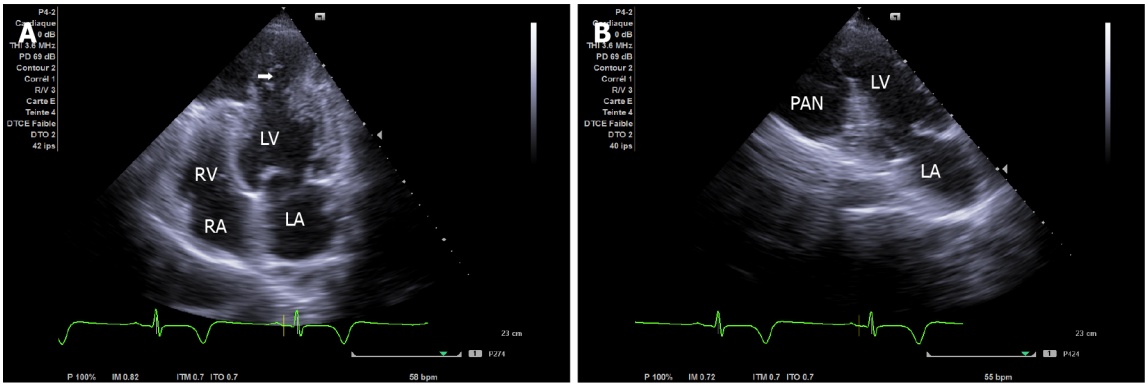
The patient was immediately started on conservative medical treatment, including a curative anticoagulant (acenocoumarolum at 4 mg/d), diuretic (furosemide at 40 mg/d), heart failure therapeutics (bisoprolol at 5 mg and ramipril 5 mg, both one pill per day) and coronary heart disease therapeutics (aspirin at 75 mg/d and atorvastatin at 20 mg/d). After collegial discussion among the care team, the decision was made to proceed with surgical repairs outside the country due to the lack of a cardiac surgery center.

OUTCOME AND FOLLOW-UP

The patient had an uneventful clinical course with medical treatment; surgery was delayed considering the suspension of air travel due to the coronavirus disease 2019 pandemic. The patient had multiple organ failure caused by acute free intrapericardial rupture, which usually causes cardiac tamponade and death, and died 4 wk after presentation.

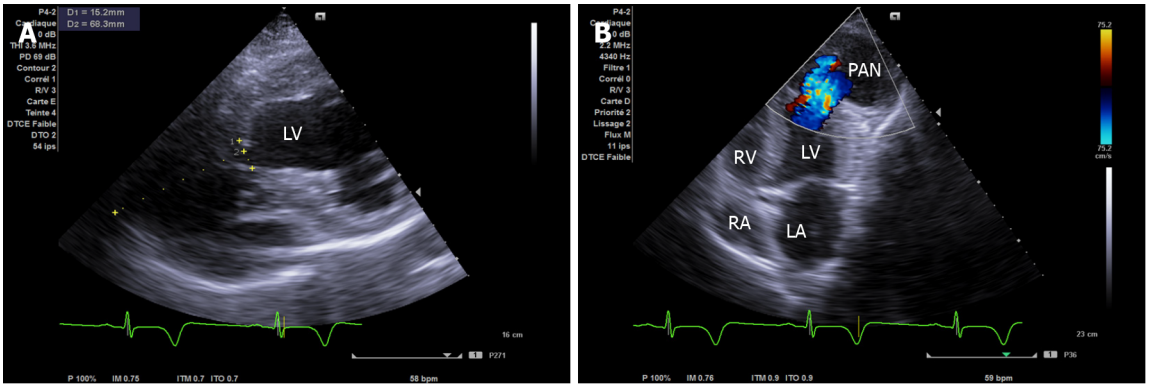
DISCUSSION

PAN is a contained progressive rupture of the LV free wall. It is commonly caused by MI but may also occur after cardiac surgery, chest trauma or infection, and endocardial electrophysiologic procedures; "although in some cases the etiology may be unknown[2]". Typically, LV PANs can also be identified by echocardiography and are typified by a PAN cavity that communicates with the LV chamber *via* a very narrow neck and frequently contains a thrombus. The characteristic to-and-fro blood flow through the site of rupture can be detected with Doppler and color flow imaging; however, "magnetic resonance imaging is necessary to establish the diagnosis if echocardiography findings are atypical[3]". While most PANs are located in the inferoposterior or inferolateral region, "some studies have concluded that the most typical location is the anterior or lateral wall[4].



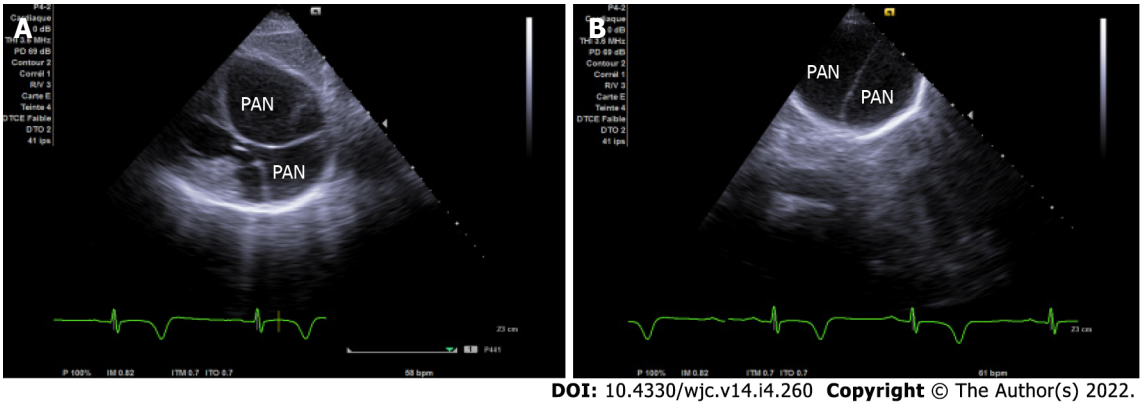
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Figure 1 Apical chamber view on transthoracic echocardiogram. A: Apical four-chamber view demonstrating the narrow neck of a pseudoaneurysm (PAN) in the apical wall (arrow indicates the site of free wall rupture); B: Apical two-chamber view demonstrating a second PAN of the infero-apical wall. LA: Left atrium; LV: Left ventricular; RA: Right atrium; RV: Right ventricular.



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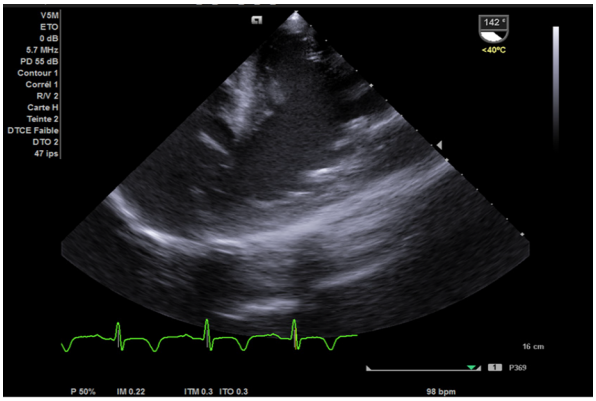
Figure 2 Transthoracic echocardiogram. A: Modified short axis view with the pseudoaneurysm dimensions (width of the neck was 15 mm and the maximal internal diameter of the aneurysmal sac was 68 mm with a neck to sac ratio of less than 0.5); B: Apical modified 4/5 chamber view showing bidirectional shunt through the left ventricular wall.



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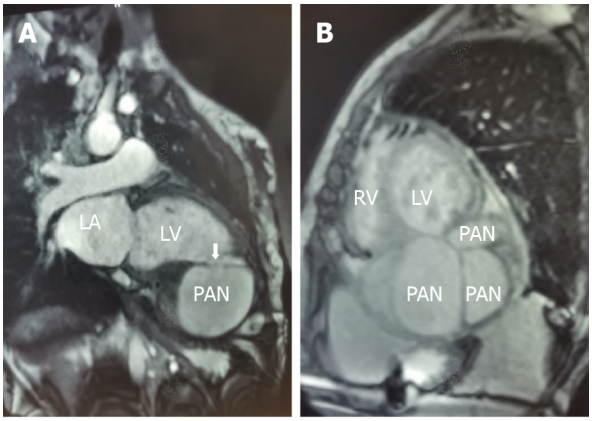
Figure 3 Subcostal and apical views on transthoracic echocardiogram. A: Subcostal view illustrating two wide pseudoaneurysms isolated by organizing fibrous tissue; B: Apical view with inclination of the probe at a right angle to the skin showing two non-communicant adjacent cavities separated by fibrous tissue.

In the last several years, the incidence of CR has decreased with the development of "primary percutaneous coronary intervention (PPCI), which has been an important protective factor[5]". Risk factors include advanced age, female sex, first infarction, large infarction, and delivery of fibrinolytic therapy more than 14 h after the onset of symptoms. Our patient was in the 5th decade of life, female sex, and hypertensive, with an untreated large anterior MI. Hence, our patient was at high risk of developing CR. "Early reperfusion and the presence of collateral circulation, which limit the extent of



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Figure 4 Two-chamber view on transesophageal echocardiogram. Two-chamber view confirming the pseudoaneurysm and flow through the left ventricle.



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Figure 5 Cardiac magnetic resonance imaging. A: Two-chamber view showing the connection between the left ventricular (LV) cavity and the LV pseudoaneurysm (PAN) (arrow); B: Short axis view showing multiple cavities corresponding to the PANs isolated by fibrous tissue. LA: Left atrium; RV: Right ventricular.

myocardial tissue damage, decrease the risk of free wall rupture[6]".

To the best of our knowledge, the presented case is the first in the literature to show more than one PAN caused by MI with long-term evolution. In this case, the onset and progression were possibly influenced by the large extension of non-revascularized MI, and the severity of hypertension explained by the advanced stage of chronic kidney failure. The first evaluation by echocardiography in the early phase of acute MI did not show the development of dyskinesia or aneurysm. In acute LV PAN, once the diagnosis is confirmed, surgical repair is the preferred treatment, although conservative medical treatment for certain high-risk patients may be associated with a good outcome, "as has been described in some retrospective studies showing that patients with an incidental finding of chronic small LV PAN, less than 3 cm in size, and patients with increased surgical risk can be managed conservatively[7]". However, the preferred approach remains surgical management. Our patient was primarily treated by medical treatment and was scheduled for surgery after discussion with the surgical team, but she died after 4 wk from acute free intrapericardial rupture, in accordance with the literature showing that "PANs have a high risk of rupture, occurring in 30% to 45% of cases[8]". In patients treated conservatively, some complications may occur, such as thromboembolism, compression of adjacent structures, and infection.

CONCLUSION

PANs are caused by rupture of the myocardial wall and are an infrequent complication of acute MI that rapidly leads to death. However, some cases may take a subacute or chronic course when a small rupture is temporarily sealed by fibrinous pericardial adhesions or thrombus. No cases of multiple PANs of LV have been reported. The best weapon against this lethal complication is timely pharma-

cologic or mechanical reperfusion.

FOOTNOTES

Author contributions: Jallal H, Belabes S, and Khatouri A contributed equally to this work; Jallal H designed the case study, reviewed the literature, and wrote the manuscript; Khatouri A reviewed the literature and contributed to manuscript drafting; Belabes S performed the radiological analyses and interpreted the imaging findings; and all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Glucose lowering does not necessarily reduce cardiovascular risk in type 2 diabetes

Angeliki Bourazana, Grigorios Giamouzis, John Skoularigis, Filippos Triposkiadis, Andrew Xanthopoulos

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Abstract

Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects millions of people worldwide. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities to severely symptomatic biventricular dysfunction with increased mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse. DM leads also to cardiac electrical remodeling reacting on various targets. Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 and glucose-dependent insulinotropic peptide and constitute a safe and effective glucose lowering treatment option in patients with type 2 DM. Despite DPP-4 inhibitors' efficacy regarding glycemic control, their effect on cardiovascular outcomes (myocardial infarction, stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization, and cardiovascular death) in diabetic patients has been neutral. The potential correlation between atrial flutter and DPP-4 inhibitors administration needs further investigation.

Key Words: Dipeptidyl peptidase-4 inhibitors; Diabetes mellitus; Outcomes; Meta-analysis; Heart failure; Atrial flutter

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Core Tip: Dipeptidyl peptidase-4 inhibitors are a safe and effective glucose lowering treatment option in patients with type 2 diabetes mellitus. However, their effect on cardiovascular outcomes in diabetic patients has been neutral. The potential correlation between atrial flutter and dipeptidyl peptidase-4 inhibitors administration is an interesting finding, but since currently there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required.

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TO THE EDITOR

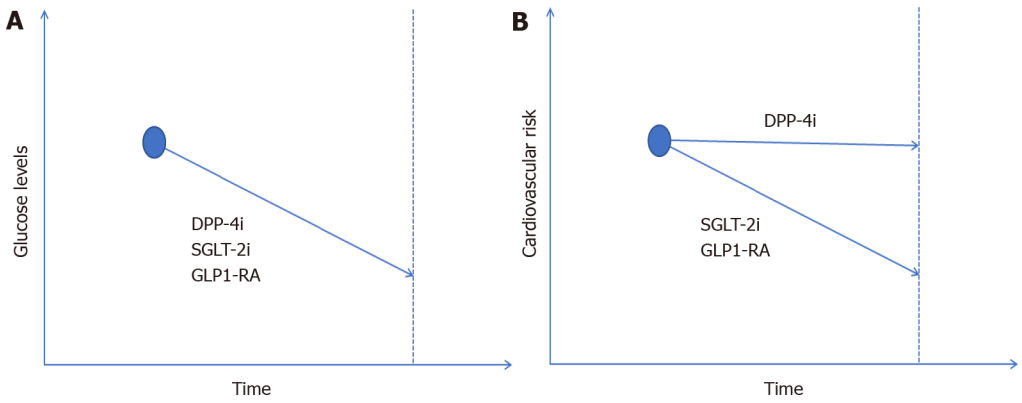
Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects 237.9 million males and 222 million females worldwide[1]. It is an established risk factor of cardiovascular disease, atrial and ventricular arrhythmias, as well as sudden cardiac death[2,3]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a safe and effective glucose lowering treatment option in patients with type 2 DM (T2DM). Nevertheless, pooled recent data on the effect of DPP-4 inhibitors on cardiovascular outcomes and major cardiac arrhythmias are lacking.

We read with great interest the paper by Patoulias *et al*[4], who attempted to close the abovementioned knowledge gap by performing a meta-analysis of six randomized controlled trials (52520 patients) concerning the impact of dipeptidyl peptidase-4 (DPP-4) inhibitors on "hard" cardiovascular outcomes and major cardiac arrhythmias. The authors concluded that DPP-4 inhibitors, compared to placebo, had no effect on fatal or non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization, and cardiovascular death and did not seem to confer any significant risk for major cardiac arrhythmias, with the exception of atrial flutter, which was associated with an increased risk equal to 52% (relative risk = 1.52, 95% confidence interval: 1.03-2.24, I^2 = 0%).

We agree with the authors' insight that the presence of DM per se increases the risk of adverse cardiovascular outcomes and arrhythmias and results in cellular destabilization of myocardial tissue altogether. For example, it has been demonstrated that diabetic patients present an increased propensity for developing heart failure[5]. Diabetic cardiomyopathy, defined as ventricular dysfunction in the absence of hypertension or coronary artery disease, has been attributed to the deregulated immune response in type-1 DM (T1DM) and to the background of obesity in the majority of T2DM patients. The amplified immune response of T1DM patients to myocardial injury, leads to the expansion of proinflammatory CD4+ T cells specific to myosin and the development of autoantibodies to MYH6 and other cardiac antigens. On the other hand, obesity that predominates over T2DM patients reduces the palliative actions of circulating natriuretic peptides on ventricular stress, pressure overload, and sympathetic activation. In the absence of natriuretic peptides' favorable actions, left ventricle hypertrophy, fibrosis, and insulin desensitization in skeletal muscles are more frequently observed in obese patients[5]. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities, developing progressively to severely symptomatic biventricular dysfunction with advanced mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse, originating in the heterogeneous risk factors that diabetes comes along, such as hypertension, hyperlipidemia, cardiovascular disease, and chronic kidney disease[6].

Except for the morphological implications on ventricular myocardium that account for the wide spectrum of left ventricular dysfunction, DM leads to cardiac electrical remodeling reacting on various targets. Among the diabetes-induced electrical disturbances, reduced conduction velocity, prolonged repolarization, and increased QT dispersion have been recognized, all predisposing to ventricular arrhythmias[7,8]. T1DM and T2DM lead to action potential duration prolongation, which becomes prominent on electrocardiography with a QRS prolongation in some diabetic patients[9]. QT duration prolongation subsequently predisposes to early after depolarizations development and an enhanced risk of torsade de pointes[10]. The proposed mechanisms are diabetes-exerted alterations in the function of several proteins involved in ion handling. More specifically, DM modifies ion channels responsible for depolarization as well as repolarization and resting phase[11]. Therefore, DM affects essentially all phases of action potential and correlates strongly to ventricular arrhythmias emergence.

The culprit pathophysiological mechanisms for the occurrence of atrial arrhythmias in DM substrate are not yet in depth elucidated. In atrial myocardium, DM favors the phenotypic switch of fibroblasts to myofibroblasts[12]. Mighty it is that diabetes induced atrial neuropathy as well as diabetes generated advanced myofibroblast differentiation promote atrial remodeling and lead to atrial cardiomyopathy



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Figure 1 Newer oral antidiabetic drugs, glucose levels, and cardiovascular risk. A: Dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and glucagon-like peptide-1 receptor agonists (GLP1-RA) are effective glucose lowering agents in patients with type 2 DM; B SGLT-2i and GLP1-RA have shown significant decreases in adverse cardiovascular events, whereas the effect of DPP-4 inhibitors on cardiovascular outcomes in diabetic patients has been neutral. DPP-4i: DPP-4 inhibitors; SGLT-2i: Sodium-glucose cotransporter 2 inhibitors; GLP1-RA: glucagon-like peptide-1 receptor agonists.

overall[13]. Nonetheless, on epidemiological basis, DM is a strong independent risk factor for atrial fibrillation (AF) and atrial flutter occurrence.

Several studies have demonstrated that antidiabetic drugs may have differing effects on the risk of new-onset AF[14]. Metformin has been associated with anti-atrial arrhythmic benefits[15]. A case control study revealed no association between sulfonylurea and incident AF, whereas the use of insulin was associated with increased risk of new-onset AF[16]. A recent meta-analysis showed that DPP-4 inhibitor treatment resulted in a non-significant decrease in the risk for AF, whereas both glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2-i) were associated with a significant decrease in the risk for AF, equal to 14% and 19%, respectively[17]. Liraglutide (a GLP1-RA) demonstrated favorable effects on electrophysiological changes regarding AF inducibility and conduction velocity decrease[18].

DPP-4 inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 and glucose-dependent insulinotropic peptide, which are called incretins. Subsequently incretins inhibit glucagon release and increase insulin secretion. Despite DPP-4 inhibitors' indisputable efficacy regarding glycemic control, their effect on cardiovascular outcomes in diabetic patients, as denoted in the aforementioned and previous studies, has been neutral[19,20]. Furthermore, the risk of hypoglycemia is admitted to be increased compared to SGLT2-i. SGLT2-i reduce hyperglycemia through inhibition of glucose reabsorption in the renal proximal tubules. Acting on glucose/Na co-transporter they promote natriuresis and display not solely hypoglycemic effects but also reduce major adverse cardiovascular events (cardiovascular and total mortality, fatal or nonfatal myocardial infarction, or stroke) and hospitalization for heart failure and improve outcome in chronic kidney disease in diabetic and non-diabetic patients[21]. GLP1-RA are oral hypoglycemic drugs that mimic the effects of the incretin hormone glucagon-like-peptide 1. GLP-RA stimulate insulin release, inhibit glucagon secretion, and slow gastric emptying. Liraglutide, albiglutide, and dualiglutide have all shown significant decreases in adverse cardiovascular events[22]. In line with this evidence, the European Society of Cardiology guidelines recommend the administration of SGLT-2i or GLP1-RA as a first option in the presence of high or remarkably high cardiovascular risk or of cardiovascular disease [23].

The potential correlation between atrial flutter and DPP-4 inhibitors administration is an interesting finding, but since there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required to establish this thesis as a widely accepted knowledge admissible in clinical practice. The authors speculated that the abovementioned correlation may stem from the inherent higher risk of atrial flutter that patients with DM carry[24]. However, it is also well known that DM per se is a risk factor of AF[24], which in the current meta-analysis was not associated with DPP-4 inhibitor use.

In conclusion, the authors should be congratulated on their attempt to provide state of the art data on the association between DPP-4 inhibitors and cardiovascular outcomes as well as major cardiac arrhythmias. The reported increased risk of atrial flutter in patients receiving DPP-4 inhibitors needs further investigation (Figure 1).

FOOTNOTES

Author contributions: Bourazana A and Xanthopoulos A wrote the letter; Giamouzis G, Skoularigis J, and Triposkiadis F revised the letter; All authors made substantial contributions to conception and design of the study, acquisition of data or analysis and interpretation of data, drafted the article or made critical revisions related to important intellectual content of the manuscript, and gave final approval of the version of the article to be published.

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MINIREVIEWS

Same day discharge after structural heart disease interventions in the era of the coronavirus-19 pandemic and beyond

Abdulaziz A Asbeutah, Muhammad Junaid, Fatima Hassan, Jesus Avila Vega, Nephertiti Efeovbokhan, Rami N Khouzam, Uzoma N Ibebuogu

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Abstract

With recent advancements in imaging modalities and techniques and increased recognition of the long-term impact of several structural heart disease interventions, the number of procedures has significantly increased. With the increase in procedures, also comes an increase in cost. In view of this, efficient and cost-effective methods to facilitate and manage structural heart disease interventions are a necessity. Same-day discharge (SDD) after invasive cardiac procedures improves resource utilization and patient satisfaction. SDD in appropriately selected patients has become the standard of care for some invasive cardiac procedures such as percutaneous coronary interventions. This is not the case for the majority of structural heart procedures. With the coronavirus disease 2019 pandemic, safely reducing the duration of time spent within the hospital to prevent unnecessary exposure to pathogens has become a priority. In light of this, it is prudent to assess the feasibility of SDD in several structural heart procedures. In this review we highlight the feasibility of SDD in a carefully selected population, by reviewing and summarizing studies on SDD among patients undergoing left atrial appendage occlusion, patent foramen ovale/atrial septal defect closure, Mitra-clip, and trans-catheter aortic valve replacement procedures.

Key Words: Mitra-clip; Transcatheter aortic valve replacement; Same-day discharge; Atrial septal defect; Coronavirus

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Core Tip: Same-day discharge can safely be done among a highly selected group of patients undergoing structural interventional cardiac procedures.

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INTRODUCTION

Same-day discharge (SDD) following percutaneous coronary interventions (PCI) in certain patient groups has been shown to have no increased risk of death, re-hospitalization, and has been associated with increased patient satisfaction[1-4]. According to the 2021 American College of Cardiology (ACC) SDD after PCI decision pathway, SDD is defined as a procedure that does not include supervised overnight monitoring in a facility or hospital after an elective procedure[5]. Several prerequisites have been postulated and the ACC consensus pathway provides a checklist that can be used to determine eligibility for SDD in patients undergoing PCI, however, no consensus has been formulated yet for patients undergoing structural interventional heart procedures[5]. Ideally, patients should be identified as candidates suitable for SDD before the procedure, have an uncomplicated procedure and recovery, be able to pick up required medications, be willing to depart on the same day, and have the means to care for themselves or have reliable caregivers to monitor them over the next 24 h. Most patients would be followed up on the same day *via* telephone-health and some are offered next day in-person visits to be assessed by the interventionalist[5,6]. This has now become important especially due to the current coronavirus disease 2019 (COVID-19) pandemic, as initially all elective procedures were recommended to be postponed by several leading health care authorities to prevent unnecessary exposure to patients and health care workers and to conserve personal protective equipment and bed availability. Delays in timely intervention among patients with structural/valvular heart disease place these patients at increased risk for adverse cardiovascular outcomes, including death[7]. A position statement from the ACC/Society for Cardiovascular Angiography and Interventions provides a framework to triage patients in need of structural heart interventions during the COVID-19 pandemic and discusses pre-procedural evaluation by a dedicated "heart team" and procedural indications[7]. In this manuscript, we aim to review and summarize the available literature on the safety of SDD among patients undergoing structural heart interventional procedures including, left atrial appendage occlusion (LAAO), patent foramen ovale (PFO)/atrial septal defect (ASD) closure, Mitra-clip, and Trans-catheter aortic valve replacement (TAVR) procedures.

SEARCH STRATEGY

We performed an extensive search of electronic databases including PubMed/Medline, Google Scholar, and ClinicalTrials.gov from inception till October 1st, 2021. We included studies that included structural intervention procedures and included patients who were discharged on the same day of the procedure. Eligible studies were reviewed and information was summarized by all authors.

LEFT ATRIAL APPENDAGE OCCLUSION DEVICE PROCEDURE

It was estimated that in the year 2010 around 9 million residents of the European Union were living with Atrial Fibrillation (AF). AF significantly increases the risk of embolic strokes and the postulated primary source of thrombus formation is the left atrial appendage[8]. Current ACC guidelines recommend the option of LAAO for patients with non-valvular AF at high risk for serious bleeding events or who have contraindications for long-term oral anticoagulation to reduce the risk of embolic

stroke[9]. Left atrial appendage occlusion can be achieved percutaneously by deploying the WATCHMAN device (Boston Scientific, Marlborough, MA, United States), at the left atrial appendage ostia *via* transseptal puncture using a 12 French sheath *via* trans-femoral venous access. In the PROTECT-AF and the PREVAIL trials, LAAO was found to be non-inferior to warfarin in the prevention of stroke, systemic embolization, and cardiovascular death[10,11]. The EWOLUTION study concluded that LAAO led to reduced incidence of stroke and non-procedural bleeding[12].

Traditional practice is to admit patients and observe them overnight after LAAO device procedures and to discharge them after around 24 h. Complications following LAAO procedures typically occur during or within a few hours after the procedure[13], hence certain groups created a clinical pathway for safe SDD after LAAO procedures. There have been four recently published studies with data regarding the feasibility of SDD among patients that underwent LAAO, with the vast majority being with the WATCHMAN device[13-16]. In a single-center, retrospective analysis of 190 successful LAAO device implantation using the WATCHMAN device, Tan *et al*[14] compared 7 and 45 d outcomes among SDD patients compared to non-SDD patients. In their study, 72 patients were discharged on the same day of the procedure compared to 118 patients that required at least one night of observation. In their study, pre-requisites for SDD were being able to ambulate two hours after the procedure to assess vascular integrity, anti-platelet and oral anticoagulant started or on hand, hemodynamic stability, no vascular access site complications, and some patients underwent a trans-thoracic echocardiogram (TTE) before discharge. The primary outcome of the study was a composite of stroke, systemic embolism, bleeding requiring blood transfusion, vascular access site complication, and death. The 7 d and 45 d primary outcomes were met by (1.2% *vs* 5.9% of SDD *vs* non-SDD patients) and (2.8% *vs* 9.3% of SDD *vs* non- SDD patients), respectively, $P = 0.26$ and $P = 0.14$. There was also no difference in re- admission or 45 d peri-device flow > 5 mm between SDD and non-SDD patients[14].

Several other smaller single-center studies reported on the feasibility of SDD among patients undergoing LAAO procedures. In a study by Gilhofer *et al*[13], 24 out of 78 patients were discharged on the same day of the LAAO procedure. Pre-requisites to SDD in their study were lack of significant frailty determined by a local scoring system, good home support, a TTE performed after 5 h of step-down observation revealing no significant pericardial effusion, and agreement to come in again the next morning for a repeat TTE and outpatient evaluation. They reported no significant events in either the SDD or non-SDD group[13]. In an effort to enhance SDD, Marmagkiolis *et al*[15] performed all WATCHMAN procedures under conscious sedation and were able to discharge 112 of their 178 patients within six hours after the procedure. They also required a TTE before discharge without evidence of significant pericardial effusion and a next-day follow-up TTE. They reported no complications in the SDD group. In another retrospective analysis of 177 LAAO procedures in the United Kingdom using various LAAO devices, 78 patients were discharged on the same day. Half of the patients had LAAO with the Amplatzer Cardiac Plug, 41% with the Amulet Occluder, and 2.5% with watchman. They reported that 1.7% of all their procedures suffered major in-hospital complications, hence were not suitable for SDD. They had required all patients to have a TTE on the day of the procedure without evidence of pericardial effusion, available transportation, and completion of the procedure before 4 pm to be considered eligible for SDD. In their study one patient from the SDD group was readmitted within 7 d, however, they concluded that it would have not been prevented by an overnight stay. Of note, all patients were discharged on DAPT for 28 d and then transitioned to SAPT thereafter, consistent with the European expert consensus statement[16,17].

MITRA-CLIP

Chronic systolic heart failure eventually leads to left ventricular dilatation and mitral regurgitation (MR) may develop secondary to ventricular remodeling and geometric dislocation of the mitral valve apparatus including the papillary muscles and chordae tendineae, impairing coaptation of the mitral leaflets[18]. In a recent meta-analysis of 45900 patients with secondary mitral regurgitation, secondary mitral regurgitation was associated with an increased risk of heart failure hospitalizations, cardiac mortality, and death[19]. The MITRA-FR study showed no difference in the primary outcome of death from any cause or hospitalization for heart failure (HF) at one year, while the COAPT trial showed a significant reduction in HF hospitalizations and all-cause mortality within 2 years[20,21]. The main reason for the observed differences was attributed to the enrollment in the COAPT trial requiring all patients to be on maximally tolerated guideline-directed medical therapy (GDMT) before enrollment, as compared with the MITRAFR trial[22]. The current 2021 ACC expert consensus HF guidelines recommend that GDMT should be optimized before percutaneous trans-catheter mitral valve repair based on evidence from previous randomized control trials[20,21,23]. The main reason for overnight observation in Mitra-clip procedures is usually to monitor for vascular access complications, as it requires a 24 French sheath introduced *via* the femoral vein, raising concern over possible bleeding complications.

In a single-center retrospective study by Marmagkiolis *et al*[24], 95 patients underwent Trans-catheter mitral valve repair, of which 82 were discharged on the same day of the procedure. In their study, 39

patients had primary MR and 43 had secondary/Functional MR due to heart failure. They included patients with a society of thoracic surgery (STS) score > 8% and deemed unsuitable for surgical mitral valve repair/replacement. The mean age of participants was 80.2 ± 2.5 years, mean EF = 45%, 20% with grade 3 MR, and 80% with grade 4 MR. They had a 100% procedure success rate and all procedures were performed under minimal conscious sedation or monitored anesthesia care and TEE guidance. All patients that had no intra-procedural complications and a stable course during observation for 6-8 h and were able to walk with no vascular access complications were considered for SDD. In their study, all patients underwent a figure of eight suture to the access site and only one patient had suffered from a minor bleeding event according to the valve academic research consortium-2 criteria[24].

In a case report by Chen *et al*[25], they describe an expedited Mitra-clip procedure for an 86-year-old patient with severe MR who was discharged on the same day during the COVID-19 pandemic. His STS risk score was 4.2%, with an EF of 40%, and NYHA III heart failure symptoms. Following the procedure, the patient was observed for four hours, a TTE showed no pericardial effusion, and confirmed the placement of the Mitraclips. The patient was sent home with a 7 d continuous rhythm-monitoring device without any documented arrhythmia and was seen on days 1 and 2 after the procedure *via* telephone-health calls[25]. These prior studies indicate that SDD is reasonable and possible for selected patients undergoing the Mitra-clip procedure without procedural complications and with adequate follow-up.

TAVR

Aortic stenosis (AS) is the most common type of valvular heart disease in the United States and is typically caused by calcific degeneration of a tri-leaflet aortic valve or stenosis of a congenital bicuspid aortic valve (AV)[26]. TAVR is an alternative to surgical aortic valve replacement for treating severe AS or Bio-prosthetic AV dysfunction in patients at high or intermediate surgical risk based on the STS score, frailty, and existing comorbidities[27]. Recently, the five-year outcomes from the PARTNER trial were published and showed no significant difference in the incidence of death or stroke in patients undergoing TAVR at intermediate surgical risk compared to SAVR[28]. Despite TAVR being a commonly performed interventional procedure in the current era, it does not come without the potential for serious procedural and post- procedural complications. As with any interventional procedure, TAVR has been associated with vascular access complications especially due to the large sheath introduced mainly *via* the femoral artery. Other complications include pericardial effusions and tamponade, peri-procedural stroke, and new conduction abnormalities such as high-grade atrioventricular block (AV) and complete heart block requiring permanent pacemaker (PPM) implantation[28,29]. Hence, the standard practice is to observe patients 24-48 h after the procedure for new or worsening conduction abnormalities[30]. However, with the COVID-19 pandemic and the patient population undergoing TAVR usually being elderly with multiple co-morbidities placing them at higher risk of COVID-19 related complications, several studies sought and reported on SDD following TAVR[6,31,32].

In a case series, three elderly patients with AS underwent TAVR and were discharged home on the same day with 7 d of continuous rhythm monitoring[31]. Authors hypothesized that SDD may be safe after TAVR in a pre-selected cohort of patients with AS and also help reduce the risk of unnecessary COVID-19 transmission, conserve hospital beds, and PPE. Since the authors recognized that the loss of a single patient secondary to preventable complications due to early discharge is a never event, they developed protocols and safety nets for their SDD protocol. They considered patients with no significant comorbidities such as end-stage kidney disease, hemoglobin < 9 mg/dL, NYHA ≥ 3 symptoms, EF < 30%, no significant pericardial effusion, new or worsening AV block, and no vascular access complications able to be discharged on the same day of the procedure after observation for 4-6 h. In order to minimize complications, they performed ultrasound-guided vascular access, performed a TTE immediately after device deployment and 4 h after deployment to detect complications, obtained serial electrocardiogram's to mainly assess QRS intervals, ambulated patients after 4 h, and performed serial lower extremity pulse checks. In their case series, there were no new conduction abnormalities detected and all patients were followed up on days 1 and 2 post-procedure. They had no deaths or re-admissions within 24 d of the procedure[31].

Rai *et al*[32] reported their experience of SDD based on 6 patients with severe symptomatic AS or bio-prosthetic valve dysfunction and proposed an SDD protocol. Since the major barrier to discharge patients after TAVR is related to new or worsening conduction abnormalities, they hypothesized that having a pre-procedure PPM or discharge with real-time continuous monitoring could allow for safe SDD. In their case series, they included patients that had predictors of next-day discharge after TAVR based on previous analyses[30]. In a recent study, rapid atrial pacing using the temporary pacing wire used for ventricular standstill during TAVR deployment while in the right atrium, had a 99% negative predictive value for pacemaker implantation after TAVR if no Wenckebach phenomenon developed at a heart rate of 120 bpm[33]. Rai *et al*[32] utilized this method in one of their patients and proposed its use prior to SDD in all patients without chronic AF, pre-existing PPM, or pre-existing AV block.

Additionally, all patients had pre-procedure and post-procedure ECGs performed and if there was a pre- existing right bundle branch block (RBBB) or new AV conduction disturbances, patients were admitted overnight for observation. Otherwise, if patients had a pre-procedure PPM, unchanged ECG from baseline, and no Wenckebach on rapid atrial pacing, they were considered for SDD after 4 h of observation given lack of vascular access site complications. Despite one of their patients developing Wenckebach at 110 bpm, he was discharged on the same day due to a low positive predictive value of the finding and the lack of other conduction abnormalities noted. All six patients were followed with continuous rhythm monitoring for seven days and followed up in person the next day. Based on their experience, they recommend patients with a baseline RBBB not be considered for SDD, as it is one of the strongest predictors for pacemaker need following TAVR[34], additionally, patients who develop a new left bundle branch block after TAVR should be kept overnight for monitoring. Of note, all 6 patients in their series underwent balloon-expandable valve replacements and these recommendations could not be generalized to patients undergoing TAVR utilizing a self-expandable system, as there has been evidence suggesting higher PPM implantation in these patients[35].

The largest study regarding SDD in TAVR was conducted by Perdoncin *et al*[6], in which they report on 29 consecutive SDD TAVR procedures at their center and compared outcomes to patients who underwent TAVR at their center that were non-SDD, who could have qualified for SDD based on their devised protocol. They considered patients with an EF > 30%, hemoglobin > 10, INR < 2, those who received a contrast load < 3 times the estimated Glomerular Filtration Rate (eGFR), without new or worsening conduction abnormalities, or hemodynamic instability for SDD. The primary outcome was to compare 30 d mortality, PPM implantation, stroke, and cardiovascular-related admissions in SDD patients and non-SDD patients. They compared 29 SDD patients to 128 patients that were non-SDD who currently met their protocol for SDD and were fairly similar with regards to baseline characteristics. Procedural characteristics were similar in both groups and all cases were performed *via* trans-femoral access under conscious sedation. Post-procedure, both groups had no in-hospital complications. At 30 d, there were no deaths, the rate of stroke was 0.6%, and delayed PPM implantation was also 0.6% in both groups combined. They noted a trend towards a higher rate of cardiovascular re-admissions in the non-SDD group compared to the SDD group. One patient in the non-SDD group was re-admitted for high-grade AV block requiring PPM implantation. Of note, both self-expanding and balloon expanding valves were used with a trend towards higher use of self-expanding valves in the SDD group. However, further studies are required to determine the feasibility of the use of self- expanding valves for SDD TAVR procedures given the potential concern of outward sub-annular radial force and risk of delayed conduction changes[36].

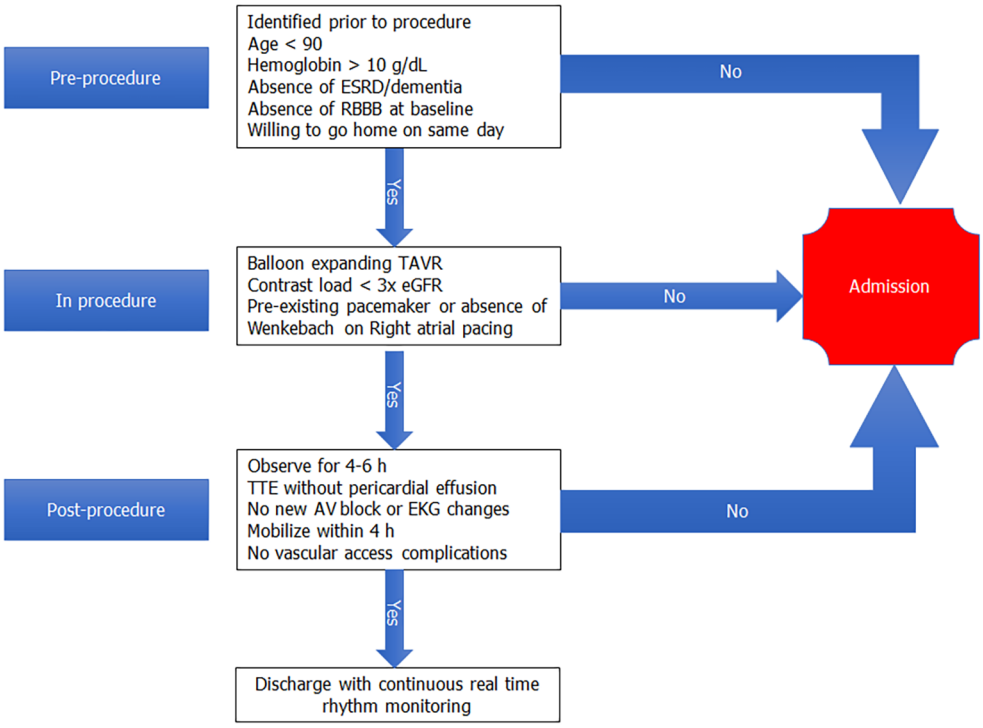
Overall, based on the prior studies the main concern for SDD in TAVR is related to new or worsening conduction abnormalities that could arise during or after the procedure. All patients considered being candidates for SDD should be identified early during a "heart team" multi-disciplinary discussion and deemed suitable based on pre-procedure pre- requisites. All patients with a baseline RBBB, new high-grade AV block after the procedure, new inter-ventricular conduction delay, or Wenckebach on right atrial pacing after valve deployment should be admitted overnight for inpatient observation. If considered for SDD, all patients must be willing to go home, have no vascular access complications after initial observation, have close follow-up arranged, and be sent home with a real-time rhythm monitor to detect arrhythmias. We present a proposed protocol for SDD following TAVR in Figure 1.

PFO/ASD CLOSURE

ASDs are one of the most common congenital heart defects found in the general population. Unrepaired ASDs can result in various cardiopulmonary adverse events such as arrhythmias, pulmonary hypertension, and paradoxical embolization. Current adult congenital heart disease guidelines recommend ASD closure in carefully selected patients with hemodynamic instability or clinical consequences resulting from their long- standing intra-cardiac shunting[37]. Additionally, up to 50% of patients with a cryptogenic stroke have been found to have an associated PFO[38]. The first three randomized controlled trials CLOSURE I, PC, and RESPECT failed to show any statistical significance in secondary stroke prevention[39-41]. More recent studies, however, have demonstrated that in carefully selected patients, PFO closure is preferable to medical therapy for secondary stroke prevention of cryptogenic strokes in patients with PFO[42,43]. In a review article published in the Journal of the American College of Cardiology, authors proposed a clinical pathway to aid in the appropriate selection of patients that should undergo PFO closure based on randomized trials showing benefit[38].

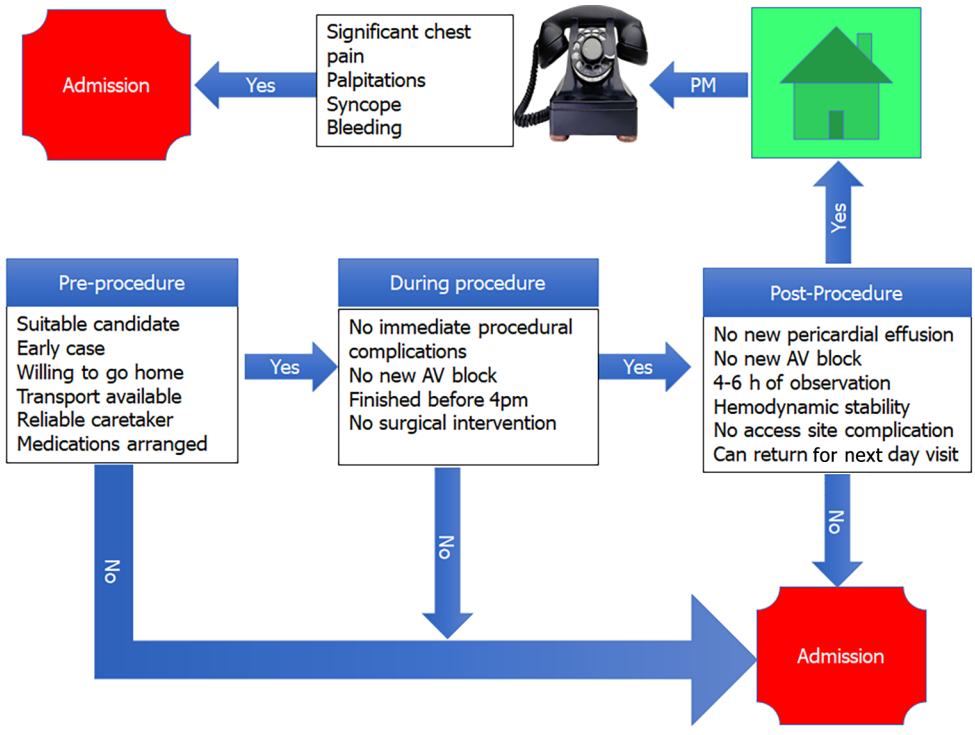
The PFO closure procedure is usually done as a day case procedure using one of only two FDA approved devices in the United States; the Gore Cardioform Septal Occluder (W.L. Gore and Associates, Inc, Newark, DE, United States) or the Amplatzer PFO Occluder (Abbott Structural, Santa Clara, CA, United States). The procedure is done under fluoroscopic and echocardiographic guidance in the form of TEE or intracardiac echocardiography (ICE) *via* femoral vein access.

In a single-center, retrospective study of 53 consecutive patients the safety and feasibility of SDD in PFO closure using ICE was evaluated[44]. In this study, a 12 Fr sheath for the occluder device and an 11



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Figure 1 Proposed algorithm for same day discharge for patients undergoing transcatheter aortic valve replacement. AV: Atrio-ventricular; eGFR: Estimated glomerular filtration rate; EKG: Electrocardiogram; ESRD: End stage renal disease; RBBB: Right bundle branch block; TAVR: Transcatheter aortic valve replacement; TTE: Transthoracic echocardiogram.



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Figure 2 Proposed algorithm for same day discharge for patients undergoing structural interventional procedures. AV: Atrio-ventricular.

Fr sheath for the ICE probe were inserted into the femoral vein using only local anesthetic and light sedation. In this study 5 of the 53 patients were found to not have PFO by ICE. The remaining 48 patients underwent successful PFO closure with the HELEX occluder (GORE, Flagstaff, AZ, *n* = 47) and the Amplatzer device (AGA medical corporation, Golden Valley, MN, *n* = 1). SDD candidates had to

Table 1 Proposed pre-requisites for same day discharge in structural cardiac procedures

Pre-procedure
Administrative buy-in
Experienced operator
Same day discharge multi-disciplinary team including social workers and nursing
Elective procedure
Reliable means for follow-up
Patient without significant co-morbidities
Willing to depart on the same day
Adequate social support
During procedure
Intra-Procedural monitoring without significant hemodynamic compromise
Successful vascular access without immediate complications
Successful deployment of device
Right atrial pacing for TAVR without wenkebach
Post-procedure
Hemodynamic monitoring for 4-6 h without instability
Able to mobilize without assistance
Vascular access site integrity
TTE without significant pericardial effusion
No new AV block or inter-ventricular conduction delays
Prescriptions arranged
Evening phone call from provider
Next day in-person follow up for imaging and laboratory investigations

AV: Atrioventricular; TAVR: Transcatheter aortic valve replacement; TTE: Transthoracic echocardiogram.

ambulate successfully following the procedure and undergo TTE prior to discharge to confirm appropriate device placement. Appropriate device positioning was confirmed on all 48 patients. Only 1 patient failed SDD due to groin hematoma requiring observation overnight and was discharged the following day. No other complications were reported. Patients were scheduled for a three-month TTE follow-up to assess for any residual shunting. At three months follow up, 45/48 (94%) had no residual shunt.

In a nonrandomized, retrospective, single-center observational study Barker *et al*[45] analyzed peri-procedural outcomes of 467 patients undergoing PFO closure. All patients underwent closure with the Amplatzer PFO Occluder; 381 patients underwent fluoroscopy-only occlusion and 86 patients with ICE guidance. ICE guidance was used as a backup modality and limited to complex atrial septal anatomy as seen on TEE. There was no significant difference in periprocedural complications between the fluoroscopy-only and ICE group. SDD occurred in 97.6% of all patients; 98.2% and 95.3% in the fluoroscopy and ICE group respectively (P = 0.246). Complete closure was seen in 94.6% of patients at the three-month TTE follow-up. There was no significant difference in death, 30-day readmission, device thrombosis, and stroke/TIA between the fluoroscopy-only and ICE group. As of the writing of this article, the literature review reveals only one prospective case series proposing a SDD clinical pathway for patients undergoing ASD/PFO closure[46]. Prerequisites for SDD following PFO closure in their study includes hemodynamic stability and the ability to ambulate 2 h post- procedure. Patients are permitted to go home 1-hour post mobilization with a 6-month TEE follow-up and 6 months of antithrombotic therapy based on the device placed. In their study of 187 patients that underwent PFO/ASD closure (PFO = 117, ASD = 70); SDD occurred in 99.4% of cases. There were no major complications, and a 6-month TEE revealed no residual shunt in 96% of patients[46].

Table 2 Summary of Studies with same day discharges for structural heart disease procedures

Ref.	Year	Procedure	Same day discharge, *n*	Outcome
Gilhofer *et al*[13]	2020	LAAO	24	No significant difference in overall events between SDD and non SDD
Tan *et al*[14]	2021	LAAO	72	No significant difference in 7 and 45 d outcomes between SDD and non SDD
Marmagkiolis *et al*[15]	2021	LAAO	112	No complications among patients that underwent SDD
Williams *et al*[16]	2018	LAAO	78	1 patient from the SDD group was readmitted within 7 d
Marmagkiolis *et al*[24]	2021	Mitra-clip	82	No intra-procedure complications, only 1 patient had minor access site hematoma
Chen *et al*[25]	2020	Mitra-clip	1	No post procedure complication
Perdoncin *et al*[6]	2021	TAVR	29	No in hospital complications, no 30 d deaths
Russo *et al*[31]	2020	TAVR	3	No deaths or re-admissions within 24 d of procedure
Rai *et al*[32]	2021	TAVR	6	No immediate complications or events on 7 d rhythm monitor
Ponnuthurai *et al*[44]	2009	PFO/ASD	48	One Patient with groin hematoma immediately after procedure
Barker *et al*[45]	2020	PFO/ASD	455	No significant difference in death, 30 d readmission, device thrombosis, and stroke/TIA

ASD: Atrial septal defect; LAAO: Left atrial appendage occlusion; PFO: Patent foramen ovale; SDD: Same day discharge; TAVR: Transcatheter aortic valve replacement; TIA: Transient ischemic attack.

FUTURE SCOPE

Adopting a standardized method for same-day discharges will help reduce adverse events. However, as most of the evidence available to date comes from case series and retrospective studies, there is a need for larger prospective studies to be undertaken to validate the safety of SDD across a greater cohort of patients undergoing structural intervention cardiac procedures, to be reflected in the guidelines, before it becomes the standard of care.

CONCLUSION

Same-day discharge appears to be feasible in appropriately selected patients undergoing TAVR, Mitra-clip, LAA, ASD/PFO closure. Safe same-day discharge has the potential to not only reduce hospital costs but also improve patient satisfaction. The availability of a "heart team" consisting of a multi-disciplinary group of providers to identify suitable patients for SDD is prudent. Additionally, only centers with significant volume and experience performing complex structural procedures should consider SDD in their pre-selected suitable patients. We propose an algorithm to facilitate SDD following structural intervention procedures based on the review of available literature (Figure 2, central figure). We also provide a framework checklist to consider when adopting a SDD approach at centers performing structural intervention procedures along with a summary of previous studies with SDD with structural heart procedures (Tables 1 and 2).

FOOTNOTES

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ORIGINAL ARTICLE

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Bioinformatics prediction of potential mechanisms and biomarkers underlying dilated cardiomyopathy

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Abstract

BACKGROUND

Heart failure is a health burden responsible for high morbidity and mortality worldwide, and dilated cardiomyopathy (DCM) is one of the most common causes of heart failure. DCM is a disease of the heart muscle and is characterized by enlargement and dilation of at least one ventricle alongside impaired contractility with left ventricular ejection fraction < 40%. It is also associated with abnormalities in cytoskeletal proteins, mitochondrial ATP transporter, microvasculature, and fibrosis. However, the pathogenesis and potential biomarkers of DCM remain to be investigated.

AIM

To investigate the candidate genes and pathways involved in DCM patients.

METHODS

Two expression datasets (GSE3585 and GSE5406) were downloaded from the Gene Expression Omnibus database. The differentially expressed genes (DEGs) between the DCM patients and healthy individuals were identified using the R package "linear models for microarray data." The pathways with common DEGs were analyzed *via* Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and gene set enrichment analyses. Moreover, a protein-protein interaction network (PPI) was constructed to identify the hub genes and modules. The MicroRNA Database was applied to predict the microRNAs (miRNAs) targeting the hub genes. Additionally, immune cell infiltration in DCM was

analyzed using CIBERSORT.

RESULTS

In total, 97 DEGs (47 upregulated and 50 downregulated) were identified. GO analysis showed that the DEGs were mainly enriched in "response to growth factor," "extracellular matrix," and "extracellular matrix structural constituent." KEGG pathway analysis indicated that the DEGs were mainly enriched in "protein digestion and absorption" and "interleukin 17 (IL-17) signaling pathway." The PPI network suggested that collagen type III alpha 1 chain (COL3A1) and COL1A2 contribute to the pathogenesis of DCM. Additionally, visualization of the interactions between miRNAs and the hub genes revealed that hsa-miR-5682 and hsa-miR-4500 interacted with both COL3A1 and COL1A2, and thus these miRNAs might play roles in DCM. Immune cell infiltration analysis revealed that DCM patients had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells.

CONCLUSION

COL1A2 and COL3A1 and their targeting miRNAs, hsa-miR-5682 and hsa-miR-4500, may play critical roles in the pathogenesis of DCM, which are closely related to the IL-17 signaling pathway and acute inflammatory response. These results may provide useful clues for the diagnosis and treatment of DCM.

Key Words: Dilated cardiomyopathy; Bioinformatics; Differentially expressed genes; Function enrichment analysis; Protein-protein interaction network; Immune cell infiltration

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Core Tip: As the most common cause of heart failure, the diagnosis and therapy for dilated cardiomyopathy (DCM) are still unsatisfactory because of its indistinct pathogenesis and specific biomarkers. Thus, we comprehensively utilized the microarray data from the Gene Expression Omnibus database to uncover the biomarker and mechanisms underlying DCM development. Collagen type III alpha 1 chain and collagen type I alpha 2 chain, which are regulated by hsa-miR-5682 and hsa-miR-4500, may play critical roles in the pathogenesis of DCM through the acute inflammatory response and interleukin 17 signaling pathway. These biomarkers and mechanisms need to be further studied.

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INTRODUCTION

Dilated cardiomyopathy (DCM) is a progressive myocardial disease. It accounts for 30%–40% of heart failure cases and leads to high mortality worldwide[1]. DCM is characterized by biventricular dilatation, cardiac systolic dysfunction, and ventricular remodeling[2]. Recently, several studies have reported that mutations, myocarditis, hypertension, and ischemia are the induction factors of DCM[3,4]. Increasing evidence shows that various gene mutations and biomarkers are associated with DCM[5-7]. Mutations in cytoskeletal proteins, including dystrophin[8] and desmin[9], impair muscular force transmission and thereby contribute to the development of DCM. Mutations in lamin A/C, a nuclear membrane protein, usually cause DCM with atrioventricular block and atrial fibrillation[10]. Li *et al*[11] reported that mutation of aryl hydrocarbon receptor nuclear translocator-like protein 1 (known as BMAL1) plays a critical role in the development of DCM through the regulation of mitochondrial fission and mitophagy *via* mitochondrial protein B cell leukemia/lymphoma 2 interacting protein 3. Mutations in thin filament regulatory proteins including cardiac troponin T, cardiac troponin I, and α-tropomyosin can cause DCM with systolic dysfunction by reducing fractional shortening and systolic calcium level[12]. Moreover, some biomarkers associated with the development of DCM have been reported. For example, syndecan-1 and syndecan-4 may serve as useful biomarkers for predicting adverse cardiovascular events in DCM patients[13,14]. Carbonic anhydrase 2 and 3 are associated with heart failure and are potential risk biomarkers for DCM[15], and serum fibroblast growth factor 21 level is linked to the prognosis of DCM [16].

Several studies have sought DCM-related genes and mechanisms *via* bioinformatic methods and found some meaningful results. Huang *et al*[17] found that Fos proto-oncogene, AP-1 transcription factor subunit, tissue inhibitor of metalloprotease-1, and serpin family E member 1 may serve as therapeutic targets in DCM. Zhao *et al*[18] identified 89 differentially expressed genes (DEGs), mainly enriched in the extracellular matrix and biological adhesion signaling pathways, which may play significant roles in the development of DCM. However, the main cause(s) and pathogenic mechanism(s) underlying DCM are still unknown; thus, DCM is mostly diagnosed late, which causes a poor prognosis in turn. More studies are urgently needed to improve the diagnostic and therapeutic efficiency in DCM. The Gene Expression Omnibus (GEO) database includes many DCM-related microarray data, which have not been fully utilized. These data can be used to identify additional candidate biomarkers and pathways to further explore the cause(s) of DCM. To investigate the candidate genes and pathways involved in DCM patients, we analyzed the two gene expression data sets GSE3585 and GSE5406. Using the "linear models for microarray data" (limma) method, we identified 97 DEGs between healthy individuals and DCM patients. In addition, we identified the mechanisms commonly regulated by the DEGs *via* Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses, and gene set enrichment analyses (GSEA). Moreover, a protein-protein interaction network (PPI) network was applied to identify the hub genes that may contribute to the pathogenesis of DCM and predict the microRNAs (miRNAs) targeting the hub genes. Furthermore, we investigated the pattern of immune cell infiltration in DCM.

MATERIALS AND METHODS

Microarray data extraction from the GEO database

The mRNA expression profiles GSE3585 and GSE5406 in the GEO database (http://www.ncbi.nlm.nih.gov/geo/), which is a shared platform in which researchers deposit their microarray data related to various diseases, were downloaded. The GSE3585 dataset, generated by Barth *et al*[19], and the GSE5406 dataset, generated by Hannenhalli *et al*[20], consisted of 7 DCM patients and 5 healthy individuals, and 86 DCM patients and 16 healthy individuals, respectively. In total, 114 samples of the left ventricular myocardium, consisting of 93 DCM and 21 healthy samples (control group), were included in this study.

Data processing and DEGs identification

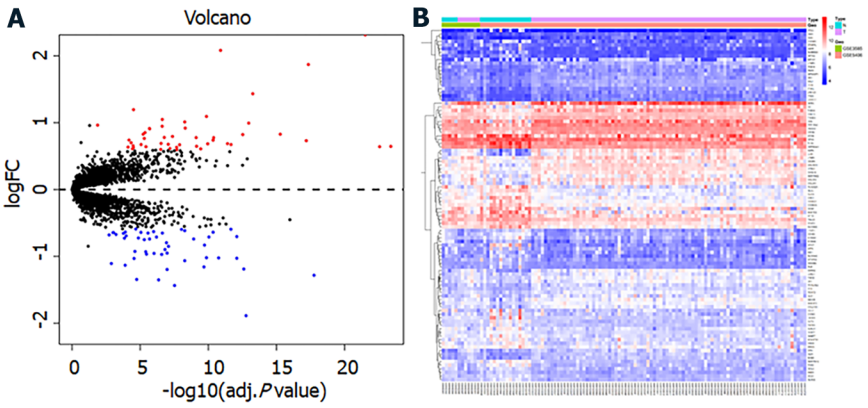
The two datasets GSE3585 and GSE5406 were loaded onto the GPL96 platform (Affymetrix Human Genome U133A Array [HG-U133A]). Additionally, the series matrix and platform annotation for the two databases were downloaded from the GEO database. The probe identity documents were transformed into gene symbols. Then, *via* the R package "Surrogate Variable Analysis," the two databases were merged, and any batch effect was removed using the "Empirical Bayes" method[21]. The R package "limma" was applied to identify the DEGs between the DCM and healthy myocardium tissues[22]. The screening criteria were set as $P < 0.05$ and $|\log \text{fold change (FC)}| > 0.589$ (FC > 1.5). Volcano and heat maps were generated using R software.

Gene expression enrichment analysis

The gene expression enrichment analysis in this study included GO analysis (https://www.geneontology.org)[23], KEGG (https://www.genome.jp/kegg)[24] pathway analysis, and GSEA (https://www.gsea-msigdb.org/gsea) analysis[25]. The DEGs were inputted into Metascape (https://metascape.org)[26]: The species was selected as *Homo sapiens*; The screening standard was set as $P < 0.05$; and The GO terms of biological process (BP), cellular component (CC), and molecular function (MF) were analyzed and KEGG pathway analysis was performed with the criteria of $P < 0.05$. GSEA interprets the biological function of the expression dataset. The expression dataset in the DCM cases *vs* healthy tissues was loaded into GSEA 4.0.3 software, set gene sets database as GO gene set (c5.all.v7.1.symbols.gmt), set number of permutations as 1000, set phenotype labels as control *vs* DCM, set collapse/remap to gene symbols as no collapse, set permutation type as phenotype, and the other parameters were set at default parameters. Then the GSEA software was used to obtain the enrichment results. The enriched terms were defined as significant with nominal $P < 0.05$.

PPI network construction and hub gene identification

The PPI network was constructed with the online website Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, https://stringdb.org/cgi/input.pl)[27] to contribute to the understanding of the interactive relationship among DEGs. The DEGs were inputted into this website, species of *Homo sapiens* was selected, and the identification criterion was set as combined score > 0.4 (medium confidence). Then the profile of interacting node pairs was imported into Cytoscape (https://cytoscape.org)[28] to visualize the PPI network. The top 10 hub genes were identified with the standard of connectivity degree by using the CytoHubba plugin. The plugin Molecular Complex



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Figure 1 Identification of differentially expressed genes. A: Volcano map, in which the red node represents the upregulated differentially expressed genes (DEGs) and the blue node represents the downregulated DEGs; B: Heatmap of DEGs.

Detection (MCODE) was applied to identify the essential module within the PPI network in Cytoscape with the default parameters (degree cutoff, 2; node score cutoff, 0.2; kcore, 2; and maximum depth, 100).

Construction of the miRNA-mRNA interaction network

miRNAs, a class of small non-coding RNAs, regulate the expression of various genes by binding to their transcripts and play critical roles in DCM progression[29]. By using the MicroRNA Database (miRDB) [30] (http://mirdb.org/), we predicted miRNAs targeting any of the top 10 hub genes. Then, we sorted these miRNAs according to their prediction scores and selected the top 10 miRNAs. The mRNA-miRNA pairs were imported into Cytoscape to visualize the miRNA-mRNA network.

Immune cell infiltration analysis

The CIBERSORT (cibersort.stanford.edu) algorithm was applied to analyze the normalized gene expression data, and the proportions of 22 types of immune cells in each sample were analyzed[31]. The gene expression data were normalized *via* "limma" and transformed into the 22 types of immune cell expression data through the source of CIBERSORT[32] *via* R. Then the results were filtered out *via* Perl (https://www.perl.org) with $P < 0.05$, and the immune cell infiltration matrix was obtained. Next, the "vioplot" package was used to draw violin diagrams to visualize the difference in immune cell infiltration between the DCM and healthy groups in detail. The "ggplot2"[33] package was applied to perform principal component analysis (PCA) and draw a PCA clustering map. The "corrplot" package was used to analyze the correlation among immune cell infiltration and draw a correlation heatmap.

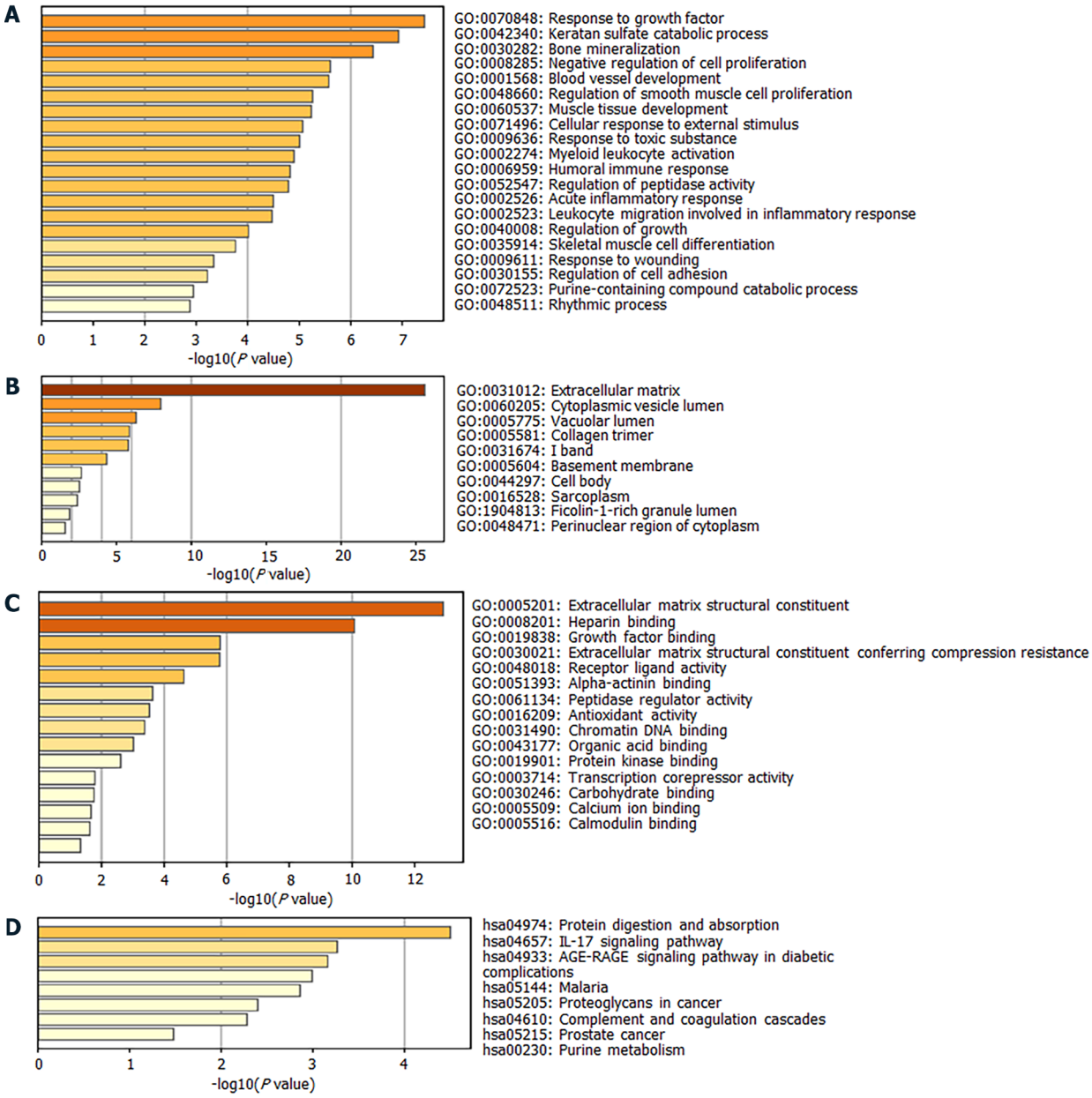
RESULTS

Identification of DEGs

After merging the two datasets, 97 DEGs, including 47 upregulated and 50 downregulated genes, were obtained in the DCM group compared with the control group. Figure 1 shows the volcano map and heatmap of the 97 DEGs. The details of the top 10 upregulated or downregulated genes are shown in Table 1.

GO and KEGG enrichment analyses

Next, the DEGs were used to perform enrichment analysis for BP, CC, MF, and KEGG pathways. By using the Metascape website, the BP of GO was found to be significantly enriched in "response to growth factor," "blood vessel development," "regulation of smooth muscle cell proliferation," "muscle tissue development," and "acute inflammatory response" (Figure 2A). The DEGs in CC were mainly enriched in "extracellular matrix," "cytoplasmic vesicle lumen," "collagen trimer," and "sarcoplasm" (Figure 2B). Regarding MF, the DEGs were mainly enriched in "extracellular matrix structural constituent," "growth factor binding," "alpha-actinin binding," and "calcium ion binding" (Figure 2C). KEGG pathway analysis revealed significant pathway enrichment of DEGs in "protein digestion and absorption," "interleukin 17 (IL-17) signaling pathway," "advanced glycation end products-receptor for advanced glycation end products signaling pathway in diabetic complications," "complement," and "coagulation cascades" (Figure 2D).



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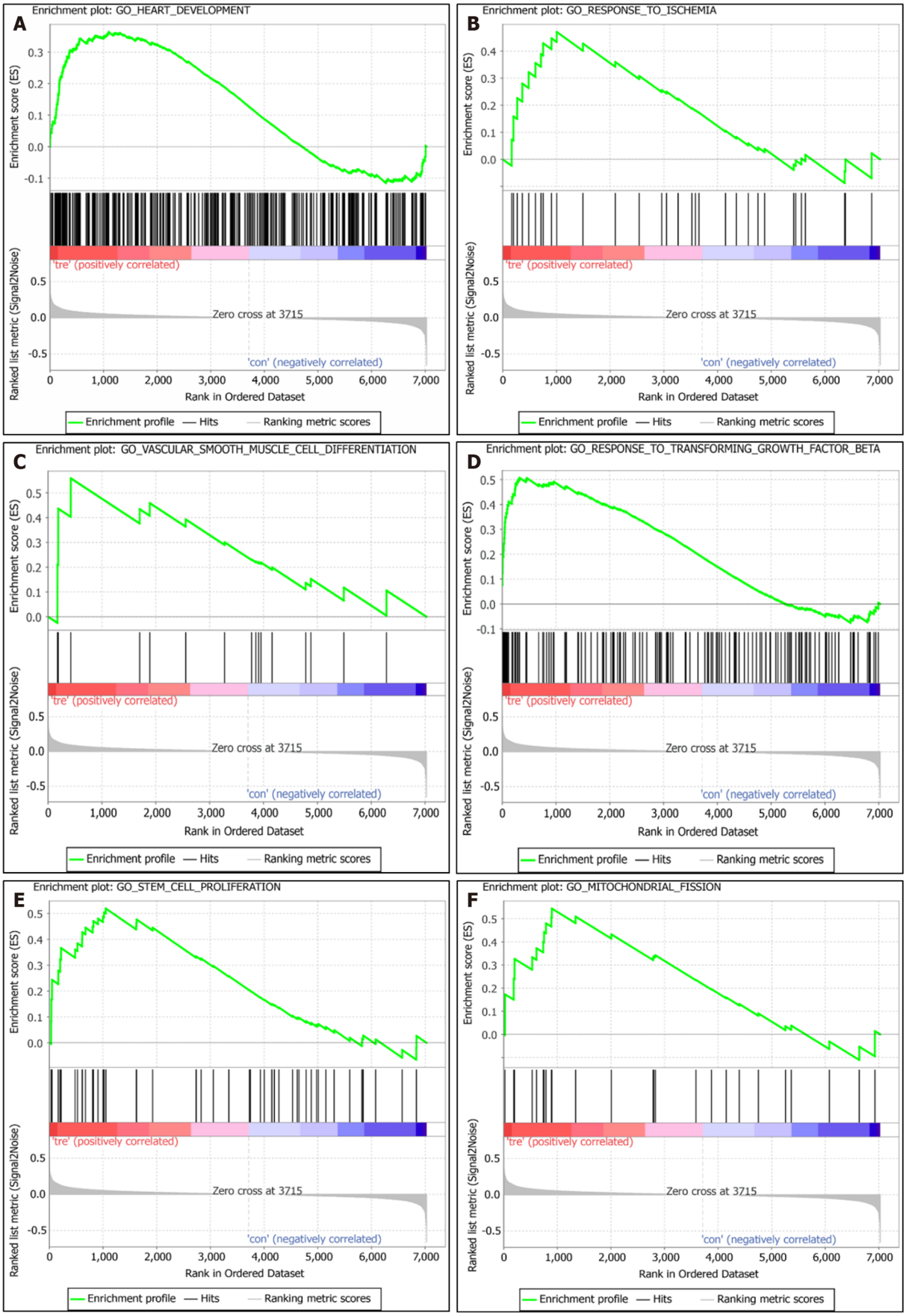
Figure 2 Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analysis of enrichment for differentially expressed genes. A: Biological process; B: Cellular component; C: Molecular function; D: Kyoto Encyclopedia of Genes and Genomes.

GSEA analysis

GSEA analysis results revealed that, compared with the control group, the DCM group was significantly enriched in GO terms "heart development," "response to ischemia," "vascular smooth muscle cell differentiation," "response to transforming growth factor beta," "stem cell proliferation," and "regulation of mitochondrial fission" (Figure 3).

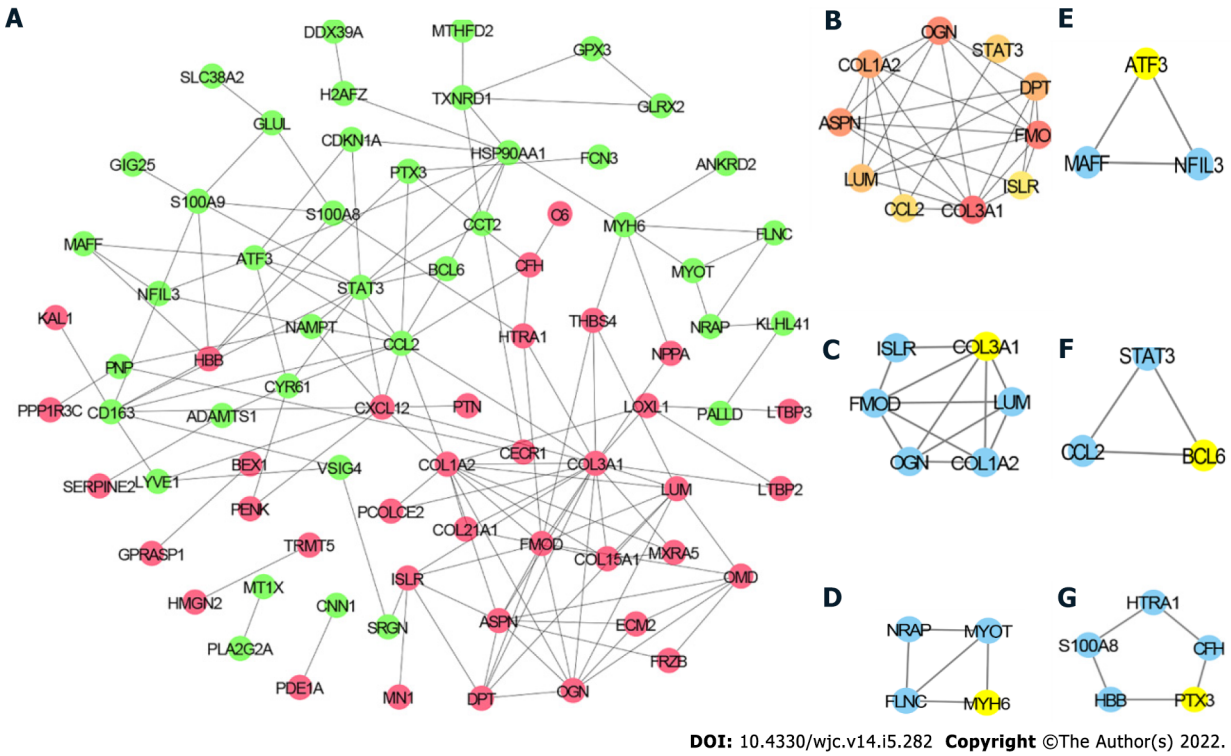
PPI network and identification of hub genes

To further explore the relationship among the DEGs at the protein level, the PPI network of the 97 DEGs was constructed using STRING with the criterion of combined score > 0.4 and visualized using Cytoscape. The PPI network consisted of 77 nodes and 145 edges (Figure 4A). The top 10 hub genes included collagen type III alpha 1 chain (COL3A1), COL1A2, signal transducer and activator of transcription 3 (STAT3), C-C motif chemokine ligand 2 (CCL2), fibromodulin (FMOD), asporin (ASPN), C-X-C motif chemokine ligand 12 (CXCL12), lumican (LUM), heat shock protein 90 alpha family class A member 1 (HSP90AA1), and osteoglycin (OGN) (Figure 4B). The detailed information of these hub genes is provided in Table 2. MCODE analysis identified five essential modules, and COL3A1, myosin heavy chain 6, activating transcription factor 3, B cell leukemia/lymphoma 6 transcription repressor,



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Figure 3 Gene set enrichment analyses of enrichment of differentially expressed genes. A: Heart development; B: Response to ischemia; C: Vascular smooth muscle cell differentiation; D: Response to transforming growth factor beta; E: Stem cell proliferation; F: Regulation of mitochondrial fission.



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Figure 4 Protein-protein interaction network. A: Protein-protein interaction (PPI) network of differentially expressed genes (DEGs), in which the red node represents upregulated DEGs and the green node represents the downregulated DEGs; B: Top 10 hub genes; C: Module 1; D: Module 2; E: Module 3; F: Module 4; G: Module 5. Yellow node represents the Seed gene of each module.

and pentraxin 3 were the seeds of clusters 1, 2, 3, 4, and 5, respectively (Figure 4C–G).

miRNA–mRNA interaction network

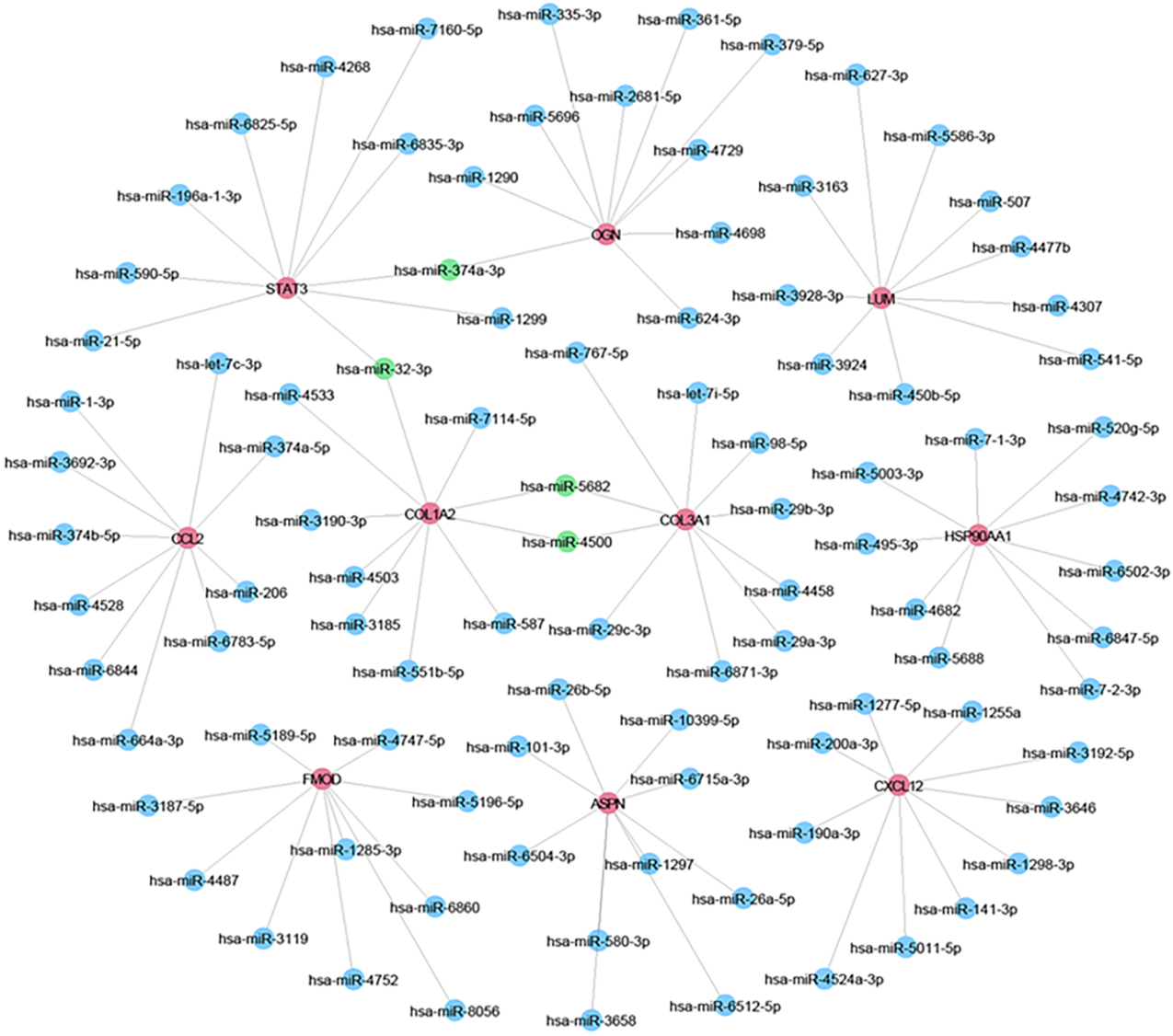
Increasing evidence shows that miRNAs play important roles in the development and progression of DCM. By using the miRDB database, we predicted miRNAs targeting any of the top 10 hub genes. Then we sorted these miRNAs according to their prediction scores and selected the top 10 miRNAs. Additionally, the top 100 miRNA–mRNA pairs were visualized using Cytoscape (Figure 5). Consequently, hsa-miR-5682, hsa-miR-4500, hsa-miR-32-3p, and hsa-miR-374a-3p were each found to target ≥ 2 hub genes.

Immune cell infiltration in DCM

Immune cells infiltrate into the myocardium upon myocardial injury[28]. Thus, a violin plot was constructed to investigate the difference in immune-cell infiltration between the DCM and control groups (Figure 6A). Compared with the control group, the DCM group had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells (DCs), whereas there was no significant difference in the remaining 18 types of immune cells. However, the PCA results showed that the control and DCM groups could not be well distinguished according to the infiltration patterns of the 22 types of immune cells (Figure 6B). We generated a correlation heatmap to assess the correlation among the 19 immune cells that were found infiltrated in the DCM or control group. As shown in Figure 6C, the number of infiltrated B memory cells was positively correlated with that of the infiltrated resting DCs, activated natural killer (NK) cells and T follicular helper cells, the number of infiltrated activated NK cells was negatively correlated with that of infiltrated resting NK cells, and the number of infiltrated resting memory CD4 T cells was negatively associated with that of infiltrated B memory cells and regulatory T cells.

DISCUSSION

DCM is one of the main reasons of sudden cardiac death and heart failure. It is a heterogeneous disease caused by various types of pathogenic factors including genetic, infectious, hormonal, and environmental factors[34]. The causes of DCM should be explored in depth to improve the diagnosis, treatment, and prognosis of DCM patients. Therefore, it is of great significance to elucidate the genetic mechanisms involved in DCM.

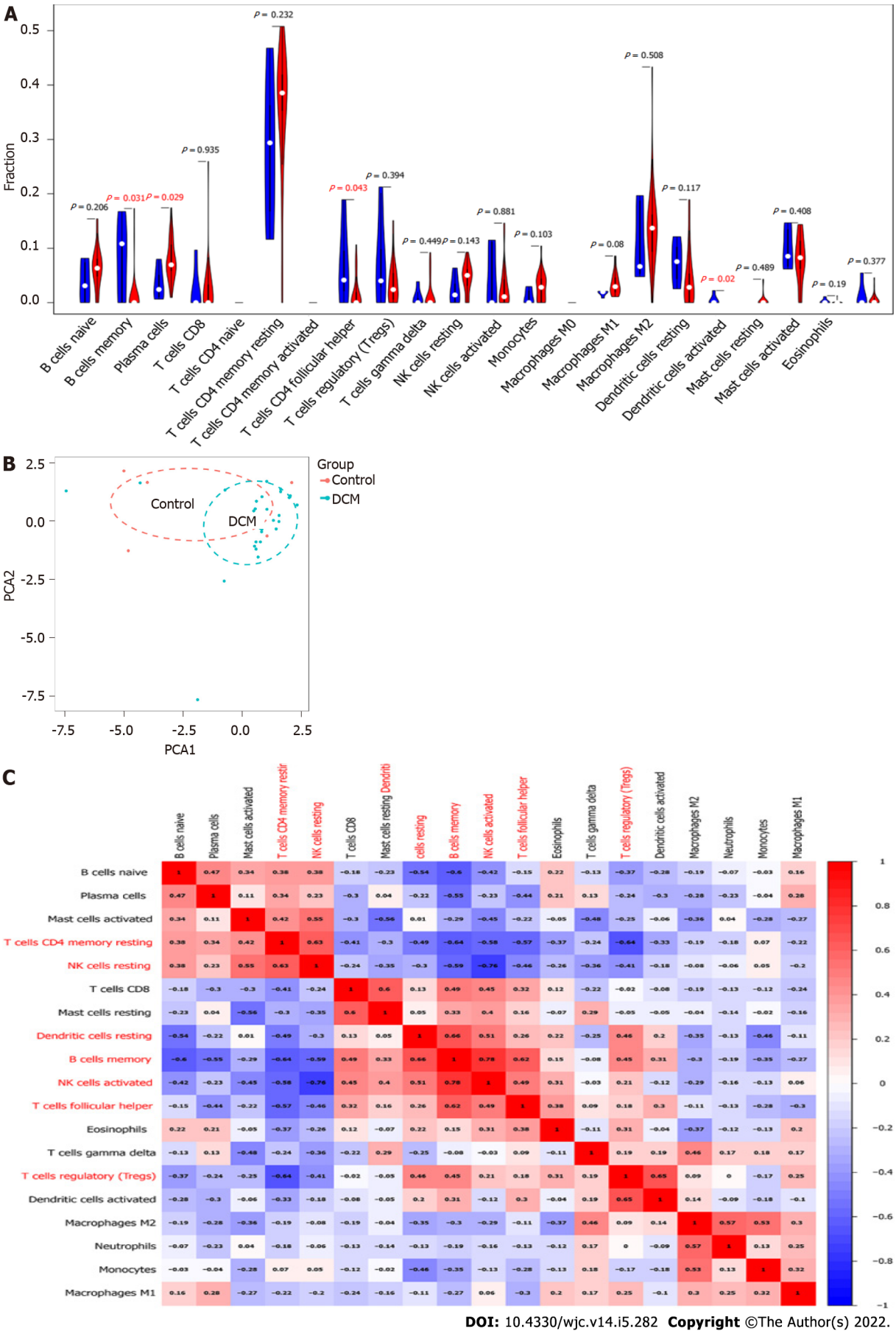


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Figure 5 MicroRNA-mRNA network. Red node represents the Hub genes; blue node represents the Targeted microRNAs; green node represents the mutual targeted miRNAs of ≥ 2 hub genes.

In this study, 97 DEGs, consisting of 47 upregulated and 50 downregulated genes, were identified between the DCM and control groups. GO of BP and GSEA analysis revealed that the DEGs were not only enriched in the development of the cardiovascular system, such as in the development of the muscle tissue, heart, and blood vessels, but also in the etiology of DCM, such as in acute inflammatory response and mitochondrial fission (Figures 2 and 3). Growing evidence shows that infiltration of inflammatory cells is associated with the pathogenesis of DCM[35-37], and prelamin A accumulation [38] and myosin binding protein C3 mutation[39] can promote DCM pathogenesis *via* regulation of inflammation. Xia *et al*[40] reported that dynamin-related protein 1 (Drp1, myocardial fission protein) is significantly upregulated in DCM patients. Moreover, Sacubitril (known as LCZ696), a novel inhibitor of the angiotensin receptor neprilysin, can alleviate the cardiac dysfunction in doxorubicin-induced DCM and reduce apoptosis by inhibiting mitochondrial fission *via* the Drp1-mediated pathway.

Regarding CC, the DEGs were enriched in sarcoplasm. Previous studies have reported that mutations in phospholamban (related to abnormal contractility)[41] and B-cell lymphoma 2-associated athanogene 3 (alter the cardiac response)[42] are closely associated with DCM in the sarcoplasmic reticulum. GO analysis of MF indicated that the DEGs were enriched in alpha-actinin binding and calcium ion binding. Alpha-actinin and calcium ion are critical for myocardial contraction[43,44]. Other studies have demonstrated that most DCM patients exhibit abnormalities related to calcium ion and α-actinin, which cause decreased heart contractility[45-47]. Cardiac troponin contributes to myocardial contraction[48]. Mutations in cardiac troponin T, troponin C, and troponin I are mainly related to DCM pathogenesis[49, 50]



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Figure 6 Immune cell infiltration analyses of differentially expressed genes. A: Violin plot, in which red represents dilated cardiomyopathy group and blue represents the normal group; B: Principal component analysis; C: Correlation heatmap.

Table 1 Top 10 differentially expressed genes in the dilated cardiomyopathy group *vs* normal group

Expression	Gene symbol	Description	logFC	adj. *P* value
	ASPN	Asporin	2.31	3.05E-22
	NPPA	Natriuretic peptide A	2.08	1.26E-11
	LUM	Lumican	1.87	4.56E-18
	MXRA5	Matrix remodeling associated 5	1.43	5.47E-14
UP	*HBB*	Hemoglobin subunit beta	1.20	3.08E-05
	COL1A2	Collagen type I alpha 2 chain	1.09	1.37E-10
	COL3A1	Collagen type III alpha 1 chain	1.05	2.39E-07
	OGN	Osteoglycin	1.01	5.38E-09
	FRZB	Frizzled related protein	0.99	1.08E-13
	EIF1AY	Eukaryotic translation initiation factor 1A Y-linked	0.96	1.33E-02
	MYOT	Myotilin	-1.89	1.70E-13
	ANKRD2	Ankyrin repeat domain 2	-1.44	3.00E-08
	PLA2G2A	Phospholipase A2 group IIA	-1.35	4.43E-07
	MYH6	Myosin heavy chain 6	-1.35	1.80E-05
	SERPINA3	Serpin family A member 3	-1.28	1.75E-18
Down	*CYP4B1*	Cytochrome P450 family 4 subfamily B member 1	-1.20	1.06E-07
	FCN3	Ficolin 3	-1.19	2.48E-13
	CNN1	Calponin 1	-1.16	2.09E-10
	PTX3	Pentraxin 3	-1.13	1.27E-04
	NRAP	Nebulin related anchoring protein	-1.11	1.30E-03

Table 2 Top 10 hub genes in the protein-protein interaction network

Gene symbol	Description	Rank	Degree
COL3A1	Collagen type III alpha 1 chain	1	18
COL1A2	Collagen type I alpha 2 chain	2	12
STAT3	Signal transducer and activator of transcription 3	3	11
CCL2	C-C motif chemokine ligand 2	3	11
FMOD	Fibromodulin	5	10
ASPN	Asporin	6	9
CXCL12	C-X-C motif chemokine ligand 12	6	9
LUM	Lumican	8	8
HSP90AA1	Heat shock protein 90 alpha family class A member 1	8	8
OGN	Osteoglycin	8	8

KEGG pathway analysis showed that the DEGs were significantly enriched in the IL-17 signaling pathway. DCM is induced by viral myocarditis, accompanying autoimmune dysfunction, affecting the secretion of IL-17 cytokine by T helper 17 cells, and IL-17 itself promotes myocardial cell injury[51]. Wang *et al*[52] reported that elevated IL-17 levels are significantly associated with DCM incidence and progression. Additionally, the serum levels of other inflammatory factors such as IL-6, tumor necrosis factor-α, and IL-21 are significantly increased in DCM patients[53]. Thus, the IL-17 signaling pathway may be one of the major signaling pathways involved in the development of DCM.

Through construction of PPI and miRNA-mRNA interaction networks, we identified the hub genes and the miRNAs targeting them. The hub genes, COL1A2 and COL3A1, encode the pro-alpha2/1 chains of type I and III collagens, respectively. Collagens I and III, the main collagens of cardiac extracellular

matrix, are classical biomarkers of cardiac fibrosis in DCM[54]. Mihailovici *et al*[55] reported that collagens I and III are upregulated in DCM patients compared with matched healthy controls. Additionally, Zhao *et al*[18] reported that COL1A2 may participate in DCM pathogenesis by regulating the cardiac remodeling characterized by collagen deposition in the extracellular matrix[56]. Consistent with our results, Liu *et al*[53] identified STAT3 as a hub gene in DCM *via* bioinformatic analysis. Other studies have also indicated a role of STAT3 in DCM. Podewski *et al*[57] showed that STAT3 protein level is significantly decreased in the cardiomyocytes of patients with end-stage DCM. Moreover, inhibition of the IL-6–mediated STAT3 signaling pathway can improve myocardial remodeling through reducing myocardial apoptosis in a mouse model of DCM[58]. Thus, the roles of COL1A2, COL3A1, and STAT3 in DCM should be further investigated. Moreover, the identified miRNAs hsa-miR-5682, hsa-miR-4500, hsa-miR-32-3p, and hsa-miR-374a-3p may participate in DCM pathogenesis through their interaction with ≥ two hub genes. Previous studies have also suggested that miRNAs play significant roles in DCM. It has been found that miR-21, miR-29a, and miR-133b are differentially expressed in DCM patients[59]. miR-133a expression is associated with fibrosis, myocyte necrosis, left ventricular function, and clinical outcome in patients with inflammatory DCM[60]. Moreover, Satoh *et al*[61] showed that a low let-7i level can serve as an independent predictor of cardiac death and heart failure (relative risk = 3.76).

Immune cells commonly infiltrate into the myocardium upon various types of cardiac damage[49, 62]. Overactivation of immune cells could be investigated in pathological examination about cardiac biopsy specimens in DCM patients. Noutsias *et al*[63] reported that the upregulation of genes associated with T cells exacerbates DCM progression. Therefore, our study also assessed the correlation between DEGs and immune cell infiltration. The results indicated infiltration of 19 types of immune cells in DCM pathogenesis. Notably, compared with the control group, the DCM group had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting DCs. However, Liu *et al* [53] have demonstrated that, compared with healthy controls, DCM patients have more infiltrated T follicular helper cells and fewer T follicular regulatory cells, and infiltration of T follicular regulatory cells is positively correlated with left ventricular ejection fraction.

Our study had some limitations. First, the gene expression data were acquired from a public database. Moreover, we did not experimentally verify the relevance of the identified DEGs with DCM and their enriched functions or hub genes. Likewise, we did not verify the predicted miRNA-mRNA interactions and their relevance.

CONCLUSION

In summary, we first identified that COL1A2 and COL3A1 may be both presumably regulated by hsa-miR-5682 and hsa-miR-4500, and play significant roles in the pathogenesis of DCM through acute inflammatory response and IL-17 signaling pathway. These results may provide useful biomarkers for the diagnosis and treatment of DCM, but further research is needed to clarify the roles of the predicted genes and pathways.

ARTICLE HIGHLIGHTS

Research background

Dilated cardiomyopathy (DCM), a disease of the heart muscle, is one of the most common causes of heart failure. However, the original cause and pathogenesis in development of DCM are still remain elusive.

Research motivation

The early diagnosis and prognosis of DCM patients are unsatisfactory because of DCM main cause and pathogenesis are still unclear. Increasing DCM datasets were provided online but little was been explored. Bioinformatics could further investigate the DCM mechanism and biomarkers for improving the diagnostic and therapeutic efficiency.

Research objectives

This study investigated the candidate genes and pathways involved in DCM patients.

Research methods

Expression datasets were downloaded from the Gene Expression Omnibus database. Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and gene set enrichment analyses investigated the key pathway in differentially expressed genes (DEGs) between the DCM patients and healthy individuals. Protein-protein interaction network identified the hub genes and modules in DCM. MicroRNA Database predicted the microRNAs which targeting the hub genes. CIBERSORT analyzed the immune-

ell infiltration in DCM.

Research results

Ninety-seven DEGs mainly enriched in "response to growth factor," "extracellular matrix," and "extracellular matrix structural constituent." Moreover, the top two pathways were "protein digestion and absorption" and "interleukin 17 signaling pathway." Collagen type III alpha 1 chain (COL3A1) and COL1A2, whose were regulated by hsa-miR-5682 and hsa-miR-4500, mainly contributed to the pathogenesis of DCM. Compared with the control group, DCM patients had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells.

Research conclusions

DCM progression closely related to IL-17 signaling pathway and acute inflammatory response. COL1A2 and COL3A1 and their targeting miRNAs, hsa-miR-5682 and hsa-miR-4500, are the potential biomarkers of DCM.

Research perspectives

This study may provide valuable pathways and biomarkers for the diagnosis or treatment of DCM. Further studies should investigate the functions of the predicted genes and pathways.

FOOTNOTES

Author contributions: Liu Z and Song YN designed this study; Chen KY collected the relevant data; Liu Z analyzed the data; Liu Z and Gao WL drafted the manuscript; Chen HJ and Liang GY reviewed and supervised this manuscript; All authors approved the final version of the article.

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ORIGINAL ARTICLE

Retrospective Study

Pledget-assisted hemostasis to fix residual access-site bleedings after double pre-closure technique

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Abstract

BACKGROUND

The use of pre-closure suture-based devices represents a widely access-site hemostasis technique in percutaneous transfemoral transcatheter-aortic-valve-replacement (TF-TAVR); yet this technique is associated with the risk of a device failure that may result in clinically relevant residual bleeding. Thus, a bailout intervention is needed. So far, the best management of pre-closure device failure has not been recognized.

AIM

To report the first clinical results obtained using a novel bailout hemostasis technique for patients with double suture-based vascular closure device failure in the setting of TF-TAVR.

METHODS

We developed a "pledget-assisted hemostasis" technique to manage residual access-site bleeding. This consists of the insertion of a surgical, non-absorbable, polytetrafluoroethylene pledget over the sutures of the two ProGlide (Abbott Vascular, CA, United States). The ProGlide's knot-pushers are used to push down the pledget and the hand-made slipknot to seal the femoral artery leak. This technique was used as a bailout strategy in patients undergoing TF-TAVR with a

systematic double pre-closure technique. Post-procedural access-site angiography was systematically performed. In-hospital complications were systematically detected and classified according to Valve Academic Research Consortium-2 criteria.

RESULTS

Out of 136 consecutive patients who underwent TF-TAVR, 15 patients (mean age 80.0 ± 7.2 years, 66.7% female) with access-site bleeding after double pre-closure technique failure were treated by pledget-assisted hemostasis. In the majority of patients, 16F sheath was used (n = 12; 80%). In 2 cases (13%), a peripheral balloon was also inflated in the iliac artery to limit blood loss during pledget preparation. Angiography-confirmed hemostasis (primary efficacy endpoint) was achieved in all patients. After the procedure, 1 patient required blood transfusion (2 units), and no other bleeding or major ischemic complication was noticed.

CONCLUSION

The "pledget assisted hemostasis" might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.

Key Words: Transcatheter aortic valve replacement; Transcatheter aortic valve implantation; Vascular complications; Preclosure device; Pledget; Hemostasis; Personalized medicine

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Core Tip: This is a retrospective pilot study to report the first clinical results obtained using a novel bailout hemostasis technique for patients with double suture-based vascular closure device failure in the setting of trans-femoral transcatheter-aortic-valve-replacement. The "pledget-assisted hemostasis" technique consists of the insertion of a surgical, non-absorbable, polytetrafluoroethylene pledget over the sutures of two ProGlide (Abbott Vascular, CA, United States). The ProGlide's knot-pushers are used to push down the pledget and the hand-made slipknot to seal the femoral artery leak. This technique was used as a bailout strategy in patients undergoing trans-femoral transcatheter aortic valve replacement with systematic double preclosure technique.

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INTRODUCTION

Despite increased operator experience and device improvement, access site complications still pose a significant concern regarding procedural safety of trans-femoral transcatheter aortic valve replacement (TF-TAVR)[1]. Accordingly, strategies to minimize the occurrence and the clinical sequelae of access-site complications are continuously investigated.

When practicing percutaneous TF-TAVR, in addition to proper access site selection and precise puncture of common femoral artery (CFA)[2], the use of vascular closure devices (VCD) is actually widely adopted. Within different VCD-based technical options, pre-implantation of suture-based closure devices has gained popularity. However, vascular complications are not abolished, and residual access site bleeding is often detected (in up to one-third of patients)[3-5] due to significant blood leakage at the level of arterial entry site. Thus, as a part of TF-TAVR procedures, strategies to bailout manage VCD failures are applied daily according to various local expertise. The best technique to manage residual bleeding after suture-based VCD failure has not yet been recognized. Thus, we herein report the description and the results obtained in the early clinical practice of a novel "pledget-assisted hemostasis" technique.

MATERIALS AND METHODS

Technique description

According to our local practice, TF-TAVR is systematically performed under conscious sedation according to the previously described "less-invasive totally-endovascular" (LITE) technique[6]. Briefly, the LITE technique combines a series of technical solutions aimed to minimize vascular complications and includes radial approach as the "secondary access" (to guide valve positioning, to check femoral-access hemostasis, and to manage eventual access-site complications) and precise CFA puncture using angiographic-guidewire-ultrasound guidance[7]. Femoral hemostasis was systematically attempted using a double pre-closure technique with two suture devices (ProGlide, Abbott Vascular, CA, United States). After prosthesis implantation and TAVR sheath removal, hemostasis with parallel double ProGlide sutures was done[8].

At this stage, before the suture threads of the ProGlide device were cut down, hemostasis was checked by selective iliac-femoral angiography performed by radial access with a multipurpose guiding catheter[6]. Digital subtraction angiography of the iliac-femoral arteries allowed to assess vascular integrity or to diagnose the occurrence of vascular damages or bleeding complications. At this stage, when significant residual bleeding at the site of femoral entry was recognized, a new "pledget-assisted hemostasis" technique was applied (Figure 1A). It consists of the application of a surgical non-absorbable polytetrafluoroethylene 6.5 mm x 4 mm x 1.5 mm pledget over the two ProGlide sutures (one of each device). The steps practiced to mount the pledget over the suture threads are depicted in Figure 2. Then, the pledget was pushed down over the two sutures using the ProGlide knot-pusher, and tied with a hand-made sliding knot to achieve a stable approximation to the surface of the vessel wall.

After pledget application, selective iliac-femoral digital subtraction angiography was repeated to check for hemostasis achievement (Figure 1B).

When massive bleeding was noticed at the first angiographic check such that manual compression was considered insufficient, a peripheral balloon was advanced and inflated in the iliac-femoral artery by radial route to prevent significant blood loss during pledget-assisted hemostasis performance.

Study population

According to the standard practice of our center, all patients were referred for TAVR based on formal, multidisciplinary, heart-team discussion. For each patient, the peripheral computed tomography was revised by at least two operators to assess the feasibility of TF approach. Clinical data and procedure details were prospectively entered into a dedicated database that allowed to assess previously the impact of EuroSCORE on coronary interventions[9] and the safety of transradial procedures[10]. At the time of heart-team consultation, patients' surgical risk was graded according to the Society of Thoracic Surgeons (STS) predicted operative mortality[11]. TAVR risk was graded according to the STS-American College of Cardiology Transcatheter Valve Therapy (STS-ACC TVT)[12] using the online TAVR in-hospital mortality risk calculator (https://tools.acc.org/tavrrisk/#!/content/evaluate/).

The antiplatelet/anticoagulant regimen was individualized according to the patient's characteristics, and no standardized protocol was available. As a general approach, most of the patients received double antiplatelet therapy, while the patients with the need for anticoagulation were kept on anticoagulant therapy plus 1 mo of single antiplatelet therapy. All procedures were performed under systemic anticoagulation with unfractionated heparin (70 UI/kg, reversed with protamine sulfate at the end of the procedure, before hemostasis).

In-hospital clinical outcomes were prospectively recorded, since the continuous monitoring of in-hospital clinical outcomes for TAVR is part of the Institutional clinical pathway dedicated to patients with heart valve diseases (http://www.policlinicogemelli.it/Policlinico_Gemelli.aspx?p=21C1F922-73FF-4B2F-A2FF-022DE91A6586) according to the European recommendations[13]. Bleeding or vascular complications were defined according to Valve Academic Research Consortium-2 (VARC-2) criteria[14].

Out of consecutive patients who underwent TF-TAVR from October 2019 to September 2020, we selected all patients with residual access site bleeding who underwent pledget-assisted hemostasis attempt after the failure of double pre-closure technique with ProGlide suture. These patients constituted the study population of the present pilot study[15].

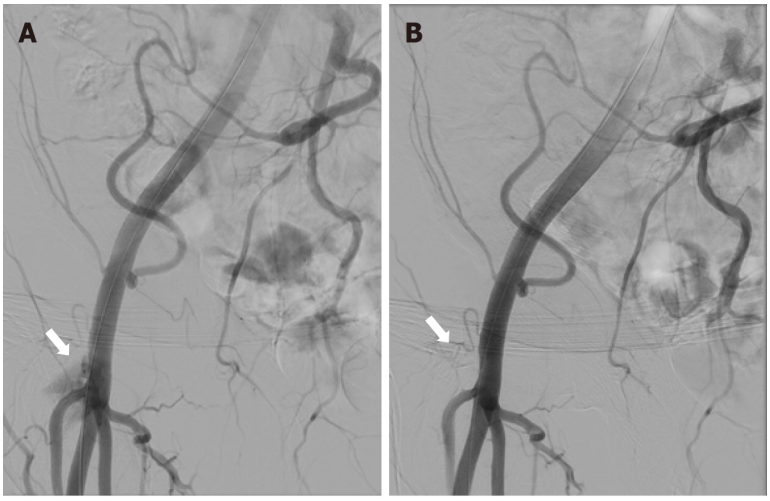
Study endpoints

The primary efficacy end-point was the achievement of angiographically-confirmed hemostasis in the operative room without the need for further bail-out interventions (surgery or endovascular).

The primary safety end-point was the occurrence of life-threatening bleedings, major bleedings, or major vascular complications as defined according to VARC-2 classification[14].

RESULTS

During the study period, 136 patients underwent TF-TAVR. The TAVR systems used included Medtronic Evolute R (n = 40, 29%), Medtronic Evolut Pro (n = 81, 60%), Edwards Sapien3 (n = 10, 7.3%),



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Figure 1 Angiography before and after pledget-assisted hemostasis. A: Residual bleeding at the transcatheter-aortic-valve-replacement access site (white arrow) after double ProGlide preclosure; B: Absence of residual bleeding (white arrow) after pledget assisted hemostasis.

and Abbott Portico (n = 5, 3.7 %).

A total of 15 patients (mean age 80.0 ± 7.2 years, 66.7% female) with residual access site bleeding after double pre-closure in TF-TAVR were prospectively included in the pilot study. The main characteristics of the study population are summarized in Table 1. The average STS mortality score was 3.7 ± 2.5, and TAVR score was 2.69 ± 0.7. In the majority of patients, 16F sheath was used (n = 12; 80%), while 14F sheath was used in 2 patients (6.7%) and 18F in 1 patient (6.7%). Direct valve implantation was done only in 1 patient. In 6 (40.0%) patients, valve post-dilatation was done. Balloon inflation in the iliac artery was performed in 2 cases (13.3%) to limit blood loss during pledget preparation and in 2 cases (13.3%) to treat an intimal flap (Table 2).

Angiographically-confirmed hemostasis was achieved in all patients (100%).

After TAVR, 1 patient required blood transfusion (2 units) (Table 2), and no other bleeding or vascular complication were noticed (Table 2). All patients were discharged after 7 ± 5 d.

DISCUSSION

The complete percutaneous approach in TF-TAVR represents a less invasive technique to treat patients with aortic valve stenosis. Suture-based VCD use according to pre-closure technique is actually widely adopted to achieve arterial haemostasis but is associated with the possibility of residual blood leakage. Thus, as a part of TF-TAVR procedures, strategies to bailout manage VCD failures are daily applied according to various local expertise.

In the present study: (1) We describe a novel technique (based on "pledget" use) to manage double suture-based device failure; and (2) We report the efficacy and safety observed in a pilot clinical observational study.

According to VARC-2 position paper, "access-related" complications are defined as any adverse clinical event possibly associated with any of the access sites used during the procedure[14]. Across the literature, wide variations regarding the occurrence of vascular complications and their impact on clinical outcomes exist[16-18]. Different sizes of the valve delivery systems used over time, evolving closure techniques, and operator experience might play a major role. In such context, the occurrence of VCD failure might determine different clinical consequences ranging from life-threatening bleedings to the absence of any significant blood loss. According to recent studies[16-18], up to 70% of VARC-2 major vascular complications were related to VCD failure. Puncture site optimization and VCD selection might modulate VCD failure occurrence. Regarding entry-site optimization, the "perfect puncture" of CFA within spots free from calcium and above the bifurcation may be pivotal in reducing complications. To select a proper puncture site, either ultrasound guidance[19] or angio-guidewire-ultrasound technique[7] might be considered. Furthermore, different vascular closure devices (VCD) are available to diminish bleeding complications and to make TF-TAVR totally percutaneous. Percutaneous haemostasis of the large-bore devices used during TAVR, requires the "preclosure" technique, which is based on the deployment of the sutures before the introduction of the large sheaths. Then, after the valve implantation at the end of the procedure, sutures are tied by pushing down the knots after introducer removal.

Table 1 Main characteristics of study population

	Patients
Patient number	15
Age, yr (mean ± SD)	80.0 ± 7.2
Female gender	10 (66.7%)
BMI, kg/m^2 (mean ± SD)	27.41 ± 3.6
Risk factors	
Diabetes	2 (13.3%)
Hypertension	13 (86.7%)
Dyslipidemia	6 (40.0%)
Smoking	0
Medical history/comorbidities	
Chronic kidney disease (not on dialysis)	3 (20.0%)
Chronic dialysis	0
Peripheral artery disease	2 (13.3%)
Atrial Fibrillation	8 (53.3%)
Previous stroke	2 (13.3%)
Chronic pulmonary disease	2 (13.3%)
Previous myocardial infarction	2 (13.3%)
Previous PCI	4 (26.7%)
Previous CABG	1 (6.7%)
STS mortality	3.7 ± 2.5
TAVR score	2.69 ± 0.7
Anticoagulant and antiplatelet therapy	
Anticoagulants	7 (46.6%)
Dual antiplatelet therapy	6 (40%)
Clopidogrel	11 (73.3%)
Acetyl salicylic acid	8 (53.3%)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; STS: Society of Thoracic Surgeons; TAVR: Transcatheter-aortic-valve-replacement; SD: Standard deviation.

Regarding VCD selection, several devices entered the clinical practice and include suture-based closure devices such as 6F ProGlide, 10 F Prostar XL (both Abbott Vascular Inc, Santa Clara, CA, United States), and plug-based 14 F or 18 F MANTA (Essential Medical Inc., Malvern, PA, United States). Among suture-based closure devices, Prostar XL is associated with a higher rate of major bleeding compared to Proglide, as demonstrated in previous studies[20-24] and meta-analysis[25]. The novel collagen-based MANTA (14 and 18F) appears to be an effective and safe device for large-bore access closure, reporting only 4% of major and 5.6% of minor access site complications in the prospective MARVEL registry[5]. Initial data comparing MANTA with Proglide did not show clear advantages for MANTA device in the terms of access site bleeding complications[26-29]. Thus, the preclosure technique with ProGlide is still popular, and prompt hemostasis failure recognition and effective bailout management strategies might be pivotal to limit the clinical impact of VCD failure. Depending on the characteristics of the access site complications, different methods and materials for bailout endovascular interventions are proposed[2], mainly to avoid the risk of urgent vascular surgery. One possible solution is the crossover balloon occlusion technique (CBOT), which has been associated with a lower risk of VARC-2 major vascular bleeding complications[30]. Of note, CBOT might be effectively performed not only from the contralateral femoral artery, but it can be done ipsilaterally by superficial femoral artery access[31] or remotely by radial access[6].

Table 2 Bleeding and vascular adverse events according to the updated standardized endpoint from Valve Academic Research Consortium-2

Adverse events	*n* (%)	Adverse event description and management
Bleeding complications		
Life-threatening bleeding (bleeding in a critical organ or causing hypovolemic shock or severe hypotension requiring vasopressors or surgery or overt source of bleeding with drop in hemoglobin ≥ 5 g/dL or transfusion ≥ 4 units)	0	
Major bleeding (bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2-3 units, or causing hospitalization or permanent injury, or requiring surgery but does not meet criteria of life-threatening or disabling bleeding)	1 (6.7%)	1 patient requiring post-operative blood transfusion (2 units) without further bleeding source
Minor bleeding (any bleeding worthy of clinical mention that does not qualify as life-threatening, disabling, or major)	0	
Vascular complications		
Major vascular complications	0	
Minor vascular complications	2 (13.3%)	
Access site or access-related vascular injury (not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment)	2 (13.3%)	Two femoral artery non-occlusive dissections successfully treated by balloon angioplasty during the index procedure
Distal embolization	0	
Any unplanned vascular intervention (endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication)		
Need for vascular repair (*via* surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)	0	
Primary safety end-point (life-threatening bleedings or major bleedings or major vascular complications)	1 (6.7%)	

When a failure of VCD is recognized and wire is still left through the arteriotomy, either a third ProGlide device or an Angio-Seal (Abbott Vascular, Redwood City, CA, United States) can be utilized with great effectiveness and safety[32,33]. Yet, if a wire is no longer available, only prolonged manual compression or endovascular techniques through other arterial accesses can be practiced. Thus, we introduced the novel option of using the Proglide's sutures to deliver a surgical pledget in order to seal residual leak. According to our experience, this "pledget-assisted hemostasis" was highly effective, allowing early achievement of complete hemostasis. This translated into the smooth clinical post-procedural course in all but 1 patient (who received blood transfusion in the absence of further blood loss source documentation).

Study limitations

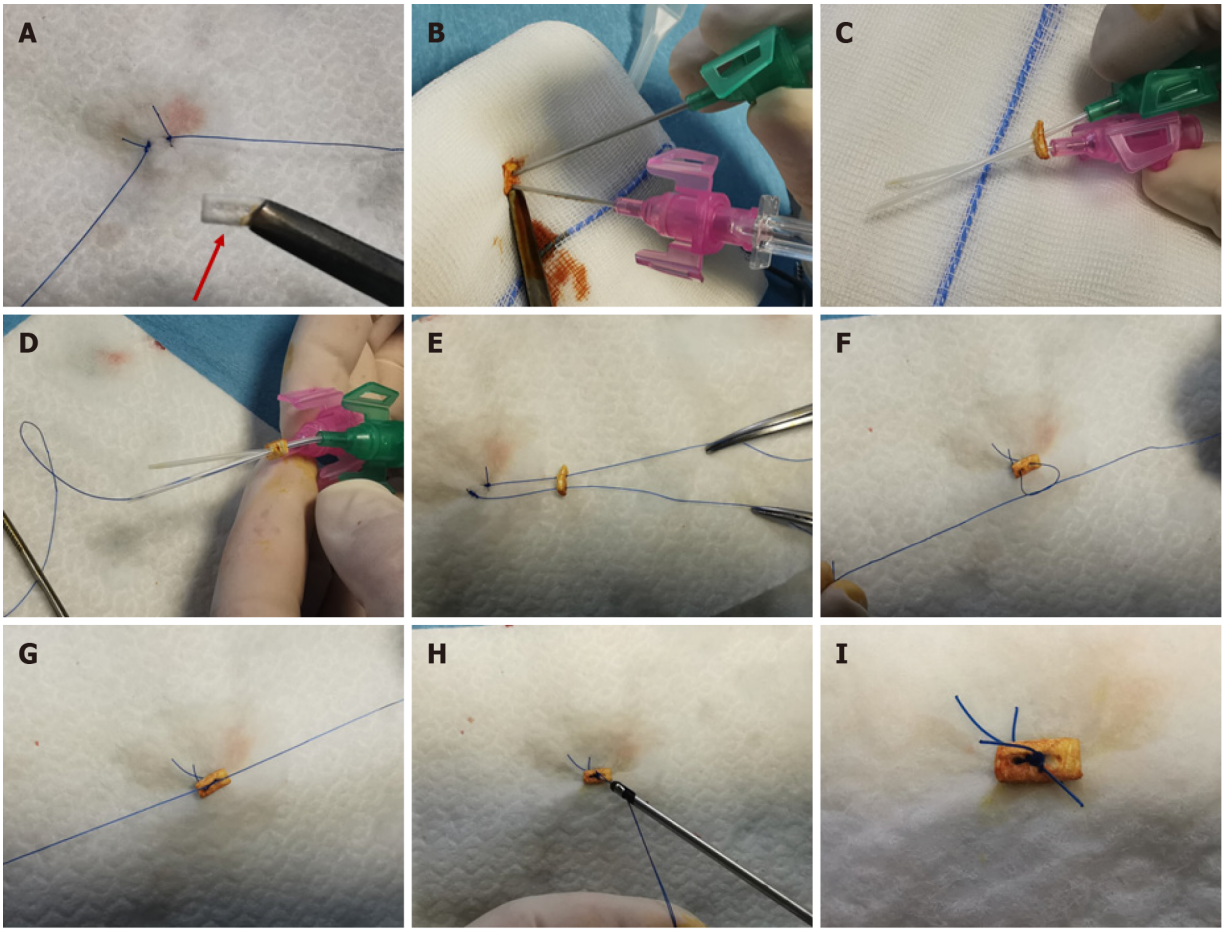
The present paper should be regarded just as a pilot study for a novel technique practiced by experienced interventional cardiologists in a limited number of procedures. Important limitations are evident (beyond the sample size) in this study.

First, the long-term safety of this technique has still to be ascertained, since specific complications (like local infections) might theoretically be triggered by the use of additional devices and we limited our follow-up to the in-hospital period.

Second, the study lacked a comparative arm. Thus, it is not possible to speculate regarding the possible benefit as compared with other bailout management strategies.

CONCLUSION

We have proposed a novel strategy to guarantee post TF-TAVR access site hemostasis using the Proglide sutures to deliver a surgical pledget in order to seal residual leak. The "pledget assisted hemostasis" might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.



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Figure 2 Steps of pledget-assisted hemostasis. The technique is shown as practiced on a white drape in order to show the steps in the absence of blood. A: Double ProGlide suture after cutting one monofilament from each device and pledget (red arrow); B: Insertion of two cannulas through the pledget (colored by iodine solution to facilitate recognition); C: Steel needles removal from the cannulas; D: Insertion of ProGlide monofilaments through the cannulas; E: Cannulas removal leaving Proglide monofilaments inserted through the pledget; F: Realization of one of two knots; G: Pledget fixation on the artery wall tightening the knots; H: Cut of residual Proglide threads; I: Final configuration achieved with pledged tightened over the two ProGlide's sutures.

ARTICLE HIGHLIGHTS

Research background

The most common technique used for hemostasis in transfemoral transcatheter aortic valve replacement (TF-TAVR) is the use of pre-closure devices. Despite favorable results in terms of successful hemostasis, sometimes it can be followed by device failure and residual bleeding.

Research motivation

Although there are different possibilities to manage residual bleeding after hemostasis device failure, such as bailout additional closure device use, balloon-assisted hemostasis, or surgery, the best management is still unclear.

Research objectives

To describe and report the results of an original technique for managing residual access site bleeding after vascular closure devices failure.

Research methods

The authors developed a novel technique to resolve residual access-site bleeding named "pledget assisted hemostasis". If residual bleeding was noticed, "pledget assisted hemostasis" with surgical non-absorbable polytetrafluoroethylene 6.5 mm x 4 mm x 1.5 mm pledget was done on the top of double pre-closure device. Proper hemostasis without residual bleeding was confirmed with control angiography.

Research results

A total of 15 consecutive patients (mean age 80.0 ± 7.2 years, 66.7% female) with residual access site bleeding after double pre-closure in TF-TAVR were prospectively included in this pilot study. In the majority of patients 16F sheath was used (n = 12; 80%), 14F sheath was used in 2 patients (6.7%), and 18F in 1 patient (6.7%). Hemostasis with the pledget technique was achieved in all patients (100%) immediately after implantation. Major bleeding defined by Valve Academic Research Consortium-2 definition did not occur. No access site infection was observed in the follow-up period.

Research conclusions

"Pledget assisted hemostasis" after pre-closure vascular device failure might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.

Research perspectives

"Pledget assisted hemostasis" might be considered as a possible bailout technique for vascular closure device failure.

FOOTNOTES

Author contributions: Burzotta F conceived the study; Burzotta F and Aurigemma C extracted, analyzed, and interpreted the data and drafted and revised the final version of the manuscript; Kovacevic M collected the clinical data and drafted and revised the final version of the manuscript; Trani C, Burzotta F, Aurigemma C, and Romagnoli E performed the procedures; Bruno P, Nesta M, Romagnoli E, Bianchini F, and Cangemi S collected the clinical data and interpreted the data; Trani C helped interpret the data and critically reviewed the manuscript for important intellectual content.

Conflict-of-interest statement: Dr. Burzotta F, Trani C and Aurigemma C received speaker's fees from Abbott, Medtronic, and Abiomed. Other authors have no conflicts of interest.

Data sharing statement: Data are collected according to our institution center record of the activity of cath laboratory. Clinical data and procedure details were prospectively entered into a TAVI-dedicated section of an electronic database.

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ORIGINAL ARTICLE

Retrospective Study

Day-to-day blood pressure variability predicts poor outcomes following percutaneous coronary intervention: A retrospective study

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Abstract

BACKGROUND

For patients with cardiovascular disease, blood pressure variability (BPV), distinct from hypertension, is an important determinant of adverse cardiac events. Whether pre-operative BPV adversely affects outcomes after percutaneous coronary intervention (PCI) is to this point unclear.

AIM

To investigate the relationship between blood pressure variability and outcomes for patients post-PCI.

METHODS

Patients undergoing PCI in a single state in 2017 were studied (n = 647). Systolic and diastolic BPV, defined as both the largest change and standard deviation for the 3-60 mo prior to PCI was calculated and patients with more than ten blood pressure measurements in that time were included for analysis (n = 471). Adverse

outcomes were identified up to a year following the procedure, including major adverse cardiac events (MACE), myocardial infarction, cerebrovascular accident, death, and all-cause hospitalization.

RESULTS

Visit-to-visit systolic BPV, as measured by both standard deviation and largest change, was higher in patients who had myocardial infarction, were readmitted, or died within one year following PCI. Systolic BPV, as measured by largest change or standard deviation, was higher in patients who had MACE, or readmissions ($P < 0.05$). Diastolic BPV, as measured by largest change, was higher in patients with MACE and readmissions ($P < 0.05$).

CONCLUSION

As BPV is easily measured and captured in the electronic medical record, these findings describe a novel method of identifying at-risk patients who undergo PCI. Aggressive risk modification for patients with elevated BPV and known coronary artery disease is indicated.

Key Words: Blood pressure variability; Percutaneous coronary intervention; Angioplasty; Major adverse cardiac events

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Core Tip: Pre-procedural visit-to-visit blood pressure variability, as measured by either standard deviation or largest change between two consecutive visits, is higher in patients who are readmitted, have complications, or die after percutaneous coronary intervention. Aggressive risk modification is indicated for patients with elevated blood pressure variability and known coronary artery disease.

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INTRODUCTION

Percutaneous coronary intervention (PCI) has long been established as an effective method of coronary revascularization for patients with coronary artery disease and is performed over 965000 times each year in the United States[1]. When patients present with acute coronary syndrome, it is estimated that approximately 60% will undergo PCI, 10%-15% will require surgical revascularization with coronary artery bypass graft (CABG), and the remainder are treated with medical therapy alone[2]. Although PCI is generally safe, known subsets of patients are at elevated risk for procedural complications after PCI. These include patients in shock, chronic heart failure, complex vascular anatomy, and diabetes mellitus, among others[3]. In addition to acute complications (such as bleeding at the entry site, vascular injuries, and arrythmias), patients may suffer from delayed complications after the procedure. Post-procedural additional major adverse cardiac events (MACE), include myocardial infarction (MI), cerebrovascular accident (CVA), hospitalization, or death. Risk factors for these delayed outcomes are less well understood. Aside from diabetes mellitus, relatively little is known about non-cardiac factors impacting outcomes after PCI.

In particular, whether preoperative blood pressure variability (BPV) affects outcomes after PCI is unclear. BPV, which is distinct from hypertension, is a measure of the degree of instability of a patient's blood pressure (BP) over time. BPV has been shown to be a risk factor for 90-day rates of complications after major surgical procedures, including coronary artery bypass graft (CABG)[4,5]. BPV may be calculated in a variety of ways, using standard deviation (SD), average change, or largest change between consecutive measurements (LC), and may be based upon either systolic or diastolic blood pressure readings[6]. BPV is most commonly reported in the literature by SD, but each method of reporting BPV may be similarly valid[7]. High outpatient BPV is associated with higher risk of all-cause hospitalization and death in ambulatory medical patients[8] and surgical patients[4], regardless of if the patient is hypertensive, normotensive, or hypotensive[9]. Indeed, BPV has recently been shown to predict cardiac events in patients with heart failure[10], and to be associated with development of end stage renal disease[11], and with cerebral small vessel disease leading to CVA[12]. The causes of BPV are likely highly multifactorial and may be due to physiological abnormalities (such as vascular wall

stiffness and hypertrophy), autonomic dysfunction, "white coat syndrome", and medication non-compliance[13,14]. For patients with cardiovascular disease, consistency of BP control has been shown to be an important determinant of adverse cardiac events[3,6,8]. BPV has also been shown to be associated with adverse outcomes in patients with cardiac failure[10], survivors of STEMI[15], in patients undergoing CABG[5], and other major surgical procedures[4]. We therefore sought to determine whether elevated BPV would be associated with adverse outcomes in patients undergoing less invasive cardiac procedures than CABG, such as PCI. In particular, we hypothesized that patients who had adverse outcomes would have higher mean BPV than those who did not have these outcomes, and that the likelihood of a poor outcome would be greater for patients with larger pre-procedural BPV.

Previously collected data was reviewed from a prospectively maintained registry of patients who underwent PCI at a single institution and whose outcomes were then prospectively tracked. Patients who had a minimum of 10 prior outpatient BP recordings 3 to 60 mo prior to the procedure were included in this study to assure accuracy of BPV calculation. Charts were retrospectively reviewed to calculate BPV as both standard deviation and largest change for both systolic and diastolic BPV. BPV in patients who had poor outcomes was compared to those who did not; logistic regressions were used to control for the indication of the procedure.

MATERIALS AND METHODS

This study was approved by the Institutional Review Boards of the University of North Dakota and the Sanford Medical Center. The subjects for this study were retrospectively drawn from a prospectively maintained database of all patients who underwent a PCI at Sanford Medical Center in Fargo, North Dakota in 2017 (n = 647). Patients within the reach of this system generally receive most of their healthcare, both inpatient and outpatient, at either the same or an affiliated institution. The electronic medical record was queried and BP recordings (n = 25844) both from within and outside the hospital from patients prior to PCI were identified. Only individuals who had a minimum of 10 BP recordings 3-60 mo before PCI (n = 471) were included for analysis. The remaining 176 patients were excluded from the study. Of these excluded, 2 were missing demographics, 75.29% were male, and the average age was 66.3

A total of 22,253 BP recordings were analyzed for 471 patients. BPV was defined as systolic and diastolic SD and largest change (LC, mmHg) between consecutive patient encounters. MACE outcomes of MI, CVA, death, and all-cause hospitalization were identified up to a year after PCI. Readmission was defined as a recurrent admission to the hospital within 1 year of discharge after hospitalization from PCI procedure. The procedural indication was categorized as staged PCI (n = 48), non-STEMI (n = 249) or other (n = 174). Other variables including demographics, prior diagnoses, and medication use were retrieved from the records.

Statistical analysis

BPV and BP characteristics along with demographics, diagnoses, medications, and indications were described for patients by MACE outcome status. Independent t-tests and chi-square analyses were used to determine any relationships between patients with or without an outcome of MACE. Logistic regressions of BPV predicting MACE, readmission, and MI outcomes after 1-year were done while controlling for age, sex, smoking status, diagnoses of hypertension or diabetes, prior cardiovascular disease, prior MI, prior PCI, prior CABG, pre-procedure creatine level, prior PCI left ventricular ejection fraction, anginal class (no symptoms as reference value, Canadian Cardiovascular Society I, II, III, or IV), on anti-anginal medications, and indication (staged PCI was used as the reference value). Although the registry data did not indicate which patients had pre-existing chronic kidney disease, we did analyze pre-procedural serum creatinine level. This was categorized as values of less than or equal to 2, 2-5, or greater than 5 mg/dL. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. Receiving operator characteristic (ROC) analysis was done to determine the best cutoff values for the four measures of BPV in determining MACE, readmission, and MI. Two-way analysis of variance (ANOVA) with interaction was done for the BPV measures between MACE and the categorical variables age, anginal class, and indication to test if the relationships between the BPVs and MACE differed for levels of those variables. SAS v. 9.4 was used for the analysis and alpha was set to 0.05.

RESULTS

Four hundred and seventy-one patients who had undergone a PCI and had 10 or more blood pressure readings 3-60 mo prior to PCI were studied. Table 1 presents the demographics of this patient sample. The average age was 68.8 (SD 11.5, range 35-95) and 72.1% were male. Five types of adverse outcomes were identified: 147 (31.2%) of the patients had MACE, 131 (27.8%) were readmitted, 47 (10.0%) had MI, 21 (4.5%) died, and 6 (1.3%) had CVA. Patients who had a MACE were an average of 2 years older (P =

Table 1 Descriptive statistics of variables in data set by adverse event for 471 patients with percutaneous coronary intervention

	No MACE (*n* = 324)			Had MACE (*n* = 147)		
	n	**mean**	**SD**	***n***	**mean**	**SD**
Systolic SD	324	13.72	6.02	147	15.38	5.26
Diastolic SD	324	8.54	3.11	147	8.93	2.71
Systolic LC	324	37.11	14.79	147	44.31	15.42
Diastolic LC	324	23.60	7.78	147	26.37	9.09
Systolic average	324	131.83	11.47	147	132.20	11.63
Diastolic average	324	74.82	7.75	147	71.33	7.64
Number of BP readings	324	40.19	35.86	147	62.81	52.85
Mean days between readings	324	59.07	37.04	147	42.19	30.70
Age	322	67.87	11.21	147	70.69	11.86
Pre PCI LVEF	252	56.44	11.73	122	53.06	13.63
Pre creatinine	307	1.15	0.98	138	1.50	1.19
		n	%		*n*	%
Sex	469					
Male		110	74.83		228	70.37
Female		37	25.17		94	29.01
Race	469					
White		142	96.60		312	96.30
Other		5	3.40		10	3.09
Hispanic		1	0.68		4	1.23
Smokes	467	22	14.97		51	15.74
Has hypertension	469	135	91.84		266	82.10
Has diabetes	469	67	45.58		122	37.65
Had prior CVD	469	39	26.53		68	20.99
Had prior MI	470	106	32.72		63	42.86
Had prior PCI	470	125	38.58		67	45.58
Had prior CABG	470	53	16.36		41	27.89
Prior creatinine	445					
0 to 2		296	91.36		118	80.27
> 2 to 5		8	2.47		18	12.24
> 5		3	0.93		2	1.36
Anginal class	469					
No symptoms		33	22.45		24	7.41
CCS I		11	7.48		39	12.04
CCS II		27	18.37		87	26.85
CCS III		43	29.25		95	29.32
CCS IV		33	22.45		77	23.77
On anti-anginal medication	469	114	77.55		204	62.96
Beta-blockers		98	66.67		164	50.62
Calcium channel blockers		37	25.17		76	23.46
Long-acting nitrates		33	22.45		41	12.65

Ranolazine		3	2.04	2	0.62
Indication	471				
Non-STEMI		82	55.78	167	51.54
STEMI		9	6.12	39	12.04
Other stage		56	38.10	118	36.42
MACE within 1 yr	471				
Readmission				131	27.81
MI				47	9.98
Death				21	4.46
CVA				6	1.27

MACE: Major adverse cardiac events; SD: Standard deviation; LC: Largest change; BP: Blood pressure; PCI: Percutaneous coronary intervention; LVEF: Left ventricular ejection fraction; CVD: Cardiovascular disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; CCS: Canadian Cardiovascular Society; STEMI: ST-segment elevation myocardial infarction; CVA: Cerebrovascular accident.

0.016). Hypertension was very common in both groups, though more so in patients with no MACE (P = 0.013). 15% more of those with a MACE were on anti-anginal medication (P = 0.003), with the largest difference found in patients taking beta blockers (16%; P = 0.002) and long-acting nitrates (10%; P = 0.011). Patients with a MACE were 5% more likely to be in anginal class CSS I and 8% more in CSS II (P < 0.001). About half were non-STEMI but twice as many MACE patients were STEMI.

BPV was measured in two ways, SD of all patient BPs in the study period and the largest change (LC) between two consecutive outpatient BP measurements. Table 1 shows the average values for the four BPV measures by MACE category. Systolic SD measures were significantly higher for patients with MACE (mean 15.38 ± 5.26) than patients with no MACE (mean 13.72 ± 6.02; P = 0.004). The diastolic SD were less than the systolic (8.54 and 8.93) but not significantly different between MACE categories (P = 0.188). Like the systolic SD, the systolic LC was significantly higher in MACE group (P < 0.001). The diastolic LC was on average 3 points higher for the MACE group (P = 0.002). Average systolic measures were comparable in each group, mean 131.83 ± 11.47 and mean 132.20 ± 11.63 (P = 0.748). The average diastolic measures of the MACE patients (mean 71.33 ± 7.64) were significantly lower than patients with no MACE (mean 74.82 ± 7.75) (P < 0.001). We also tested the metrics for gathering the BPs and found that those with MACE had 12 more BP readings on average (P < 0.001) though this variable was badly skewed. MACE patients had 17 fewer days between readings on average than non-MACE patients (P < 0.001).

Logistic regressions (controlling for demographics and health status) were used to estimate the risk of higher BPV for adverse outcomes. Only the outcomes of MACE, all-cause hospitalization, and MI were used for these analyses due to relatively small number of patients who experienced the other specific outcomes. Figure 1 shows the ORs for BPV predicting the outcomes. No BPV measures significantly increased the risk of MI when controlling for demographics and health status. The risk of all-cause hospitalization was increased significantly by higher systolic BPV as calculated by both LC (OR = 1.024, 95%CI: 1.006-1.042) and SD (OR = 1.049, 95%CI: 1.000-1.099). The risk of MACE was also increased significantly by higher systolic BPV as calculated by LC (OR = 1.024, 95%CI: 1.007-1.042) and SD (OR = 1.049, 95%CI: 1.003-1.100). Although eight of the risks of these outcomes were not statistically significant, we noted a trend where patients with high BPV had increased risk of any outcome.

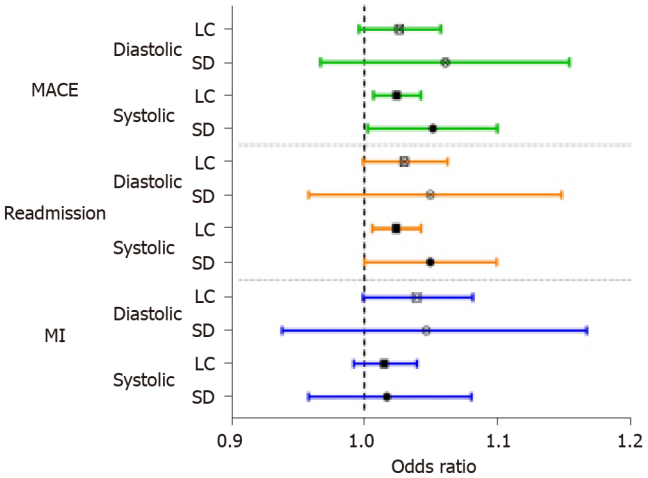
Receiving operator characteristic (ROC) curves were generated to determine cutoff values of the four BPV measures for predicting MACE, hospitalizations, and MI (Figure 2). The systolic BPVs appeared better at predicting outcomes. Table 2 shows the cutoff value used that maximized sensitivity and specificity, the area under the ROC curve (AUC) and corresponding 95% confidence intervals. The cutoff values for systolic SD determining MACE was 12.0, 14.0 for readmission, and 13.5 for MI. Diastolic SD ranged from 8 to 9, systolic LC was 33 to 48, and diastolic LC was 15 to 26. Sensitivities ranged from 45% to 82%, and specificities from 44% to 77%. All AUCs were significantly different from 50%.

The relationships between the four BPVs and MACE were tested with subgroups of age, anginal class, and indication. Significant interaction in a two-way ANOVA indicated the relationship may differ according to groups. There were no significant interactions with anginal class and indication, suggesting the relationships between the BPV and MACE did not differ by those subgroups. Age (Figure 3) had significant interactions for systolic SD (P = 0.0429) and systolic largest change (P < 0.001).

Table 2 Receiver operative characteristic analysis of cutoff values for four measures of blood pressure variability predicting adverse events

	Cutoff	Sensitivity	Specificity	AUC	95% confidence interval	
					Low level	Upper level
MACE						
Systolic SD	12.0	0.7755	0.4475	0.6300	0.5752	0.6792
Diastolic SD	8.0	0.6395	0.5216	0.5674	0.5102	0.6195
Systolic LC	33.0	0.7891	0.4414	0.6510	0.5957	0.7001
Diastolic LC	26.0	0.5102	0.6235	0.5837	0.5262	0.6359
Readmission						
Systolic SD	14.0	0.5573	0.6324	0.6348	0.5792	0.6846
Diastolic SD	8.0	0.6565	0.5206	0.5734	0.5149	0.6267
Systolic LC	33.0	0.8168	0.4412	0.6592	0.6039	0.7083
Diastolic LC	25.0	0.5573	0.6176	0.6018	0.5426	0.6549
MI						
Systolic SD	13.5	0.6596	0.5684	0.6234	0.5371	0.6967
Diastolic SD	9.0	0.4894	0.6604	0.5730	0.4800	0.6533
Systolic LC	48.0	0.4468	0.7665	0.6609	0.5649	0.7393
Diastolic LC	26.0	0.6170	0.6038	0.6255	0.5370	0.7004

AUC: Area under the ROC curve; MACE: Major adverse cardiac events; SD: Standard deviation; LC: Largest change; MI: Myocardial infarction.

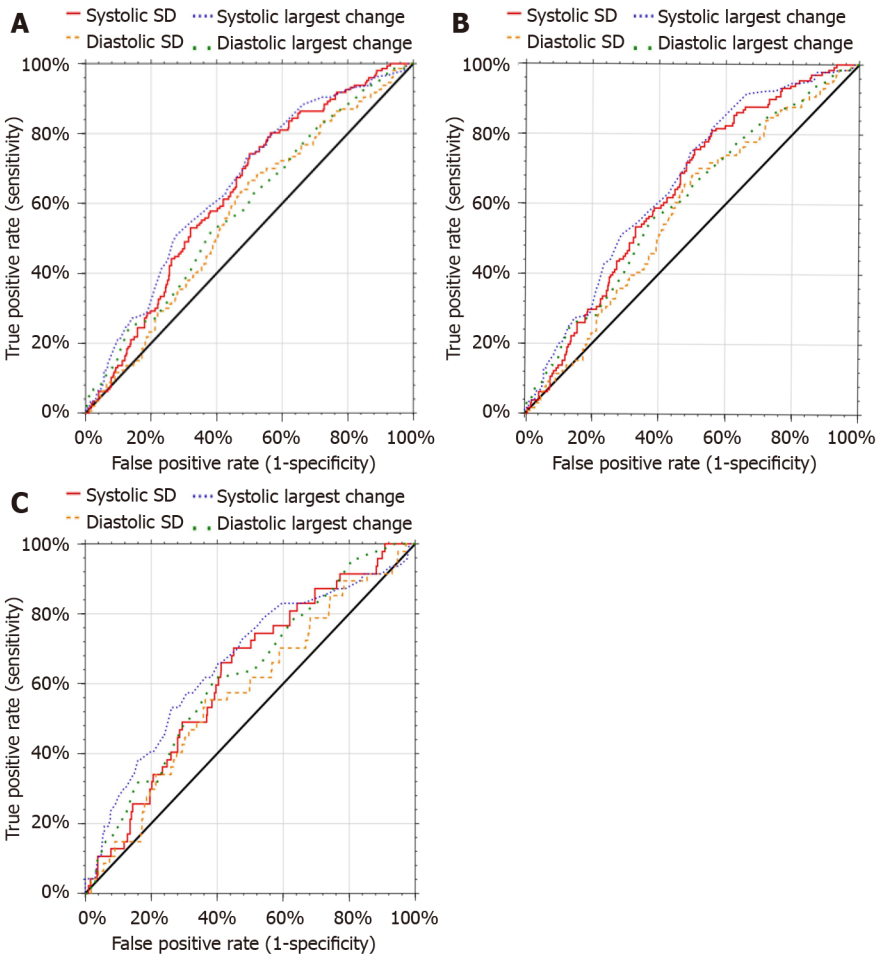


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Figure 1 Adjusted odds ratios with 95% confidence intervals from logistic regressions of preoperative blood pressure variability predicting outcomes after percutaneous coronary intervention. Odds ratios were controlled for age, sex, smoking status, diagnoses of hypertension or diabetes, prior cardiovascular disease, prior myocardial infarction, prior coronary artery bypass graft, prior percutaneous coronary intervention (PCI) left ventricular ejection fraction (LVEF), prior creatinine, anginal class, on anti-anginal medications, indication, and average systolic or diastolic blood pressure. Due to some missing values, myocardial infarction was not adjusted for PCI LVEF and creatinine. MACE: Major adverse cardiac events; MI: Myocardial infarction; LC: Largest change; SD: Standard deviation.

DISCUSSION

Chronic outpatient BPV, distinct from hypertension, has been shown to be associated with poor patient outcomes, not only in the general population, but in those who undergo surgical procedures[4] including CABG[5]. BPV can be studied as either systolic or diastolic variability, and each can be calculated by standard deviation as well as the largest change between two consecutive measurements.



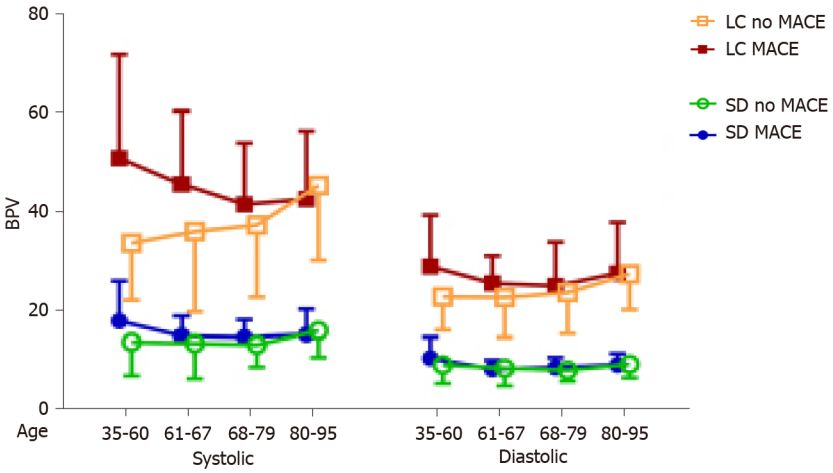
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Figure 2 Receiver operating characteristic curves for blood pressure variability predicting major adverse cardiac events, readmission, and myocardial infarction for patients one year after undergoing percutaneous coronary intervention. A: Major adverse cardiac events blood pressure variability (BPV); B: Readmission BPV; C: Myocardial infarction BPV. SD: Standard deviation.

A minimum of 10 outpatient BP recordings to measure BPV was previously used by other authors, ourselves included, because it was found to include enough measurements over a long enough timeframe to define BPV, yet short enough to be practical as patient physiology can drastically change with too large of a time interval[8]. Our key findings from this study were three. First, high pre-operative BPV gives patients elevated risk for poor outcomes following PCI. Second, systolic BPV may be a more sensitive indicator of adverse outcomes than diastolic BPV. Third, calculating BPV by LC seemed more indicative of adverse outcomes than calculating BPV by SD (following PCI).

While high BPV has been associated with worse post-operative outcomes after complex and highly invasive procedures such as CABG, colectomy, and total hip replacement[4,5], this is to our knowledge the first study investigating how BPV affects these outcomes after a much less invasive procedure such as PCI in patients who are known to have cardiac disease. This study confirms that patients with higher BPV are more likely to have poor outcomes after undergoing PCI. This is important because most patients who undergo PCI are already at higher baseline risk of adverse health outcomes, and thus preoperative BPV predisposes these individuals to an even higher risk. Patients who suffered from MI, all-cause hospitalization, and death within one year of the procedure had a significantly higher mean SD of their systolic BP. These patients also had a significantly larger mean greatest difference of both systolic and diastolic pressures. Moreover, when procedural indication was adjusted for, we found that risk for developing MI, all-cause hospitalization, and MACE was significantly increased when BPV was measured by LC.

Long term BPV has been shown to be a risk factor for MACE in several populations including type 2 diabetics, the elderly, younger populations, those with end stage renal disease, and post-operative patients[4,11,16-18]. Our results suggest that MACE occurs more frequently after PCI in patients with higher systolic BPV, and this remained true even when adjusted for indication. Regardless of how it is measured, even small changes in BPV can be clinically significant and associated with adverse outcomes for patients. Physicians should consider BPV while counseling patients who are considering elective PCI on the risks of the procedure. If a patient has high BPV, this may present an opportunity for physicians



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Figure 3 Mean blood pressure variability by age and major adverse cardiac event status of patients one year after undergoing percutaneous coronary intervention. BPV: Blood pressure variability; LC: Largest change; MACE: Major adverse cardiac events; SD: Standard deviation.

to educate their patients on their other cardiac risk factors. Perhaps patients could be more motivated to modify controllable risk factors, such as smoking or a sedentary lifestyle, if they know that they have additional non-modifiable risk factors such as BPV. Moreover, although all patients are followed carefully, when a patient with high BPV undergoes PCI it may be vital to conduct additional thorough follow-up and vigilant surveillance to identify and intervene if such outcomes may occur.

The etiology of BPV is not well understood, although a couple hypotheses exist on what contributes to BPV. One hypothesis is that BPV is related to differing coronary physiology due to vascular wall stiffness, hypertrophy, and cardiovascular plaque stability among others. Greater BPV in young people with an absence of cardiovascular disease has been shown to be related to central aortic stiffness[18]. BPV is associated with unstable coronary plaques in patients with stable angina[14] and with carotid arterial stiffness in elderly patients[17]. Blood pressure control may facilitate the regression of left ventricular hypertrophy, and it has been suggested that increased blood pressure variability may be a contributing cause of idiopathic cardiac hypertrophy[19,20]. BPV has been shown to increase arthroscopic plaque vulnerability[14,21] which could be a factor in some of these adverse outcomes. Surgical risks could be directly affected by autonomic instability which has been indicated in patients with BPV [20]. Any of these could cause a different response to PCI as compared to patients who have better blood pressure stability.

Others have suggested that BPV may be a proxy for differences in inflammatory responses to the physiologic stressors and the acute coronary illness that follows[22]. Components of both the innate and adaptive immune system, specifically various cytokine differences, toll-like receptors, and inflammasomes, have been shown to play a role in pathogenesis of elevated blood pressure[23]. Although this relationship has not yet been specifically studied in blood pressure variability, it is possible that inflammatory changes that are associated with hypertension might also lead to BPV within that hypertension. Such differences could alter the acute response to the trauma caused by PCI, thus putting patients at a higher risk for later adverse outcomes. Although further extrapolation of the etiology of BPV is certainly warranted, it seems likely that both intrinsic baseline biology and anatomy and differences in patients' physiologic reactions to stress may all be associated with BPV in these patients and may contribute to their subsequent risk.

Although we[8] and others[7] have previously suggested that how BPV is calculated may be inconsequential, the results of this study seem to contrast with this idea. In this post-PCI population, systolic BPV seemed to be more sensitive of a predictor of adverse outcomes than diastolic BPV. Additionally, largest change may have been a more powerful predictor of adverse outcomes than standard deviation. This is potentially important because SD seems to be the most common way that BPV is analyzed in the literature. Increased systolic BPV showed statistical significance as a risk factor for each adverse outcome in this population as measured by LC. Systolic BPV as a more indicative measure of adverse outcomes after PCI may partially be due to the relatively high age of the patients who undergo this procedure. Systolic BP is known to have more use as a prognostic indicator with increasing age[22] and the average age of this population was 68.8 ± 11.5. Another factor to consider is that the association between elevated BPV and coronary atheroma progression was more strongly associated with systolic BPV[21].

Increased diastolic BPV also showed statistical significance for three outcomes but did not achieve statistical significance with any outcomes when calculated by SD. This suggests that diastolic BPV can also be a predictor of adverse outcomes when measured by LC. Although patients who experienced

adverse outcomes were not shown to be significantly different than those who did not have adverse outcomes when measuring diastolic BPV by SD, we did observe a trend in this direction and it is possible that this might have become statistically significant with a larger sample size since we did observe statistical significance when diastolic BPV was assessed using LC. Additionally, although six of the risks of the outcomes measured by logistic regression were not statistically significant, a general trend was noted in that patients with high BPV had elevated risk of any outcome occurring. Although age is a potential hypothesis for the differences between systolic and diastolic BPV as a risk factor for adverse outcomes, work remains to be done to determine the etiologic differences that exist between systolic and diastolic BPV.

Although it is possible that LC may be a more sensitive indicator of risk than SD in patients undergoing PCI, this may also be an artifact of this particular sample. Regardless, it seems clear that LC is at least as useful, if not more useful than SD in risk estimation. This is important because until electronic medical records are programmed to automatically calculate BPV for every patient, the average physician will find LC to be much easier to calculate, less time consuming, and more intuitive than attempting to determine SD. The physician may simply scan a list of blood pressure readings and find the largest change between consecutive encounters to rapidly screen patients for BPV prior to selection for PCI. Further studies need to be done to determine if LC could indeed be a stronger predictor of adverse outcomes than SD.

In cardiovascular trials, different authors use various defined composite clinical endpoints, one of which is commonly MACE. 3P MACE and 4P MACE exist depending on whether 3 or 4 individual event endpoints are used, with some variability of what these endpoints are 3 endpoint MACE are commonly defined to include MI, death, and CVA[24]. Although not commonly reported as a MACE, hospitalization is a commonly used endpoint related to heart failure or other post-operative trials, so we believe that it is appropriate to use all cause hospitalization as a composite endpoint for a major adverse cardiac event[24]. Therefore, we used a somewhat original 4P MACE for our study which we defined as all-cause hospitalization, MI, death, and CVA.

This study has limitations. 27% of the patients who underwent angioplasty during the study period were excluded *a priori* because they did not have 10 outpatient BP readings 3-60 mo prior to PCI. We had made this decision in advance of collecting our data because our previous analysis[8] suggested that BPV can be very accurately calculated with at least 10 readings. These 171 patients otherwise had remarkably similar demographics to the patients who were included in the study, making it less likely that selection bias has affected our results. Another potential concern is whether we missed complications in patients who may have gone to a separate healthcare system with their post-procedural complications. However, Sanford Health has a large catchment area and shares access to surrounding health systems' electronic records. Moreover, there seems no particular reason to postulate that patients with low or high BPV would have been more likely to seek attention at outside facilities which was indicative in that the outcomes we ascertained had 100% follow up prospectively. Another potential concern is that the BP readings that were used in this study were derived from chart review after routine clinical practice rather than being measured by pre-designed specified protocols. Clinical trials often utilize very precise practices to measure BP precisely because without such practices BP measurement may differ from how it is routinely measured in the clinical setting. Our BP measurements do lack standardization, which thus could be interpreted as a weakness in that measurements were not taken at fixed intervals with fixed protocols. However, the BP measurements used here do reflect how physicians would routinely assess patients' BPV in the clinic. Thus, one might conversely propose that this apparent limitation actually makes our study results more relevant to the real world. While considering kidney disease simply by pre-procedural serum creatinine levels is not ideal and represents a limitation to this study, the diagnosis of chronic renal failure was not included in the data available for analysis. While it would have been interesting to calculate a Kaplan-Meier survival curve for MACE, the specific dates for these key complications were unfortunately not included in the registry and so these data were unfortunately unavailable for analysis.

CONCLUSION

High outpatient BPV predicts adverse outcomes after PCI, including all-cause hospitalization, death, MI, and CVA, regardless of whether the patient is chronically hypertensive or normotensive. Calculating BPV by largest change was a stronger predictor than standard deviation for MACE within 1 year of the procedure. This was true for both systolic and diastolic BPV, although systolic BPV seemed to be a more sensitive indicator of poor outcomes. Prior to PCI, patients with high BPV should be counseled by their physician about their increased risk for adverse outcomes and should be followed more vigilantly after their procedure. Most percutaneous coronary interventions are relatively urgent and cannot be postponed for long periods of time for patients to attempt to modify risk factors prior to PCI. Furthermore, further research is still required to identify changes or pharmacologic interventions that patients may undertake to usefully reduce their BPV. However, patients with higher BPV who are about to undergo PCI can and should be counselled that they are at a higher risk of post-procedural

complications and that they should subsequently address any other modifiable risk factors that are also associated with poor post-operative outcomes to best optimize their individual post-procedural outcomes. Physicians performing PCI may also wish to consider BPV as they decide how aggressive to be in their procedures, while quality comparisons of PCI programs or research on future PCI interventions should consider as an additional risk factor in multivariate analyses of outcomes. Work remains to be done to discover the true etiology of BPV as well as why systolic and diastolic variability may have differing impacts on the patients' outcomes.

ARTICLE HIGHLIGHTS

Research background

Blood pressure variability (BPV), distinct from hypertension, is known to be a risk factor for long term complications, and has recently been shown to increase the acute risk of postoperative death, hospitalization, or other complications for patients undergoing major surgical procedures.

Research motivation

The impact of BPV on outcomes after the less invasive procedure of percutaneous coronary interventions (PCI) has not previously been explored despite the high risk nature of these patients.

Research objectives

To determine whether BPV represents an independent risk factor for poor outcomes after percutaneous coronary angioplasty.

Research methods

Six hundred and forty-seven patients undergoing PCI in a single state in 2017 were prospectively enrolled in a patient registry which was then retrospectively analyzed. Systolic and diastolic BPV were calculated as both the largest consecutive change between blood pressure measurements and the standard deviation of all blood pressure measurements for the 30-60 mo prior to PCI, considering only the 471 patients with more than ten blood pressure measurements for analysis. Other variables including demographics, prior diagnoses and medication use were retrieved. Procedural indications were categorized as staged PCI, non-STEMI, or other. Adverse outcomes were identified for up to a year following the procedure, including MACE, myocardial infarction, cerebrovascular accident, death, and all-cause hospitalization.

Research results

Even after taking into account other patient characteristics, visit-to-visit systolic BPV, as measured by both standard deviation and largest change, was higher in patients who had myocardial infarctions, were readmitted, or died within one year following PCI. Systolic BPV was higher in patients who had major adverse cardiac events (MACE), or readmissions ($P < 0.05$). Diastolic BPV, as measured by largest change, was higher in patients with MACE and readmissions ($P < 0.05$).

Research conclusions

BPV represents an independent risk factor for poor outcomes after PCI.

Research perspectives

BPV is easily measured and captured from the electronic medical record. Cardiologists performing PCI should consider high BPV in choosing among procedural outcomes or observation, and should follow patients with high BPV more closely after PCI. Patients with high BPV should be counseled about this risk factor in the informed consent process and should be counseled to work more aggressively to reduce other more modifiable risk factors after PCI in the face of their BPV.

FOOTNOTES

Author contributions: Weisel CL, Dyke CM, Haldis TA, and Basson MD designed the research study; Weisel CL, Dyke CM, Klug MG, Haldis TA, and Basson MD performed the research study; Klug MG contributed new analytic tools; Weisel CL, Klug MG, and Basson MD analyzed the data; Weisel CL, Dyke CM, Klug MG, Haldis TA, and Basson MD wrote the manuscript; and All authors have read and approved the final manuscript.

Institutional review board statement: The institutional review board determined, on 2/28/2018, that the proposed activity is not human research.

Informed consent statement: There are no informed consent documents because this was a retrospective study.

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

Data sharing statement: No additional data are available.

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META-ANALYSIS

Comparative efficacy and safety of adenosine and regadenoson for assessment of fractional flow reserve: A systematic review and meta-analysis

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Abstract

BACKGROUND

Adenosine is a coronary hyperemic agent used to measure invasive fractional flow reserve (FFR) of intermediate severity coronary stenosis.

AIM

To compare FFR assessment using adenosine with an alternate hyperemic agent, regadenoson.

METHODS

PubMed, Google Scholar, CINAHL and Cochrane databases were queried for studies comparing adenosine and regadenoson for assessment of FFR. Data on FFR, correlation coefficient and adverse events from the selected studies were extracted and analyzed by means of random effects model. Two tailed *P*-value less than 0.05 was considered significant. Heterogeneity was assessed using I^2 test.

RESULTS

Five studies with 248 patients were included in the final analysis. All included patients and coronary lesions underwent FFR assessment using both adenosine and regadenoson. There was no significant mean difference between FFR measurement by the two agents [odds ratio (OR) = -0.00; 95% confidence interval (CI): (-0.02)-0.01, $P = 0.88$]. The cumulative correlation coefficient was 0.98 (0.96-0.99, $P < 0.01$). Three of five studies reported time to FFR with cumulative results favoring regadenoson (mean difference 34.31 s; 25.14-43.48 s, $P < 0.01$). Risk of adverse events was higher with adenosine compared to regadenoson (OR = 2.39; 95%CI: 1.22-4.67, $P = 0.01$), which most commonly included bradycardia and hypotension. Vast majority of the adverse events associated with both agents were

transient.

CONCLUSION

The performance of regadenoson in inducing maximal hyperemia was comparable to that of adenosine. There was excellent correlation between the FFR measurements by both the agents. The use of adenosine, was however associated with higher risk of adverse events and longer time to FFR compared to regadenoson.

Key Words: Adenosine; Regadenoson; Fractional flow reserve; Meta-analysis

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Core Tip: Regadenoson has comparable efficacy in inducing maximal coronary hyperemia in patients undergoing invasive coronary angiography with lower risk of side effects compared to adenosine. To compare fractional flow reserve (FFR) assessment using adenosine with an alternate hyperemic agent, regadenoson. PubMed, Google Scholar, CINAHL and Cochrane databases were queried for studies comparing adenosine and regadenoson for assessment of FFR. There was excellent correlation between the FFR measurements by both the agents. The use of adenosine, was however associated with higher risk of adverse events and longer time to FFR compared to regadenoson.

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INTRODUCTION

Coronary angiography has long been the gold standard for assessment of severity of coronary artery disease[1]. This modality is however limited to providing anatomic information with little physiologic and clinical correlation, and more notably has marked intra- and inter-observer variability with very little reproducibility[2,3]. Data has shown that reliability on angiography for assessment of stenosis to perform percutaneous coronary intervention may, in fact, result in higher rates of revascularization procedures without significant improvement in clinical outcomes[4]. Physiologic assessment of coronary stenosis is achieved through use of fractional flow reserve (FFR) which is the ratio of intracoronary pressures distal and proximal to the lesion. The distal pressure measurement can be recorded using a pressure wire sensor placed distal to the lesion and the proximal pressure can be recorded *via* the guide catheter. The resting FFR measurement may not unmask the true physiological significance of the lesion and is better unmasked under maximal coronary hyperemic conditions with the use of agents such as adenosine. This is especially useful in assessing hemodynamic significance of intermediate severity stenosis as shown by the FFR *vs* angiography for guiding percutaneous coronary intervention (FAME) and FFR-guided percutaneous coronary intervention plus optimal medical treatment *versus* optimal medical treatment alone in patients with stable coronary artery disease (FAME 2) trials[5,6].

Adenosine is the gold standard to achieve maximal hyperemia for adequate measurement of FFR, however due to non-selective receptor activation, it may cause transient shortness of breath, atrioventricular conduction blockade and chest pain. Regadenoson on the other hand is a selective A_{2A} receptor agonist and has a more favorable side effect profile and straightforward dosing (400 μg *vs* variable weight-based infusion dosing for adenosine, *i.e.*, 140 μg/kg/min for 2 min). Herein, we systematically reviewed published literature comparing the efficacy of regadenoson to adenosine for achieving maximal hyperemia, the correlation in FFR measurements, and the adverse effects to ascertain the safer and more cost-effective hyperemic agent.

MATERIALS AND METHODS

This investigation was conducted in accordance with the Cochrane collaboration guidelines and the results have been reported per the PRISMA statement[7]. Literature review was performed independently by two authors (Gill GS, Gadre A) in PubMed, Cochrane, CINAHL and Google Scholar

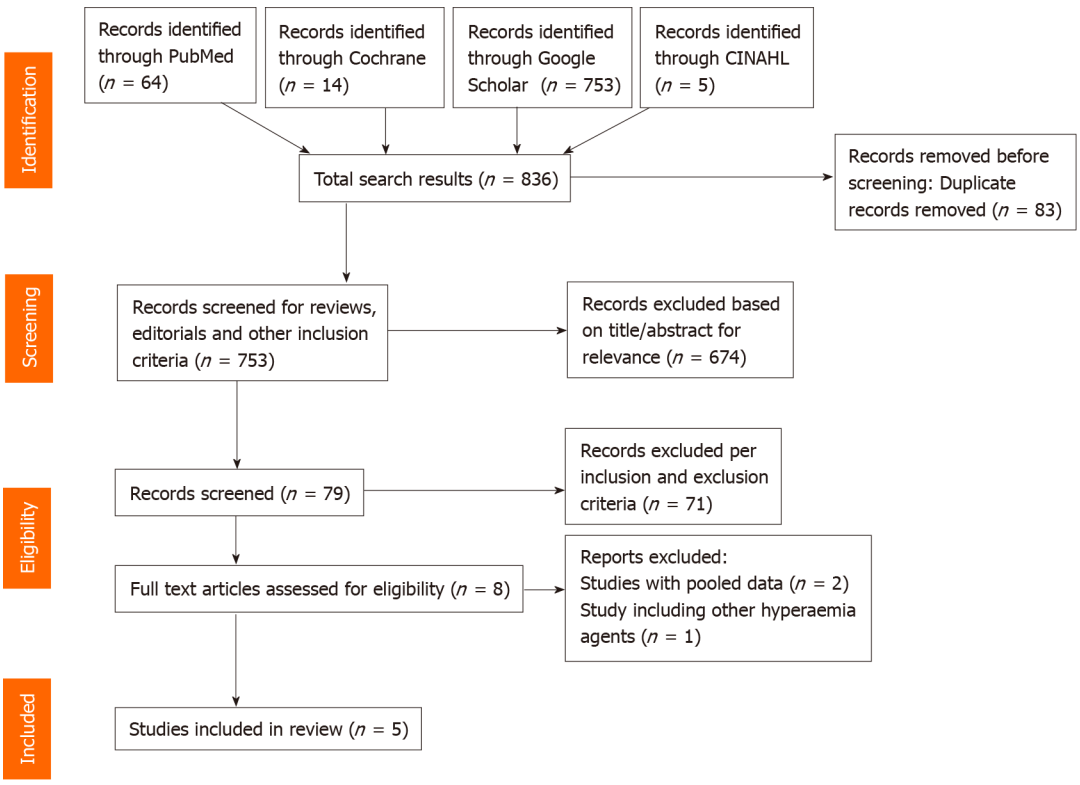
Table 1 Study characteristics of included investigations

Ref.	Country	Patients (*n*)	Population	Enrollment period	Adenosine dosing	Regadenoson dosing	Inclusion/exclusion criteria	Measured outcomes
Nair *et al* [10], 2011	United States	25	Prospective, single-center	July 2009-December 2010	IV adenosine infusion at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Elective angiography, intermediate stenosis (40%-70%), remainder per ADVANCE trial (2)	FFR correlation, flushing, dyspnea, headache, chest discomfort, nausea, diaphoresis, metallic taste
Arumugham *et al*[11], 2013	United States	20	Prospective, single-center	October 2009-September 2010	IV adenosine infusion at 175 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Intermediate stenosis (50%-80%). Exclusion: STEMI within 5 d, significant left main coronary artery stenosis, heart block, pregnancy, asthma or hypersensitive to either adenosine or regadenoson	FFR correlation, time to achieve FFR, effect on blood pressure and heart rate, heart block, bronchospasm, severe chest pain
Prasad *et al* [12], 2014	United States	57[1]	Prospective, multi-center	May 2011-November 2011	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Intermediate stenosis (50%-70%). Exclusion: Age < 18 years old, 3-vessel CAD, ACS within 1 wk, prior MI in territory supplied by target lesion, hypersensitivity to adenosine or regadenoson, reactive airway disease, 2nd or 3rd heart block, currently receiving dipyridamole, hemodynamic instability	FFR correlation, blood pressure, change in heart rate, dizziness, shortness of breath, heart block, flushing, arrhythmias
Van Nunen *et al*[13], 2015	Netherlands	100	Prospective, single-center	NA	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Ages 18-80 years old, lesions in proximal to mid coronary artery segments, at least 2 mm diameter, > 30% stenosis. Exclusion: Severe AS, 2nd-3rd heart block, acute MI within 5 d, bradycardia, severe hypotension, tortuous/calcified coronary vessels, severe asthma, pregnancy, inability to obtain femoral approach, dipyridamole within 48 h and methylxanthines within 12 h	FFR correlation, heart block, chest discomfort, blood pressure, heart rate, shortness of breath, nausea
Edward *et al* [14], 2018	United States	46	Prospective, single-center	April 2012-May 2014	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Elective angiography, < 30%, >90% stenosis. Exclusion: Sinus node dysfunction, 2nd-3rd degree AV block without pacemaker, severe hypotension, acute MI within 30 d, severe AS, pregnancy, aberrant coronary anatomy or calcification	FFR correlation, time to reversal with aminophylline, side effects

[1]60 lesions from 57 patients were included in the analysis.

IV: Intra-venous; STEMI: ST-segment elevation myocardial infarction; FFR: Fractional flow reserve; CAD: Coronary artery disease; ACS: Acute coronary syndrome; MI: Myocardial infarction; AV: Atrioventricular; AS: Aortic stenosis; NA: Not available; IC: Intra-coronary.

databases using the keywords "adenosine", "regadenoson", "fractional flow reserve", "FFR" and "hyperemia" in different combinations. 836 titles and abstracts were found, of which 83 were removed as duplicate. Of the remaining 753 titles, 674 were excluded based on title and abstract. 79 abstracts, original investigations, editorials and review articles were screened to assess for inclusion and exclusion criteria. Eight articles and their references were manually screened for any additional studies that could qualify for inclusion, of which, three were excluded from final analysis (systemic review, retrospective and pooled analyses) (Figure 1). The five included studies met following criteria: (1) Published as full manuscripts in English; (2) Involved patients with angiographic evidence of coronary artery stenosis; and (3) Assessed and reported at least one of the outcomes (FFR correlation, time to achieve FFR, adverse effects) with both adenosine and regadenoson. The following studies were excluded: (1) Duplicates of previous publications; (2) Pooled studies and systematic reviews; (3) Studies that included comparison of adenosine or regadenoson with nicorandil; (4) Abstracts, editorials, reviews, and commentaries; and (5) Animal studies. Any disagreement during the study screening and selection



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Figure 1 Flowchart depicting study selection for inclusion in the meta-analysis.

process was resolved by consensus among all authors.

The primary outcome of interest was FFR correlation, and secondary outcomes were time to achieve FFR, and a composite of all reported adverse effects. Data extraction was performed using a standardized data extraction form by two independent authors (Gill GS, Gadre A). Any disagreement on data was resolved by consensus among all authors. For all outcomes in our analyses, pooled odds ratio (OR) with their corresponding 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel random-effects model for dichotomous variables and Inverse variance model for the continuous variables, and presented as Forest plots[8]. For the correlation coefficient Fisher's *Z* transformation was performed and reverse transformation with restricted maximum likelihood method to obtain meta-summary correlation coefficient. Heterogeneity across the studies was assessed using the chi-square-based Cochrane *Q* test and quantified using I^2 statistics. I^2 index values of < 25%, 25%-50% and > 50% were considered low, intermediate, and high heterogeneity, respectively[9]. Exclusion sensitivity analysis was performed by excluding one study at a time and repeating the analysis. Publication bias was assessed using Begg's dissemination selectivity test and visually inspected using funnel plots. All analyses were conducted using the Review Manager Version 5.4 software, STATA software version 16 (StataCorp 2019, College Station, TX, United States) and the IBM SPSS software Version 26 (IBM Corp, Armonk, NY, United States). There was no duplicate data within included studies. A two-sided *P* value of < 0.05 was considered statistically significant.

RESULTS

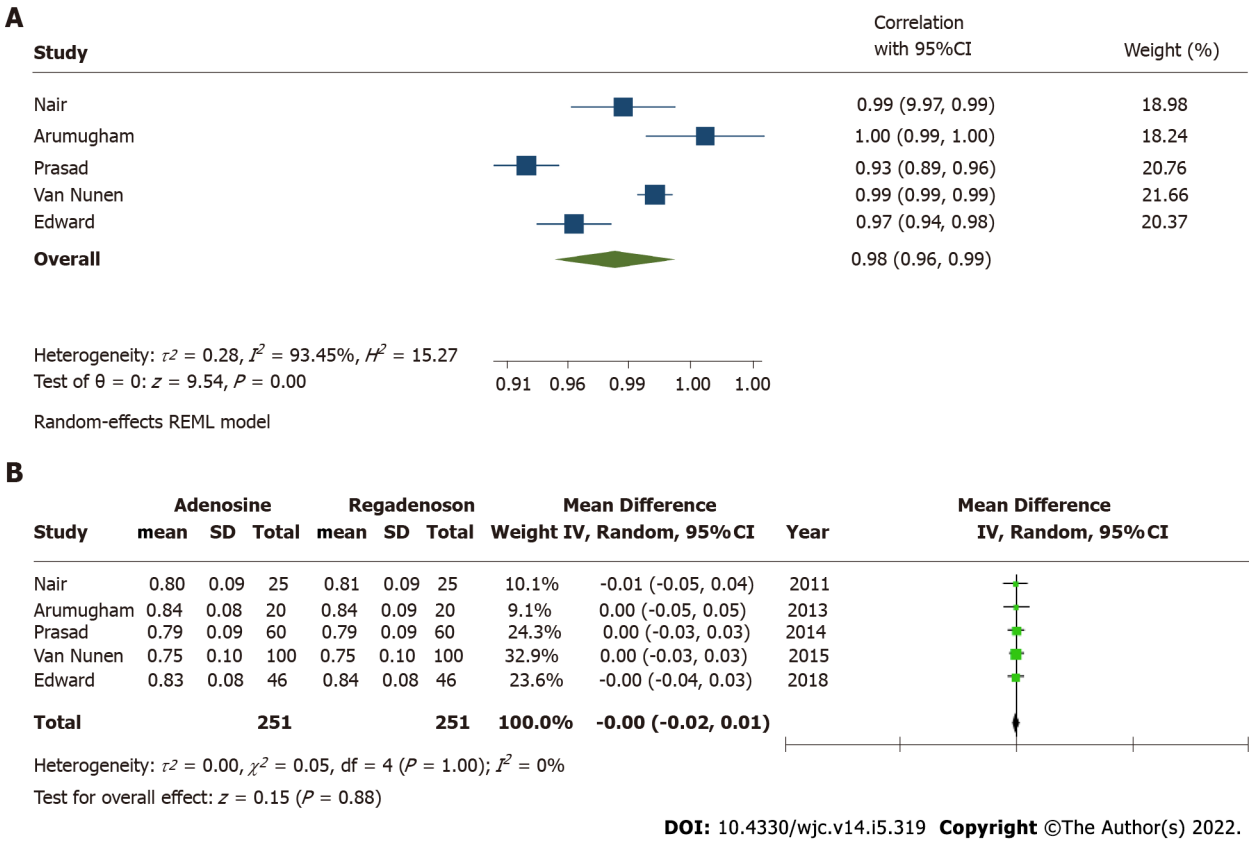
A total of eight investigations were reviewed to include five prospective studies involving 248 patients undergoing FFR analysis for 251 lesions in the final meta-analysis (Figure 1 and Table 1)[10-14]. A flowsheet of the study selection process in accordance with the PRISMA guidelines is shown in Figure 1. Study designs, infusion protocols, inclusion and exclusion criteria, and reported outcomes are represented in Table 1; and baseline characteristics of patients are reported in Table 2. Mean age of the study population was 63 years with women accounting for 25% of the participants. All studies were prospective with all 248 patients receiving both IV adenosine and IV regadenoson in a sequential manner.

FFR correlation was reported in all five studies. The cumulative correlation coefficient for FFR measurement was 0.98 (95%CI: 0.96-0.99) with I^2 estimate for heterogeneity at 93% (Figure 2A). Mean difference in measured FFR values with adenosine and regadenoson in pooled analysis was -0.00 [95%CI: (-0.02)-0.01; *P* = 0.88], with I^2 estimate for heterogeneity 0%. An exclusionary sensitivity analysis

Table 2 Baseline characteristics of patients from studies included in the meta-analysis

	Nair *et al*[10]	Arumugham *et al*[11]	Prasad *et al*[12]	van Nunen *et al*[13]	Edward *et al*[14]
Number	25	20	57 (60 lesions)	100	46
Age [yrs ± SD or yrs (CIs)]	63 ± 11	63.9 ± 9	57 ± 8	66 ± 8	63 ± 10
Women, *n* (%)	12 (48)	4 (20)	10 (18)	25 (25)	9 (20)
Body mass index (mean ± SD)	30.0 ± 5.7	NA	27.7 ± 4.1	26.7; H kg	33 ± 7
Hypertension, *n* (%)	21 (84)	NA	51 (90)	54	44 (96)
Diabetes mellitus, *n* (%)	6 (24)	NA	26 (46)	21	26 (57)
Hyperlipidemia, *n* (%)	21 (84)	NA	39 (68)	36	44 (96)
Tobacco use, *n* (%)	8 (32)	NA	24 (42)	20	7 (15)
CKD, *n* (%)	NA	NA	NA	NA	9 (20)
Prior MI, *n* (%)	5 (20)	NA	23 (40)	36	NA
Prior PCI, *n* (%)	8 (32)	NA	NA	43	NA

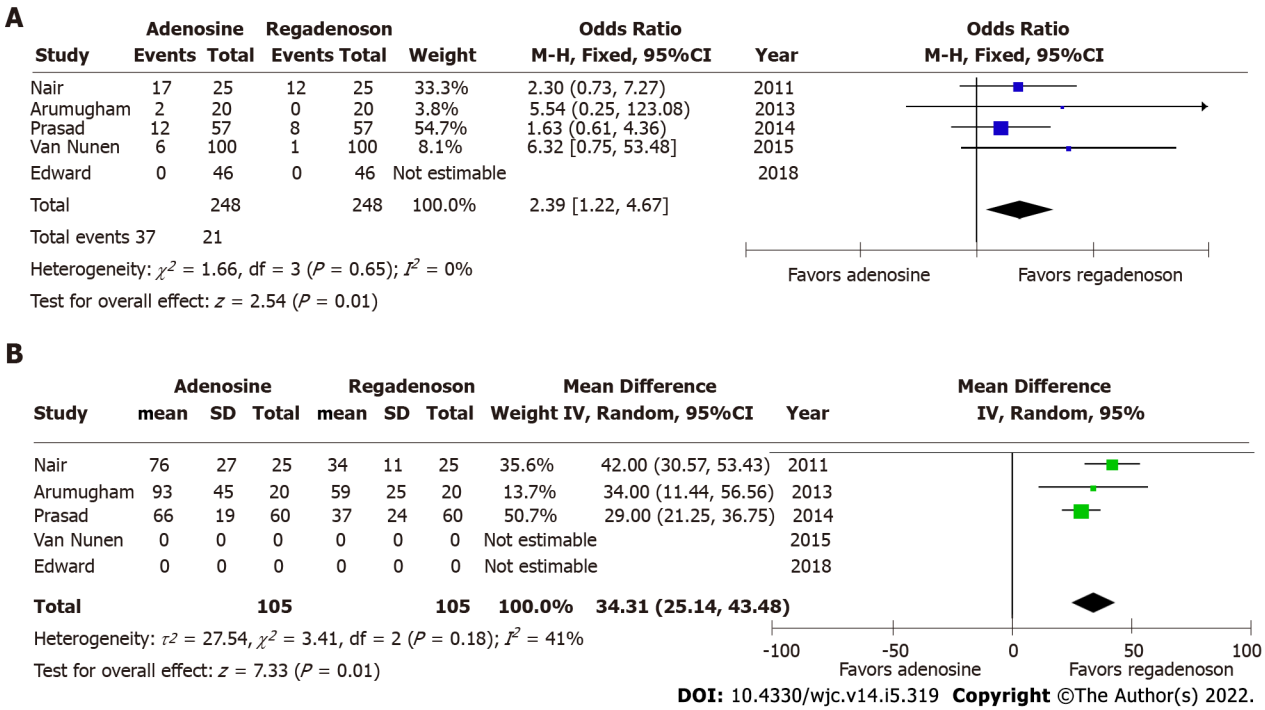
CI: Confidence interval; CKD: Chronic kidney disease; MI: Myocardial infarction; PCI: Percutaneous intervention; NA: Not available.



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Figure 2 Primary outcomes – adenosine *versus* regadenoson cumulative. A: correlation coefficient for fractional flow reserve (FFR) measurements; B: Mean difference in FFR measures. CI: Confidence interval.

was performed with exclusion of studies with lesions including low- and high-grade stenosis (Van Nunen *et al*[13] and Edward *et al*[14]), where results remained consistent with mean difference -0.00 [(-0.03)-0.02; P = 0.92] (Figure 2B). Time to achieve FFR was reported in three of five studies, and was significantly lower with regadenoson with a mean difference of 34.31 s (95%CI: 25.14-43.48 s; P < 0.01) (Figure 3A). The degree of heterogeneity albeit higher than remainder results, was still moderate with I^2 index = 41% in this three-study analysis.



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Figure 3 Secondary outcomes. A: Adverse event rates; B: Time to achieve fractional flow reserve (FFR) with adenosine versus regadenoson induced hyperemia for FFR measurement. CI: Confidence interval.

Pooled odds for any adverse effect were significantly higher for patients after administration of adenosine, than after receiving regadenoson (OR = 2.39, 95%CI: 1.22-4.67; P = 0.01) (Figure 3B). There was no evident heterogeneity among included studies with I^2 estimated at 0%. There was no evidence of dissemination bias on visual inspection of the funnel plot and Begg's test. There were no adverse effects reported in either arm of the study by Edward *et al*[14] among forty-six participants in the analysis where aminophylline were administered after regadenoson, while side effects reported in other studies were only transient and did not necessitate discontinuation of infusion or FFR measurement. In the study by Arumugham *et al*[11], a higher dose of IV adenosine was infused, while significant adverse event rates were not higher.

DISCUSSION

The major findings of this analysis are: (1) FFR correlation was excellent among both IV adenosine and IV regadenoson; (2) IV regadenoson achieved maximal hyperemia in a shorter interval; and (3) Adverse effects, including transient atrioventricular conduction block, chest pain, shortness of breath, hypotension, flushing and headache were higher with adenosine. Anatomic as well as physiologic assessment of coronary vasculature are integral elements to defining coronary artery disease in a patient. Over the past few decades, there have been advances in anatomic evaluation beyond traditional angiography, and have included developments in intravascular imaging, such as, intravascular ultrasound and optical coherence tomography. Studies comparing translation of anatomic *vs* physiologic assessment of coronary artery disease into clinical outcomes have concluded in comparable results[15]. Furthermore, investigations attempting to correlate optimum minimal lumen area to FFR values have concluded that their reciprocity may be vessel dependent[16]. This can be explained by the independent role of these modalities in assessing flow and identifying vulnerable plaques, respectively [17]. Due to easy availability and low cost, FFR based assessment of intermediate stenosis has been widely incorporated to practice.

Adenosine has traditionally been the gold standard for inducing maximal hyperemia while measuring FFR, although different agents have been investigated for efficacy and side effects with comparable results[10-14,18-22]. There is excellent correlation in FFR estimated by adenosine and regadenoson which is consistent with prior studies that have shown both agents achieve comparable hyperemia in animal as well as human models[23,24]. Adenosine is a non-selective activator of 4 receptors, A_1, A_{2A}, A_{2B} and A_3[25]. The activation of A_1 and A_3 receptor subtypes decreases cyclic adenosine monophosphate (cAMP) levels while activation of receptors A_{2A} and A_{2B} increases the cAMP levels[26]. cAMP is an important mediator of smooth muscle relaxation and therefore, activation of A_{2A} and A_{2B} receptors leads to coronary and peripheral arterial vasodilation and hyperemia. The non-

selective receptor activation by adenosine also causes bronchoconstriction and other side effects. Regadenoson, however, is a selective A_{2A} receptor agonist, and thus causes preferential coronary vasodilation with fewer side effects when compared to adenosine[27]. In cases where patients may experience adverse effects from regadenoson, they can be reversed using intravenous aminophylline[14, 28]. This easy reversibility makes physiologic evaluation feasible in patients with mild-to-moderate reactive airway disease and obstructive airway disease[27]. Another secondary outcome, time to FFR, was also shorter in patients who received regadenoson, thus favoring its use. This can potentially be explained by the non-weight-based bolus dosing of intravenous regadenoson, accommodated by the longer half-life (2-4 min) when compared to weight-based infusion of intravenous adenosine, which is administered preferably through central venous access due to its extremely short half-life (0.6-10 s). Because of its short half-life, administration of adenosine is challenging and could be time consuming. Our study results show that time to maximal hyperemia is shorter by about 30 s with the use of regadenoson. Further, this time does not take in to account the time taken for preparing the adenosine infusion which could take up to several minutes. This could potentially increase the duration of the procedure, and therefore, use of regadenoson may save valuable time for the catheterization laboratory and its staff while potentially leading to cost benefits despite the higher price of regadenoson.

As discussed above, our study demonstrates lower risk of adverse effects with regadenoson use. In study by Arumugham *et al*[11], a higher adenosine infusion rate was used (175 μg/kg/min), and to negate its effects, we conducted an exclusionary sensitivity analysis, where results remained similar (P = 0.02). We then conducted sensitivity analysis using jackknife approach for another secondary outcome, time to FFR, where heterogeneity was moderate with I^2 = 41% in the overall analysis. Here, we systematically excluded one study at a time, and noted a reduction in I^2 to 0% with exclusion of study by Nair *et al*[10], the oldest investigation. Outcome favoring regadenoson use remained unchanged (P < 0.01). Lastly, two of the five included studies did not limit the lesions to intermediate stenosis and a sensitivity analysis was conducted by excluding these investigations. The results remained unchanged with significant correlation between estimated FFRs (P = 0.92, I^2 = 0%).

The decision to use one agent over the other is further influenced by factors such as requirement of central venous access and cost. Although adenosine can be administered both *via* central or peripheral access, the onset of action is earlier and steady state hyperemia is more stable with central venous catheter. Regadenoson, on the other hand, has limitations including cost and unpredictability in the duration of hyperemia[13]. For this reason, regadenoson may not be the ideal agent, especially when evaluating multiple coronary arteries, and will require multiple dose administrations with incremental increase in the costs[29]. Regadenoson has near completely replaced adenosine for nuclear stress testing because of the ease of its administration and relatively fewer side effects and therefore is more appealing to be used for invasive FFR assessment. Our meta-analysis results clearly demonstrate that regadenoson is an acceptable alternative to adenosine for invasive FFR assessment of intermediate severity coronary stenosis.

Limitations and strengths

Our meta-analysis has inherent limitations as well as those inherited from the included studies. First, among the studies included in this meta-analysis, there is considerable variability in the definition of intermediate severity stenosis. Second, the study by Arumugham *et al*[11] used a higher adenosine infusion rate when compared to other investigations in an attempt to mitigate effects of deactivation of peripherally administered adenosine. This variability in dosing may have affected all outcomes, and potentially, strengthened the association between adenosine use and adverse effects. Third, the studies included in our analysis varied in drug infusion protocol in terms of peripheral *vs* central access which may be of importance when using an agent with short half-life, and investigating a time sensitive outcome, such as time to achieve FFR. Fourth, since these studies included patients undergoing elective angiography, these results may not be extrapolated to populations with unstable angina or other acute coronary syndromes. Lastly, in an attempt to conduct the analysis in consistency with PRISMA guidelines, this study may be subject to publication bias[30]. Inherently however, our investigation had limited risk of residual bias since all included studies had a prospective design with patients receiving both hyperemic agents. We performed several sensitivity analyses to document the consistency of our results despite the aforementioned limitations. We employed jackknife approach and excluded individual studies to investigate outcomes and re-calculate I^2. Given the lack of large multicenter studies addressing these differences in a well-designed prospective fashion, our analysis provides valuable insights into the differential outcomes of FFR measurement in patients with adenosine *vs* regadenoson use.

CONCLUSION

Our meta-analysis demonstrates that use of regadenoson for FFR measurement among patients undergoing elective angiography is associated with shorter time to achieve FFR, and lower risk of side effects while providing excellent correlation with the results obtained with adenosine and therefore may

be an acceptable alternative for FFR measurement in the cardiac catheterization laboratory. The ease of its use, and a relatively favorable side effect profile make regadenoson a very appealing alternative to adenosine.

ARTICLE HIGHLIGHTS

Research background

Regadenoson is a selective adenosine receptor agonist that causes coronary hyperemia and in limited studies has been shown to have comparative efficacy to adenosine in evaluating coronary fractional flow reserve (FFR).

Research motivation

Considering the evidence is limited in supporting the use of regadenoson as an alternative to adenosine in evaluating FFR, we hypothesized that using meta-analysis we can improve the strength of evidence comparing regadenoson *vs* adenosine in evaluating FFR in intermediate severity coronary stenosis.

Research objectives

To perform meta-analysis to evaluate regadenoson *vs* adenosine for efficacy and safety.

Research methods

Pooled meta-analysis of published studies. Comparing correlation coefficient and adverse events using random effects model. Visual inspection for bias and heterogeneity assessment using I^2 test.

Research results

The FFR correlation coefficient between regadenoson and adenosine was 0.98 [95% confidence interval (CI): 0.96-0.99, $P < 0.01$]. Time to achieve FFR was shorter by 34.31 s (95%CI: 25.14-43.48) in the regadenoson group. The risk of adverse events was higher with adenosine with odds ratio of 2.39 (95%CI: 1.22-4.67, $P = 0.01$).

Research conclusions

Regadenoson had comparable efficacy in obtaining FFR compared to adenosine and this was achieved in a shorter duration of time and with lower incidence of adverse effects.

Research perspectives

Regadenoson presents an alternative to adenosine in evaluating FFR in patients with intermediate severity coronary artery stenosis with lower risk of side effects and also saves time.

FOOTNOTES

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OPINION REVIEW

Metabolic and cardiovascular benefits with combination therapy of SGLT-2 inhibitors and GLP-1 receptor agonists in type 2 diabetes

Awadhesh Kumar Singh, Ritu Singh

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Abstract

Both GLP-1 receptor agonists (GLP-1RA) and SGLT-2 inhibitors (SGLT-2I) are newer classes of anti-diabetic agents that lower HbA1c moderately and decrease body weight and systolic blood pressure (SBP) modestly. Combination therapy with GLP-1RA plus SGLT-2I have shown a greater reduction in HbA1c, body weight, and SBP compared to either agent alone without any significant increase in hypoglycemia or other side effects. Since several agents from each class of these drugs have shown an improvement in cardiovascular (CV) and renal outcomes in their respective cardiovascular outcome trials (CVOT), combination therapy is theoretically expected to have additional CV and renal benefits. In this comprehensive opinion review, we found HbA1c lowering with GLP-1RA plus SGLT-2I to be less than additive compared to the sum of HbA1c lowering with either agent alone, although body weight lowering was nearly additive and the SBP lowering was more than additive. Our additional meta-analysis of CV outcomes with GLP-1RA plus SGLT-2I combination therapy from the pooled data of five CVOT found a similar reduction in three-point major adverse cardiovascular events compared to GLP-1RA or SGLT-2I alone, against placebo. Interestingly, a greater benefit in reduction of heart failure hospitalization with GLP-1RA plus SGLT-2I combination therapy was noted in the pooled meta-analysis of two randomized controlled trials. Future adequately powered trials can confirm whether additional CV or renal benefit is truly exerted by GLP-1RA plus SGLT-2I combination therapy.

Key Words: GLP-1 receptor agonists; SGLT-2 inhibitors; Combination therapy, Metabolic outcomes; Cardiovascular outcomes; Renal outcomes

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Core Tip: GLP-1 receptor agonist (GLP-1RA) plus SGLT-2 inhibitor (SGLT-2I) dual therapy causes a greater reduction in HbA1c, body weight, and systolic blood pressure (SBP), compared to either agent alone with similar adverse events. However, lowering of HbA1c, body weight, and SBP with combination therapy appeared to be less, nearly equal, and more than additive, respectively, compared to the sum of either agent alone. Our meta-analysis from five cardiovascular outcome trials suggests a similar reduction in major adverse cardiovascular events with dual therapy compared to GLP-1RA or SGLT-2I alone, but an additional benefit in heart failure hospitalization is likely. Future trials are needed to confirm these findings.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) has a complex nature of pathophysiology, and therefore, most patients will eventually require a combination of antidiabetic agents (ADD) with different mechanisms of action (MOA) to achieve optimal glycemic control. GLP-1 receptor agonists (GLP-1RA) are a newer class of ADD that lower plasma glucose both by enhancing insulin secretion and inhibiting glucagon secretion [1]. SGLT-2 inhibitors (SGLT-2I) are another newer class of ADD that lower plasma glucose by promoting urinary glucose excretion through the kidney by inhibiting glucose reabsorption[2]. Notably, both classes of these drugs have shown a favorable effect on body weight and blood pressure. Importantly, several recent cardiovascular (CV) outcome trials (CVOT) conducted with SGLT-2I or GLP-1RA have shown that certain agents within each class can reduce the incidence of CV events and mortality in people with T2DM[3,4]. In this comprehensive opinion review, we attempt to answer three contemporary questions: (1) What is the rationale of this combination therapy in the management of T2DM; (2) What additional metabolic control can we achieve with this combination therapy; and (3) Do we get an additional CV and renal benefit by combining both classes of drug?

WHAT IS THE RATIONALE OF THIS COMBINATION THERAPY IN THE MANAGEMENT OF T2DM?

Since GLP-1RA and SGLT-2I work through different MOA in different organs, combination therapy with these agents is expected to have a complementary or perhaps synergistic effect on metabolic outcomes. Combination of GLP-1RA and SGLT-2I can potentially correct seven of the eight pathophysiologic defects (Ominous Octet) of T2DM[5]. GLP-1RA lower plasma glucose concentration by augmenting insulin secretion and inhibiting glucagon secretion *via* β-cells and α-cells in the pancreas, respectively, in a glucose-dependent manner[1,6]. SGLT-2I lower plasma glucose concentration by producing glucosuria, which in turn causes a compensatory and "paradoxical" increase in endogenous glucose production (EGP) accompanied by a significant increase in plasma glucagon as well as a significant decrease in the fasting plasma insulin concentration. Thus, SGLT-2I administration can lead to a marked increase in plasma glucagon-to-insulin ratio (GIR) by 50%-100%[7,8]. This increase in EGP by SGLT-2I appears to counterbalance or offset nearly 40%-50% of the amount of glucose that is lost in the urine during glucosuria and, therefore, attenuates the overall decrease in HbA1c caused by the SGLT-2I class of drugs[7]. Since increase in plasma GIR contributes to an increase in EGP caused by SGLT-2I (at least in part), any pharmacological agents that reverse this ratio and in turn prevent an increase in EGP would likely amplify the decrease in HbA1c by SGLT-2I[9,10]. This led to the belief that the addition of GLP-1RA to SGLT-2I would stimulate insulin secretion and inhibit glucagon secretion and, thus, prevent an increase in plasma GIR and, therefore, is expected to mitigate any increase in EGP caused by SGLT-2I. This would allow amplification of plasma glucose lowering with SGLT-2I in combination with GLP-1RA. Indeed, a study (n = 36) that evaluated the acute effects of a single dose of liraglutide (GLP-1RA), canagliflozin (SGLT-2I), and combination of liraglutide plus canagliflozin on serum insulin, glucagon, and EGP found that acute administration of a single dose of liraglutide prevented the insulin decline and blocked the glucagon rise observed with canagliflozin, although it did not inhibit the increase in EGP[11]. Similarly, a 16-wk trial (n = 45) that evaluated the chronic effect of

liraglutide, canagliflozin, and liraglutide plus canagliflozin combination therapy on serum insulin, glucagon, and EGP, found that canagliflozin caused a significant 9% increase in EGP ($P < 0.05$) accompanied by a significant 50% increase ($P < 0.05$) in plasma GIR, while liraglutide inhibited EGP and reduced plasma glucagon concentration. Interestingly, EGP increased by a significant 15% ($P < 0.05$) in canagliflozin plus liraglutide combination arm, despite the fact that canagliflozin induced plasma glucagon concentration was blocked by liraglutide and no change in plasma insulin from the baseline was observed[12]. These findings hint that factors other than insulin and glucagon may contribute to the stimulation of EGP with SGLT-2I induced glucosuria, and these include the contribution of renal gluconeogenesis, which is insensitive to plasma glucagon concentration[13].

Other logic of this combination therapy also stems from the fact that while SGLT-2I cause a significant reduction of body weight, chronic administration may lead to a plateau effect due to a compensatory increase in appetite that may partially offset weight reduction[14]. Contrarily, GLP-1RA delays gastric emptying and is associated with appetite suppression; therefore, combination therapy may overcome SGLT-2I induced hyperphagia. Figure 1 summarizes the potential effect of combined SGTL-2I and GLP-1RA therapy. Importantly, early initiation of GLP-1RA and SGLT-2I in combination does not potentiate hypoglycemia and adverse events significantly and will allow a timely achievement of glycemic goals. Consequently, this combination has the potential of lowering the risks of diabetes-related morbidity and mortality in patients with T2DM, especially in the light of positive CV and renal outcomes with these agents as demonstrated in their respective CV and renal outcome trials[15].

WHAT ADDITIONAL METABOLIC CONTROL CAN WE ACHIEVE WITH THIS COMBINATION THERAPY?

Several short- and long-term randomized controlled trials (RCTs)[12,16-23] and observational studies [24-30] (ranging from 12-104 wk), and meta-analyses of RCTs[31-34] have assessed the efficacy and safety of GLP-1RA and SGLT-2I combination therapy, either simultaneously or sequentially. All these studies have demonstrated a significantly greater benefit on metabolic outcomes (HbA1c, body weight, and systolic blood pressure) with combination therapy compared to either agent alone or placebo. Table 1 summarizes the results from both randomized and observational studies, while Table 2 summarizes the results of meta-analyses. Collectively, reduction in HbA1c, body weight, and SBP was significantly greater with GLP-1RA plus SGLT-2I combination therapy compared to the placebo or GLP-1RA or SGLT-2I alone. However, in these RCTs, HbA1c lowering with simultaneous combination therapy of GLP-1RA and SGLT-2I was found to be less than additive compared to the sum of HbA1c lowering with either agent. Notably, body weight lowering appeared to be nearly additive, while SBP lowering was more than additive with simultaneous GLP-1RA and SGLT-2I combination therapy when compared to the sum effect with either agent alone across the RCTs. Table 3 summarizes these findings from RCTs. From the safety perspective, no obvious increase in odds of severe hypoglycemia was noted with combination therapy compared to either agent alone. Similarly, no obvious increase in gastrointestinal (GI) side effect or genital tract infection (GTI) was observed with GLP-1RA and SGLT-2I combination therapy compared with GLP-1RA or SGLT-2I alone, respectively.

The less than additive effect on HbA1c is commonly observed with many combination treatments including SGLT-2I plus metformin or SGLT-2I plus DPP-4 inhibitors or SGLT-2I plus GLP-1RA. It may be partly due to the "floor effect", as the efficacy of each individual agent depends on baseline HbA1c. When given in combination, one ADD would lower HbA1c more rapidly than the other due to the differential time to onset of action for each drug, thereby resulting in a smaller "effective baseline HbA1c" for the second ADD of combination therapy. Thus, the second ADD would then result in a smaller decline in HbA1c compared with its use in monotherapy, given the lower starting glycemic load. Second, it could be related to the MOA of the individual components. Third, despite a notable reduction in GIR and EGP with GLP-1RA alone, there was no decrease in EGP with combination therapy of GLP-1RA plus SGLT-2I, which can partly explain less than additive effect on HbA1c. Summarily, the overall effect on HbA1c with combination therapy depends upon multiple factors including onset of action and MOA of each drug and may not necessarily be synergistic despite having complimentary MOA. Another unique finding that has emerged about simultaneous GLP-1RA and SGLT-2I dual therapy compared to either therapy alone is weight reduction in short term *vs* long-term trials. In the longest conducted RCT (DURATION-8; 26-, 52- and 104-wk), Δweight reduction with GLP-1RA plus SGLT-2I dual therapy (exenatide QW and dapagliflozin combination) and GLP1-RA therapy (exenatide QW) alone decreased over time when compared to Δweight reduction at 28 wk[16-18]. Contrarily, SGLT-2I (dapagliflozin) recipients alone achieved greater Δweight reduction at 104 wk compared with Δweight reduction at 28 wk. This hint to a time-dependent diminution in body weight lowering is attributed to GLP-1RA rather than the SGLT-2I and, therefore, this finding defies the logic of "plateau" effect on body weight reduction with long-term use of SGLT-2I. Lastly, it is unclear whether simultaneous initiation or sequential administration of GLP-1RA and SGLT-2I has any difference in metabolic outcome based on available evidence. This is because all available studies that have evaluated sequential administration were primarily placebo-controlled trials. To know the metabolic outcome

Table 1 Studies with GLP-1 receptor agonists plus SGLT-2 inhibitors *vs* SGLT-2 inhibitors or GLP-1 receptor agonists

Type of study	Ref.	Comparator agent	*n*	Duration	ΔHbA1c (%), (95%CI or mean ± SD)	ΔWeight (kg), (95%CI)	ΔSBP (mmHg), (95%CI)	OR for severe Hypo's (95%CI)	GI S/E	GTI
Simultaneous initiation of GLP-1RA plus SGLT-2I *vs* SGLT-2I										
RCT, DB/ DURATION-8	Frías *et al*[16], 2016	EXE QW + DAPA *vs* DAPA	695	28 wk	-0.6 (-0.8; -0.3)	-1.22 (-2.00; -0.44)	-2.4 (-4.5; -0.3)	1.00 (0.02; 50.61)	EXENA + DAPA-16%; DAPA-12%	EXENA + DAPA-4%; DAPA- 6%
RCT	Ikonomodis *et al* [19], 2018	LIRA + EMPA *vs* EMPA	40	12 wk	-0.70 (-2.55; 1.15)	NR	0.00 (-5.70; 5.70)	NR	NR	NR
RCT, OL	Ali *et al*[12], 2020	LIRA + CANA *vs* CANA	45	16 wk	-0.78 (-1.52; -0.04)	-2.50 (-4.35; -0.65)	-8.90 (-16.19; -1.61)	1.00 (0.02; 53.66)	NR	NR
Sequential addition of GLP-1RA to SGLT-2I *vs* SGLT-2I										
RCT, DB/AWARD-10	Ludvik *et al*[20], 2018	DULA + SGLT-2I *vs* PBO + SGLT-2I	424	24 wk	-0.73 (-0.88; -0.58)	-0.75 (-1.47; -0.03)	-2.45 (-4.78; -0.12)	2.50 (0.06; 104.85)	DULA + SGLT-2I-26.5%; PBO-17%	DULA + SGLT-2I-0%; PBO-1%
RCT, DB/SUSTAIN-9	Zinman *et al*[21], 2019	SEMA + SGLT-2I *vs* PBO + SGLT-2I	302	30 wk	-1.40 (-1.58; -1.22)	-3.80 (-4.67; -2.93)	-6.30 (-9.07; -3.53)	9.27 (0.50; 173.02)	SEMA + SGLT-2I-37.3%; PBO-13.2%	NR
RCT, DB/LIRA-ADD2SGLT2i	Blonde *et al*[22], 2020	LIRA + SGLT-2I *vs* PBO + SGLT-2I	303	26 wk	-0.68 (-0.89; -0.47)	-0.82 (-1.67; 0.03)	1.40 (-1.65; 4.45)	1.00 (0.02; 64.81)	LIRA + SGLT-2I-26%[1]; PBO-6.0%[1]	NR
Simultaneous initiation of SGLT-2I plus GLP-1RA *vs* GLP-1RA										
RCT/DURATION-8	Frías *et al*[16], 2016	DAPA + EXE QW *vs* EXE QW	695	28 wk	-0.4 (-0.6; -0.1)	-1.87 (-2.66; -1.08)	-2.9 (-5.0; -0.8)	1.00 (0.02; 50.61)	EXENA + DAPA-16%; DAPA-15%	EXENA + DAPA-4%; EXENA-2%
RCT	Ikonomodis *et al* [19], 2018	EMPA + LIRA *vs* LIRA	40	12 wk	-0.20 (-2.16; 1.76)	NR	-1.00 (-6.57; 4.57)	NR	NR	NR
RCT	Ali *et al*[12], 2020	CANA + LIRA *vs* LIRA	45	16 wk	-0.23 (-1.18; 0.72)	-4.10 (-6.32; -1.88)	-9.00 (-18.49; 0.49)	1.00 (0.02; 53.66)	NR	NR
Sequential addition of SGLT-2I to GLP-1RA *vs* GLP-1RA										
RCT, DB/CANVAS	Fulcher *et al*[23], 2016	CANA + GLP-1RA *vs* PBO + GLP-1RA	95	18 wk	-1.03 (-1.34; -0.72)	-2.72 (-3.70; -1.74)	-8.05 (-14.13; -1.97)	2.5 (0.05; 114.6)	NR	CANA + GLP-1RA-12.3%; PBO-5.3%
Non-randomized studies (all Δ from baseline)										
Simultaneous initiation of SGLT-2I plus GLP-1RA										
Obs	Goncalves *et al*[28, 29], 2017	SGLT-2I with LIRA	33	62	-2.0	-10.0	-13.0	NR	NR	NR
Sequential addition of SGLT-2I to GLP-1RA										
Obs	Saroka *et al*[24],	CANA added to GLP-	75 (60 on insulin)	10.7 mo (mean)	-0.39 ± 0.88	-4.6 ± 4.3	-4.0 ± 12	NR	1.3%	GTI: 8%

	2015	1RA								
Retro, Obs	Curtis *et al*[25], 2016	DAPA added to GLP-1RA	14 (10 on insulin)	48 wk	-4.4 (-5.7; -2.7)	-5.47 (-22.9; -5)	NR	NR	NR	NR
Retro, Obs	Deol *et al*[26], 2016	SGLT-2I added to GLP-1RA	37 (DAPA = 36, CANA = 1)	3-6 mo 139 d (mean)	-1.05 (-1.41; -0.69)	-3.07 (-4.36; -1.78)	-1.16 (-6.01; 8.42)	NR	NR	NR
Non-R, OL, PMS	Harashima *et al*[27], 2017	CANA added to LIRA	71	52 wk	-0.7 (-0.89; -0.51)	-3.29 (-3.86; -2.72)	-7.9 (-10.7; -5.1)	9.9% (mild)	NR	7.1%
Obs	Goncalves *et al*[28, 29], 2017	SGLT-2I added to LIRA	46	76 wk	-0.9	-4.0	-7.0	NR	NR	NR
Non-R	Seino *et al*[30], 2018	LUSEO added to LIRA	76	52 wk	-0.68 (-0.87; -0.49)	-2.71 (-3.18; -2.23)	-7.1 (-10.4; -3.9)	6.6% (mild)	13.2%	3.9%

[1]Nausea. CANA: Canagliflozin; DAPA: Dapagliflozin; DB: Double blind; EMPA: Empagliflozin; EX QW: Exenatide once weekly; GI: Gastrointestinal; GLP-1RA: GLP-1 receptor agonists; GTI: Genital tract infections; Hypo's: Hypoglycemia; LIRA: Liraglutide; LUSEO: Luseogliflozin; Non-R: Non-randomized; NR: Not reported/retrievable; Obs: Observational; OL: Open label; OR: Odds ratio; PBO: Placebo; PMS: Post marketing study; RCT: Randomized controlled trial; Retro: Retrospective; SBP: Systolic blood pressure; SGLT-2I: SGLT-2 inhibitors; S/E: Side effect; SEMA: Semaglutide.

difference between simultaneous *vs* sequential approach, one requires comparison of three-arm trials - arm with simultaneous GLP-1RA plus SGLT-2I combination *vs* arm with GLP-1RA initiation and subsequent addition of SGLT-2I *vs* arm with SGLT-2I initiation and subsequent addition of GLP-1RA.

Several other studies with combination therapy with GLP-1RA plus SGLT-2I are currently in progress that can further enlighten their synergistic metabolic effect as compared to either therapy alone. Dapagliflozin plus exenatide on central regulation of appetite in diabetes type 2 (DECREASE; NCT03361098) is a double-blind, 16-wk RCT (n = 65) investigating the separate and combined actions of GLP-1RA plus SGLT-2I on food intake, body weight, activity within the central satiety and reward circuits in response to food-related stimuli, and whether the combination can prevent the increased intake observed with SGLT2-I in obese T2DM[35]. Effects of combined dapagliflozin and exenatide *vs* dapagliflozin and placebo on ectopic lipids in patients with uncontrolled type 2 diabetes mellitus (EXENDA, NCT003007329) is a triple-blind, 24-wk RCT (n = 34) investigating the effect of combination therapy *vs* SGLT-2I alone on hepatic lipid content (primary outcome) and myocardial and pancreatic lipid content (secondary outcome) as measured by magnetic resonance spectroscopy[36]. Another randomized, controlled, double blind study is ongoing to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW *vs* dapagliflozin alone in obese (BMI > 30 kg/m^2) patients with type 2 diabetes mellitus (RESILIENT; EudraCT 2015-005242-60). This study is evaluating the effect of exenatide QW plus dapagliflozin *vs* dapagliflozin alone compared with placebo on adjusted mean reduction in total body fat mass (as determined by dual-energy X-ray absorptiometry, DEXA) after 32 wk of treatment (n = 110)[37]. A 6-wk (n = 17), open-label, randomized, cross-over study to evaluate the albuminuria lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes (DECADE, EudraCT 2017-004709-42) is also currently underway[38]. Results from these studies of GLP-1RA plus SGLT-2I dual therapy would further add to our knowledge.

Table 2 Meta-analysis of randomized controlled trials comparing GLP-1 receptor agonists + SGLT-2I *vs* SGLT-2I or GLP-1 receptor agonists

Ref.	Types of studies included, *n*	Comparator arm	*N*	ΔHbA1c (%), (95%CI)	ΔWeight (kg), (95%CI)	ΔSBP (mmHg), (95%CI)	Adverse events (GI, GTI, Hypo's) with SGLT-2I + GLP-1RA *vs* SGLT-2I
Zhou *et al* [31], 2019	RCT, 3	GLP-1RA + SGLT-2I *vs* SGLT-2I	1421	-0.80 (-1.14; -0.45)	-1.46 (-2.38; -0.54)	-2.88 (-4.52; -1.25)	Increased risk of GI S/E (RR: 1.68; 95%CI: 1.14-2.47) but similar GTI (RR: 0.82; 95%CI: 0.39-1.75) and hypo's (RR: 2.10; 95%CI: 0.75-5.90) in combo arm
Castellana *et al*[32], 2019	RCT, 4	GLP-1RA + SGLT-2I *vs* SGLT-2I	1610	-0.74 (-1.15; -0.33)	-1.61 (-2.83; -0.38)	-3.32 (-4.96; -1.68)	Similar hypo's (RR: 1.43; 95%CI: 0.46-4.52). GTI and GI S/E not reported
Patoulias *et al* [33], 2019	RCT, 3	GLP-1RA + SGLT-2I *vs* SGLT-2I	1042	-0.91 (-1.41; -0.42)	-1.95 (-3.83; -0.07)	-3.64 (-6.24; -1.03)	Increased risk of nausea (RR: 3.21; 95%CI: 1.36-7.54) and hypo's (RR: 2.62; 95%CI: 1.15-5.96) in combo arm. GTI not reported
Mantsiou *et al* [34], 2020	RCT, 7	GLP-1RA + SGLT-2I *vs* SGLT-2I	1913	-0.85 (-1.19; -0.52)	-1.46 (-2.94; +0.03)	-2.66 (-5.26; -0.06)	No difference in severe hypo's (OR: 2.39; 95%CI: 0.47-12.27). GTI and GI S/E not reported
		GLP-1RA + SGLT-2I *vs* GLP-1RA		-0.61 (-1.09; -0.14)	-2.59 (-3.68; -1.51)	-4.13 (-7.28; -0.99)	No difference in severe hypo's (OR: 1.38; 95%CI: 0.14-13.14). GTI and GI S/E not reported

GI: Gastrointestinal; GLP-1RA: GLP-1 receptor agonists; GTI: Genital tract infections; Hypo's: Hypoglycemia; OR: Odds ratio; RR: Risk ratio; RCT: Randomized controlled trial; SBP: Systolic blood pressure; S/E: Side effect; SGLT-2I: SGLT-2 inhibitors.

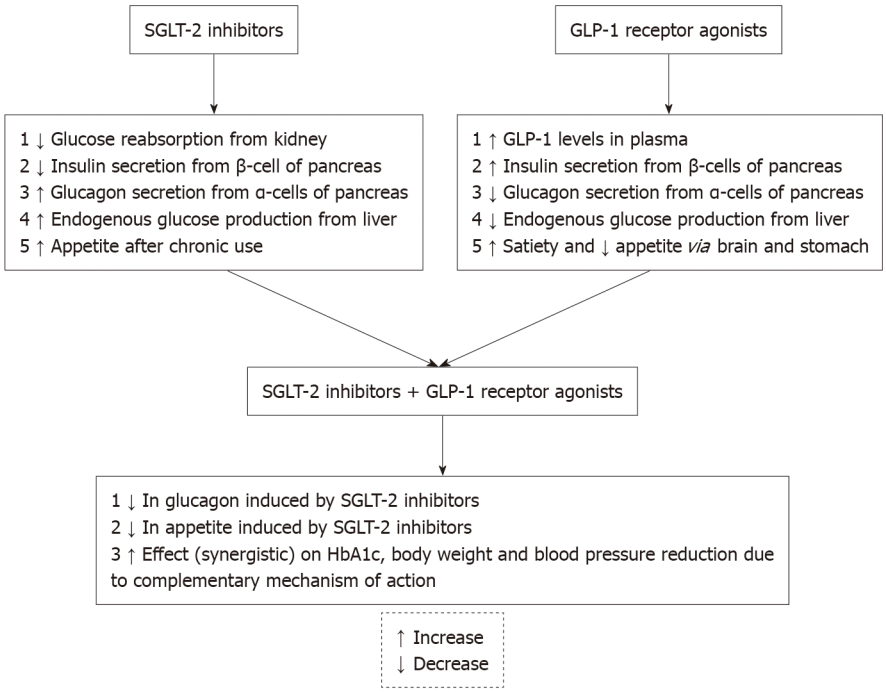
Table 3 Effect of simultaneous application of GLP-1 receptor agonists + SGLT-2I therapy on HbA1c (%), body weight (kg), and systolic blood pressure (mmHg) in randomized controlled trialx

Ref.	Parameters studied	Duration (wk)	(A) ΔGLP-1 RA	(B) ΔSGLT-2I	(C) ΔGLP-1 RA + SGLT-2I	(A + B) ΔSum of GLP-1 RA and SGLT2i	Effect of (C) compared to (A + B)
Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018	HbA1c	28	-1.60	-1.40	-2.00	-3.00	Less than additive
		52	-1.38	-1.23	-1.75	-2.61	Less than additive
		104	-1.29	-1.06	-1.70	-2.35	Less than additive
Ikonomidis *et al*[19], 2018	HbA1c	12	-1.30	-0.80	-1.50	-2.10	Less than additive
Ali *et al*[12], 2020	HbA1c	16	-1.44	-0.89	-1.67	-2.33	Less than additive
Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018	Body weight	28	-1.56	-2.22	-3.55	-3.78	Nearly additive
		52	-1.51	-2.28	-3.31	-3.79	Nearly additive
		104	-0.80	-3.00	-2.50	-3.80	Less than additive
Ikonomidis *et al*[19], 2018	Body weight	12	NR	NR	NR	NR	NR
Ali *et al*[12], 2020	Body weight	16	-1.90	-3.50	-6.00	-5.40	More than additive
Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018	SBP	28	-1.20	-1.80	-4.30	-3.00	More than additive
		52	-0.70	-2.70	-4.50	-3.40	More than additive
		104	-0.10	-1.10	-3.10	-1.20	More than additive
Ikonomidis *et al*[19], 2018	SBP	12	-3.00	-4.00	-4.00	-7.00	Less than additive
Ali *et al*[12], 2020	SBP	16	-5.10	-5.20	-14.10	-10.30	More than additive

GLP-1RA: GLP-1 receptor agonists; HbA1c: Glycated haemoglobin; NR: Not reported; SBP: Systolic blood pressure; SGLT-2I: SGLT-2 inhibitors.

DO WE GET AN ADDITIONAL CV AND RENAL BENEFIT BY COMBINING BOTH CLASSES OF DRUGS?

The mechanism by which both SGLT-2I and GLP-1RA exert their CV benefit appears to be mostly independent of glucose lowering and likely to be complementary owing to their differential MOA and



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Figure 1 Complementary mechanism of action of SGLT-2 inhibitor and GLP-1 receptor agonist dual therapy.

differential CV benefits. Available data from CVOT and renal outcome trials do hint that GLP-1RA primarily reduce the risk of atherosclerotic cardiovascular diseases (ASCVD) (ischemic stroke benefits being greater) with a modest effect on kidney function and minimal effect on heart failure, whereas SGLT-2I significantly reduced the risk of heart failure hospitalizations (HHF) and improved kidney function with a modest effect on ASCVD. Consequently, it is alluring to consider that combination therapy of SGLT-2I and GLP-1RA would achieve greater metabolic and cardio-renal benefits in patients with T2DM, compared with either class of drugs alone. This has gained further importance in the light of the latest American Diabetes Association and the European Association for the Study of Diabetes consensus report[39] and the European Society of Cardiology guidelines[40] that have put SGLT-2I, GLP-1RA, and their combination therapy much early in hierarchy in the presence of high CV risk, despite the lack of clarity on whether beneficial CV effects of individual GLP-1RA and SGLT-2I are retained, enhanced, or mitigated in combination therapy. To date, no dedicated randomized CVOT have yet evaluated the cardio-renal outcome with combination therapy of these two drug classes. A real-world propensity-matched study (n = 25168) using insurance claims databases from the United States has found addition of SGLT-2I to GLP-1RA therapy to be associated with lower rates of major adverse cardiovascular events (MACE) and HHF compared to initiation with sulfonylureas, in people with T2DM[41]. Another 12-mo randomized blinded study (n = 160) reported a significant increase of global myocardial work index with GLP-1RA plus SGLT-2I combination therapy (17.4%) or GLP-1RA alone (12.7%) compared with insulin (3.1%) or SGLT-2I (2%). Similarly, a significantly (P < 0.05 for all comparisons) greater decline of pulse wave velocity (PWV), including central and brachial systolic blood pressure, was observed with GLP-1RA plus SGLT-2I combination therapy (PWV, 13%) or SGLT-2I (PWV, 10.1%) as compared with GLP-1RA (PWV, 8.6%) or insulin (PWV, 3.6%). The dual therapy of GLP-1RA plus SGLT-2I showed a significantly (P < 0.05) greater effect on all measured markers in patients with left ventricular ejection fraction < 55%[42]. Summarily, GLP-1RA and SGLT-2I dual therapy showed a significantly better improvement of endothelial glycocalyx thickness (a marker of endothelial dysfunction) and myocardial work index and a larger reduction in arterial stiffness compared with insulin therapy despite a similar glucose reduction.

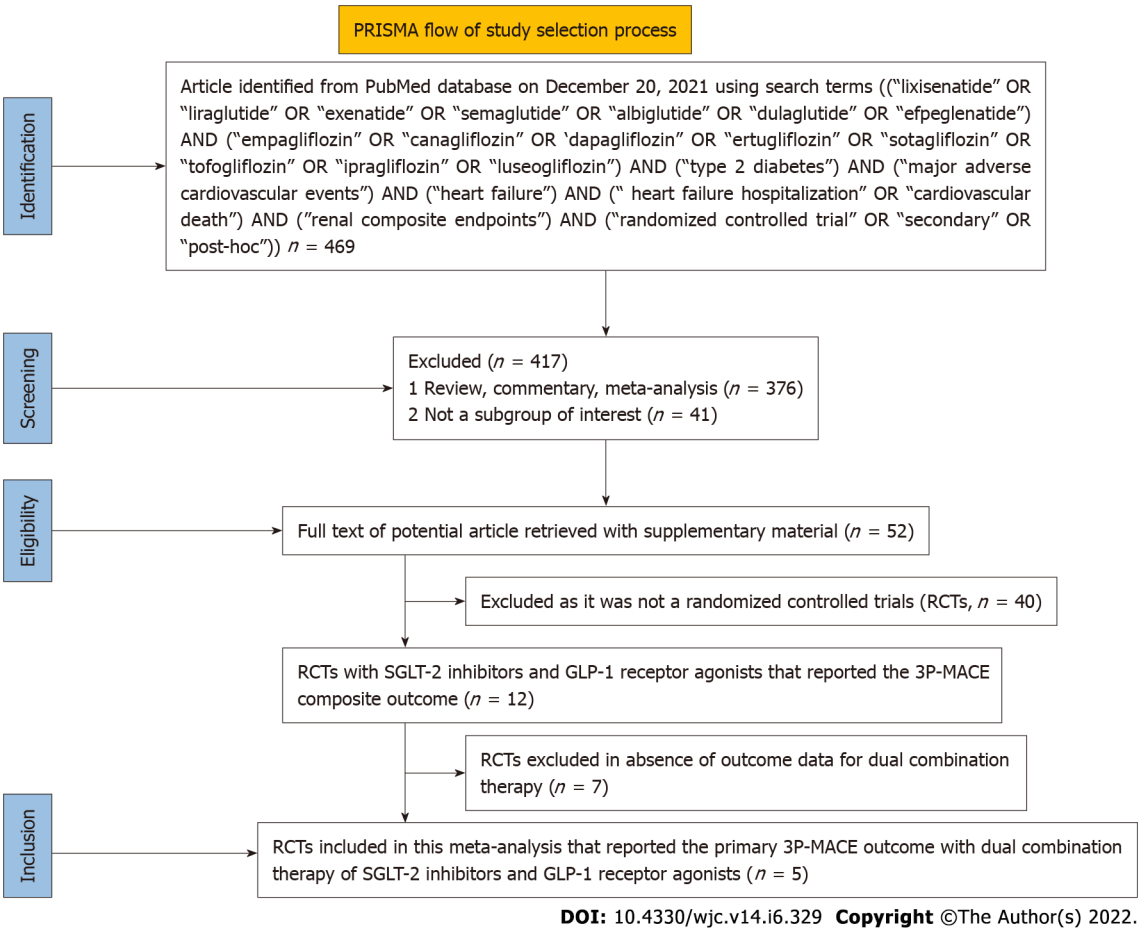
The study of combination therapy with GLP-1RA plus SGLT-2I in the recently conducted CVOT has been rare. The prevalence of baseline SGLT-2I use in GLP-1RA CVOT ranged from 0% to 5.3%, with the exception being AMPLITUDE-O study of efpeglenatide, where 15.2% (n = 618) were using SGLT-2I at the baseline[43-45]. Likewise, the prevalence of baseline GLP-1RA use in SGLT-2I CVOT ranged from 2.5% to 4.4% (CANVAS, n = 407; DECLARE-TIMI, n = 750; VERTIS-CV, n = 277)[45-48]. To understand the CV effect of GLP-1RA plus SGLT-2I combination therapy, we systematically reviewed the literature and pooled the data of the primary three-point MACE (3P-MACE) outcomes from five CVOT that reported the results against placebo[43,45-48]. Figure 2 represents the search criteria and flow diagram according to PRISMA statements. Additionally, we also pooled the data of HHF and renal composite that were available for two RCTs - AMPLITUDE-O and DECLARE-TIMI[45,47]. Table 4 summarizes the

Table 4 Meta-data of three-point composite of major adverse cardiovascular events, heart failure hospitalization, and renal outcome in cardiovascular outcome trials of SGLT-2 inhibitors and GLP-1 receptor agonists

Trial eponym, drugs	Background GLP-1RA + SGLT-2I therapy; *n*	Active arm (*n*/*N*), % or rate-per 100-patient-yr[1]	Placebo arm (*n*/*N*), % or rate-per 100-patient-yr[1]	HR, (95%CI)	*P* value of interaction
3-point composite of major adverse cardiovascular events outcome					
CANVAS[46], Canagliflozin	Yes; 407	NR	NR	0.73 (0.36-1.46)	0.94
	No; 9735	NR	NR	0.86 (0.76-0.98)	
DECLARE-TIMI[47], Dapagliflozin	Yes; 750	31/397, 7.8%	31/353, 8.8%	0.87 (0.53-1.43)	0.84
	No; 16410	725/8185, 8.9%	772/8225, 9.4%	0.94 (0.85-1.04)	
VERTIS-CV[48], Ertugliflozin	Yes; 277	21/192, 3.54[1]	9/85, 3.79[1]	0.94 (0.43-2.05)	NR
	No; 7961	632/5301, 3.91[1]	318/2660, 4.02[1]	0.97 (0.85-1.11)	
EXSCEL[43], Exenatide QW	Yes; 1144[2]	NR/572, 3.29[1]	NR/572, 4.81[1]	0.68 (0.39-1.17)	NR
	No	NR	NR	NR	
AMPLITUDE-O[45], Efpeglenatide	Yes; 618	25/412, 6.1%, 3.4[1]	17/206, 8.3%, 5.0[1]	0.70 (0.37-1.30)	0.68
	No; 3458	164/2305, 7.1%, 4.0[1]	108/1153, 9.4%, 5.4[1]	0.74 (0.58-0.94)	
Heart failure hospitalization outcome					
DECLARE-TIMI[47], Dapagliflozin	Yes; 750	4/397, 1.0%	18/353, 5.1%	0.20 (0.07-0.60)	0.01
	No; 16410	208/8185, 2.5%	268/8225, 3.3%	0.77 (0.64-0.92)	
AMPLITUDE-O[45], Efpeglenatide	Yes; 618	3/412, 0.7%; 0.4[1]	6/206, 2.9%, 1.6[1]	0.23 (0.05-0.97)	0.35
	No; 3458	37/2305, 1.6%, 0.9[1]	25/1153, 2.2%, 1.2[1]	0.70 (0.42-1.17)	
Renal outcome					
DECLARE-TIMI[47], Dapagliflozin[3]	Yes; 750	4/397, 1.0%	10/353, 2.8%	0.36 (0.11-1.15)	0.49
	No; 16410	123/8185, 1.5%	228/8225, 2.8%	0.54 (0.43-0.67)	
AMPLITUDE-O[45], Efpeglenatide[4]	Yes; 618	37/412, 9.0%, 5.1[1]	34/206, 16.5%, 10.0[1]	0.52 (0.33-0.83)	0.38
	No; 3458	316/2305, 13.7%, 8.2[1]	216/1153, 18.7%, 11.9[1]	0.70 (0.59-0.83)	

[1]Rate-per 100-patient-yr.
[2]Open-label, propensity-matched.
[3]Renal composite outcome consist of sustained decrease of 40% or more in eGFR to less than 60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal causes.
[4]Renal composite outcome consists of incident macroalbuminuria (UACR > 300 mg/g or 33.9 mg/mmol) plus ≥ 30% rise of UACR from baseline, a sustained ≥ 30 d decrease in eGFR by ≥ 40%, renal replacement therapy, and a sustained (≥ 30 d) eGFR < 15 mL/min/1.73 m^2.
3P-MACE: Three-point composite of major adverse cardiovascular events; CVOTs: Cardiovascular outcome trials; HHF: Heart failure hospitalization; GLP-1RA: Glucagon-like petide-1 receptor agonists; HR: Hazard ratio; *n*: Number of events; *N*: Total number of patients; NR: Not reported/retrievable; PBO: Placebo; SGLT-2I: Sodium glucose transporter-2 inhibitors.

findings from five CVOT that reported the outcomes stratified on combination therapy users. Subsequently, a meta-analysis was conducted by applying the inverse variance-weighted averages of pooled logarithmic hazard ratio (HR) using a fixed-effects model with Comprehensive Meta-Analysis software Version 3, Biostat Inc., Englewood, NJ, United States. A two-sided *P* value of < 0.05 was considered statistically significant. Heterogeneity was measured using Higgins I^2 and Cochrane *Q* statistics and it was considered low (I^2 ≤ 25%) or moderate (> 25%-50%) or high (> 50%)[49]. While we did not use Cochrane tool to assess the bias risk assessment considering the robust quality of trials included in this meta-analysis, publication bias for CV outcome was evaluated by applying funnel plot using the "trim and fill" adjustment, rank correlation test, and the Egger's test. A sensitivity exclusion analysis was additionally performed to determine whether any subgroups included in this meta-analysis could have influenced the aggregate result or changed the heterogeneity significantly. Our meta-analysis of five CVOT (*n* = 40, 760) that reported the outcome with or without combination therapy, found a significant reduction in composite of 3P-MACE (hazard ratio [HR] = 0.90; 95% confidence interval [CI]: 0.85-0.96; *P* = 0.001), without any heterogeneity. This finding was similar regardless of baseline GLP-1RA or SGLT-2I use: GLP-1RA without SGLT-2I (1 RCT; *n* = 3458; HR = 0.74; 95%CI: 0.58-0.94; *P* = 0.02), SGLT-2I without GLP-1RA (3 RCT; *n* = 34106; HR = 0.92; 95%CI: 0.86-0.99; *P* = 0.02), and GLP-1RA plus SGLT-2I combination therapy (5 RCT; *n* = 3196; HR = 0.77; 95%CI: 0.59-1.01;



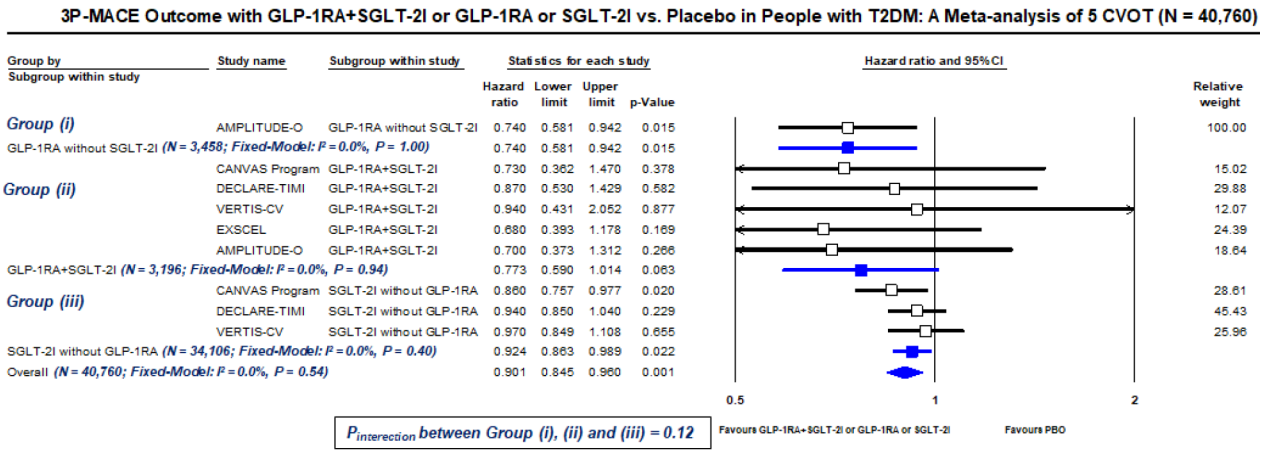
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Figure 2 PRISMA flow diagram for randomized controlled trials chosen for meta-analysis. RCT: Randomized controlled trial.

P = 0.06), without any significant heterogeneity and interaction ($P_{interaction}$ = 0.12) (Figure 3). Sensitivity analysis showed that no individual subgroup significantly affected the aggregate results or heterogeneity (Supplementary Table 1). No obvious publication bias was noted amongst the three subgroups, and Trim and Fill imputed point estimates were similar to the final results (Supplementary Figure 1). Our analysis suggests no incremental or attenuated 3P-MACE benefits with GLP-1RA plus SGLT-2I combination therapy, although that needs to be confirmed through large adequately powered clinical trials. Our findings are congruent to two recent network meta-analyses that did not report additional CV benefit with GLP-RA and SGLT-2I combination therapy[50,51].

Unlike 3P-MACE, a possible additive beneficial effect on heart failure and renal events with GLP-1RA and SGLT-2I combination therapy is very likely mechanistically because both drug classes have shown a consistent reduction in urinary protein excretion and rate of estimated glomerular filtration rate (eGFR) decline. Since both classes of drugs cause natriuresis (albeit by different mechanisms), a synergistic effect on HHF reduction is also mechanistically possible. Indeed, in a *post hoc* subgroup analysis of DECLARE-TIMI (n = 750) stratified by baseline GLP-1RA use, a greater benefit ($P_{interaction}$ = 0.014) on HHF was noted in patients with baseline dapagliflozin plus GLP-1RA user (HR = 0.20; 95%CI: 0.07-0.60) compared to dapagliflozin alone (HR = 0.77; 95%CI: 0.64-0.92)[47]. Similarly, a greater benefit ($P_{interaction}$ = 0.03) on composite of CV death/HHF was also noted in DECLARE-TIMI in patients with baseline dapagliflozin plus GLP-1RA use (HR = 0.37; 95%CI: 0.18-0.78) compared with dapagliflozin alone (HR = 0.86; 95%CI: 0.75-0.98)[47]. However, the benefit of dapagliflozin on renal endpoints in DECLARE-TIMI was similar ($P_{interaction}$ = 0.49) amongst baseline dapagliflozin plus GLP-1RA users (HR = 0.36; 95%CI: 0.11-1.15) compared to dapagliflozin alone or GLP-1RA non-users (HR = 0.54; 95%CI: 0.43-0.67)[47]. A *post hoc* analysis of the CANVAS program also noted a similar effect on the composite renal outcome in canagliflozin plus GLP-1RA users *vs* GLP-1RA non-users ($P_{interaction}$ = 0.43)[46].

Similar trends were also noted in GLP-1RA CVOT although it was inconsistent. In an exploratory analysis of AMPLITUDE-O with GLP-1RA efpeglenatide (n = 618), a nonsignificant trend ($P_{interection}$ = 0.35) of greater HHF reduction was observed in baseline efpeglenatide plus SGLT-2I users (HR = 0.23; 95%CI: 0.05-0.97) *vs* SGLT-2I non-users (HR = 0.70; 95%CI: 0.42-1.17)[45]. Similarly, improvement in renal composite outcome in AMPLITUDE-O was insignificantly ($P_{interection}$ = 0.38) greater in baseline efpeglenatide plus SGLT-2I users (HR = 0.52; 95%CI: 0.33-0.83) compared to SGLT-2 non-users (HR = 0.70; 95%CI: 0.59-0.83)[45]. Notably, a propensity matched *post hoc* analysis (n = 1144) of EXSCEL



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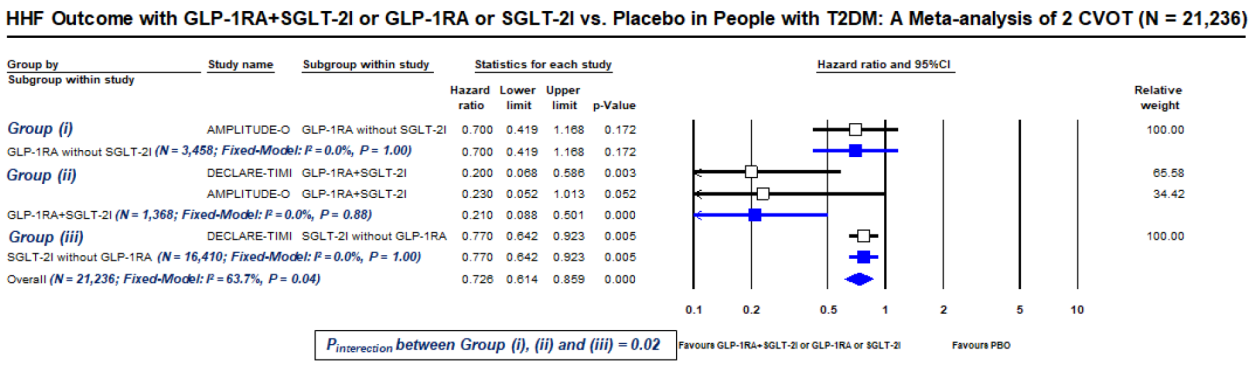
Figure 3 Three-point major adverse cardiovascular event outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of five cardiovascular outcome trials.

reported a nominally significant reduction in all-cause mortality (adjusted HR = 0.38, 95%CI: 0.16-0.90) and CV death (adjusted HR = 0.17; 95%CI: 0.04-0.77) and improvement in estimated eGFR slope (adjusted HR = +1.94 mL/min; 95%CI: 0.94-2.94 mL/min/1.73 m^2/year) with exenatide QW plus SGLT-2I combination therapy compared to the placebo[43]. Importantly, exenatide QW plus SGLT-2I combination also demonstrated a nominally significant reduction in all-cause mortality (HR = 0.41; 95%CI: 0.17-0.95) and CV death (HR = 0.21; 95%CI: 0.05-0.93) and improved eGFR slope (HR = +2.38 mL/min; 95%CI: 1.40-3.35 mL/min/1.73 m^2/year) as compared to exenatide QW alone in a propensity-matched analysis of 1150 participants[43].

Our meta-analysis from the pooled data of two RCTs that reported the outcomes of HHF and renal composite suggested a greater benefit ($P_{interaction}$ = 0.02) on HHF outcomes with GLP-1RA plus SGLT-2I dual therapy (HR = 0.21; 95%CI: 0.08-0.50, P < 0.001) compared with GLP-1RA without SGLT-2I (HR = 0.70; 95%CI: 0.42-1.17; P = 0.17) and SGLT-2I without GLP-1RA (HR = 0.77; 95%CI: 0.64-0.92; P = 0.005) against placebo (Figure 4). No significant difference ($P_{interection}$ = 0.11) was noted on the composite of renal outcome between the combination therapy (HR = 0.50; 95%CI: 0.32-0.76; P = 0.001), GLP-1RA without SGLT-2I (HR = 0.70; 95%CI: 0.59-0.83, P < 0.001), or SGLT-2I without GLP-1RA (HR = 0.54; 95%CI: 0.43-0.67; P < 0.001) against placebo (Figure 5). Collectively, these findings hint to a possible synergistic CV and renal effect of GLP-1RA plus SGLT-2I combination therapy. Nevertheless, some caution must be exercised while interpreting these findings in the light of following limitations: Exploratory, *post hoc* analysis with a small number of participants in each subgroup compounded by a very small number of events (9 events of HHF in AMPLITUDE-O and 14 events for renal outcome in DECLARE-TIMI in combination arm); uncategorized type of heart failure; results with wide confidence interval (imprecise point estimates); allocation bias; applying the aggregate trial-level results for the meta-analysis in the absence of individual patient data; inclusion of adjusted HR from propensity-matched analysis of EXSCEL; and no correction made for multiplicity in the subgroups analysis. Moreover, baseline GLP-1RA or SGLT-2I addition in SGLT-2I or GLP-1RA CVOT, respectively, may have been determined by the patient preference, cost, availability of treatment, and local guidelines, and thus, precludes true randomization. Future randomized trial PRECIDENTD (PREvention of CardIovascular and DiabEtic kidNey disease in Type 2 Diabetes), which has been planned to evaluate cardiovascular and renal outcomes with either SGLT-2I or GLP-1RA or both, in nearly 9000 T2DM having high CV risk, will further enlighten the effect of combination therapy[52].

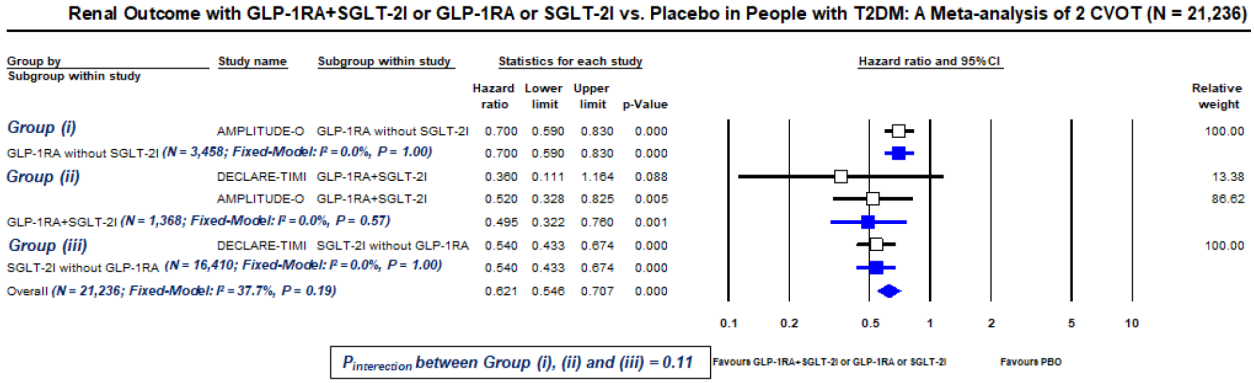
CONCLUSION

GLP-1RA plus SGLT-2I combination therapy lower HbA1c, body weight, and SBP significantly greater than GLP-1RA or SGLT-2I therapy alone. While HbA1c lowering with this combination therapy is less than additive compared to the sum of HbA1c lowering with individual agents, body weight lowering seems to be nearly additive and SBP lowering is found to be more than additive. Importantly, combination therapy with GLP-1RA and SGLT-2I does not potentiate hypoglycemia, GI side effects, or GTI compared to either agent alone. While 3P-MACE risk reduction with GLP-1RA plus SGLT-2I combination therapy appears to be similar compared with either GLP-1RA or SGLT-2I alone, improvement in HHF and possibly renal outcomes could be likely additive. Future adequately powered large RCT are needed to confirm additional benefit of GLP-1RA plus SGLT-2I combination therapy on



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Figure 4 Heart failure hospitalization outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of two cardiovascular outcome trials.



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Figure 5 Renal outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of two cardiovascular outcome trials.

CV, renal, and mortality outcomes.

FOOTNOTES

Author contributions: Singh AK made conception and design of the study and collected the data; Singh AK and Singh R did the statistical calculations, drafted the manuscript, and revised the manuscript critically; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict interest for this article.

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MINIREVIEWS

COVID-19 vaccination and cardiac dysfunction

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Abstract

The coronavirus disease 2019 (COVID-19) mRNA vaccine against severe acute respiratory syndrome coronavirus 2 infections has reduced the number of symptomatic patients globally. A case series of vaccine-related myocarditis or pericarditis has been published with extensive vaccination, most notably in teenagers and young adults. Men seem to be impacted more often, and symptoms commonly occur within 1 wk after immunization. The clinical course is mild in the majority of cases. Based on the evidence, a clinical framework to guide physicians to examine, analyze, identify, and report suspected and confirmed cardiac dysfunction cases is needed. A standardized workup for every patient with strongly suspicious symptoms associated with the COVID-19 mRNA vaccine comprises serum cardiac troponin measurement and a 12-lead electrocardiogram (ECG). For patients with unexplained elevation of cardiac troponin and pathologic ECG, echocardiography is recommended. Consultation with a cardiovascular expert and hospitalization should be considered in this group of patients. Treatment is primarily symptomatic and supportive. Deferring a 2nd dose of the COVID-19 mRNA vaccination in individuals with suspected myocarditis or pericarditis after the 1st dose is suggested until further safety data become available.

Key Words: Cardiac dysfunction; Myocarditis; Pericarditis; COVID-19; mRNA vaccine; Electrocardiography; Echocardiography; SARS-CoV-2

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Core Tip: A possible hypersensitivity myocarditis with a consistent relationship to administering an mRNA coronavirus disease 2019 (COVID-19) vaccination was reported. While the actual prevalence of this adverse event is unclear at this time, the clinical manifestation and pathological findings point to a link with an inflammatory reaction to a COVID-19 immunization. However, acute myocarditis following mRNA COVID-19 vaccination was very low and mostly self-limited. Moreover, the high efficacy of mRNA COVID-19 vaccines in preventing further pandemic conditions, reducing disease severity, and the occurrence of a very low incidence of myocarditis following immunization should be a strength of an mRNA COVID-19 vaccine for public trust.

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INTRODUCTION

Myocarditis or pericarditis is an inflammatory heart condition caused by infections, drug exposure, or immune system activation[1,2]. It has a wide range of clinical manifestations and courses, with most cases resolving spontaneously. However, it is also a cause of sudden cardiac death in young people. Furthermore, in some instances, inflammation can induce significant scarring, which causes left ventricular (LV) remodeling and finally leads to dilated cardiomyopathy or a predominant hypokinetic nondilated phenotype of cardiomyopathy[3,4]. Myocarditis has previously been reported following non-mRNA vaccine immunization. The incidence of myocarditis after a live smallpox vaccination was 2.2-7.8 *per* 100000, which occurred within 30 d after immunization[5,6]. The majority of adverse events that occur after vaccination in these people resolve without long-term consequences. Measles-mumps-rubella, chickenpox, yellow fever, and oral polio vaccine, have a 0.24 *per* 100000 immunization risk of pericarditis or myocarditis in the 42 d following vaccination[7].

During post-marketing pharmacovigilance surveillance, a considerably higher incidence of myocarditis or pericarditis than predicted was detected after coronavirus disease 2019 (COVID-19) immunization using mRNA vaccines[8]. As a result, the United States Food and Drug Administration, followed by the European Medicines Agency, listed myocarditis and pericarditis as extremely uncommon adverse drug reactions in the product information for Moderna and Pfizer-BioNTech[9,10]. Myocarditis or pericarditis is becoming more common as an unusual consequence of the COVID-19 mRNA vaccines, particularly in young adults and adolescent men. This article delves deeper into this phenomenon and its possible pathophysiology. We also examine the trade-off between the danger of myocarditis or pericarditis from mRNA vaccination and the cardiac and other hazards associated with COVID-19.

INCIDENCE AND CLINICAL MANIFESTATIONS OF MYOCARDITIS AFTER COVID-19 VACCINATION

Witberg *et al*[11] analyzed Clalit Health Services, Israel's biggest health care organization, for the myocarditis patients who had been immunized with one dose of the mRNA vaccine BNT162b2 (Pfizer–BioNTech). Clalit Health Services provided health care for 4.7 million patients (52% of the total population) regarding socioeconomic status and prevalence of co-existing diseases. They explored 2558421 members who were vaccinated with one dose of the mRNA vaccine; along with 2401605 members who were vaccinated with 2 doses. They discovered 54 patients who satisfied the research criteria for myocarditis. There were 41 mild cases, 12 moderate cases, and 1 fatal case. The median age of these patients was 27 (21-35) years, with 94% of them being males. Within 42 d of the first dosage, the incidence of myocarditis *per* 100000 vaccinated people was 2.13 (1.56-2.70) (mild = 1.62, intermediate = 0.47, and severe = 0.04). There was a higher incidence among male patients than female patients, with 4.12 (2.99-5.26) and 0.23 (0-0.49) *per* 100000 vaccinations, respectively (Table 1). Among all patients aged 16 years to 29 years, the incidence was 5.49 (3.59-7.39) *per* 100000 vaccinations. The incidence was reduced to 1.13 (0.66-1.60) *per* 100000 vaccinations among the patients who were 30 years of age or older. Male patients between the ages of 16 and 29 had the greatest incidence, with 10.69 (6.93-14.46) occurrences *per* 100000 immunizations. The most common clinical presentation was chest pain in 82% of the patients. Only 1 patient presented with hemodynamic instability. The electrocardiogram (ECG) showed 53% ST-segment elevation, 24% minor abnormalities, and a 21% normal pattern at presentation. All available data for cardiac troponin T (41 cases) showed a median peak of troponin T of 680 ng/L

Table 1 Incidence and clinical manifestations of myocarditis after coronavirus disease 2019 mRNA vaccination

Ref.	Type of vaccine	Study population	Incidence	Cardiac assessment methods	Main findings and clinical outcomes
Witberg *et al* [11], Israel	Pfizer-BioNTech	54/2558421 (21-63 yr)	2.13/100000	Clinical presentation, ECG, ECHO, MRI, Troponin T	Myocarditis = 10.69/100000 in male ages 16-29 yr, 25.92% had LV dysfunction, 76% = mild, 22% = intermediate, 1 case had cardiogenic shock, 1 case died of unknown cause, 0.51/100000 after 1st dose and 2.15/100000 after 2nd dose
Mevorach *et al* [12], Israel	Pfizer-BioNTech	136/9289765 (≥ 16 yr)	1.46/100000	Clinical presentation, ECHO, MRI, Troponin T, Endomyocardial biopsy	Myocarditis = 15.07/100000 in male ages 16-19 yr, 0.35/100000 after 1st dose, 2.28/100000 after 2nd dose, 94.85% = mild, 4.41% = intermediate, 1 case was fatal, endo-interstitial edema with neutrophils and mononuclear-cells infiltrates with no giant cells
Montgomery *et al*[13], United States	Pfizer-BioNTech/Moderna	23/2810000 (20-51 yr)	0.82/100000	Clinical presentation, ECG, ECHO, MRI, Troponin T	Myocarditis = 1.88/100000 after 1st dose, 3.49/100000 after 2nd dose, and 4.36/100000 in male after 2nd dose
Perez *et al* [14], United States	Pfizer-BioNTech/Moderna/Johnson and Johnson	7/175472 (12-106 yr)	55.35/100000, Person-yr	Clinical presentation, ECG, ECHO, MRI, Troponin T	The overall incidence rate was 55.35 (22.25–114.00) *per* 100000 person-yr during the 2 wk after a dose of vaccine. The IRR for myocarditis following COVID-19 mRNA vaccination was increased for males at 6.69 (2.35–15.52), but it was not statistically significant for females at 1.41 (0.03–8.45)
Das *et al*[15], United States	Pfizer-BioNTech	25/7735071 (12-17 yr)	0.32/100000	Clinical presentation, ECG, ECHO, MRI, Troponin T, CRP	Myocarditis = 0.04/100000 after 1st dose, 0.28/100000 after 2nd dose, and 0.26/100000 in male after 2nd dose
Li *et al*[16], United States	Pfizer-BioNTech/Moderna/Janssen	Age ≥ 12 yr	0.598/100000	VAERS	Pfizer–BioNTech had a higher incidence rate of 0.670/100000 than the rate of 0.498/100000 found for Moderna. The incidence rate following the 2nd dose was twice that of the 1st dose and was the highest in adolescents aged 12-17 yr, at 2.094/100000. The Janssen vaccine was not associated with myocarditis or pericarditis
Patone *et al* [17], United Kingdom	Pfizer-BioNTech/Moderna/AstraZeneca	1615/38615491 (Age ≥ 16 yr)	4.18/100000	NIMS	The IRR of myocarditis = 1.76, 1.45, 8.38 after 1st dose of AstraZeneca, Pfizer-BioNTech, Moderna. IRR of myocarditis = 1.75, 23.10 after 2nd dose of Pfizer-BioNTech, Moderna. There was an increase in the risk of myocarditis within 1 wk after 1st dose of adenovirus and mRNA vaccines and a higher increased risk after 2nd dose of both mRNA vaccines, especially in under 40 yr
Simone *et al* [18], United States	Pfizer-BioNTech/Moderna	15/2392924 (Age ≥ 18 yr)	0.63/100000	KPSC members with clinical presentation, ECG, ECHO, Troponin I	Myocarditis = 0.08/100000 after 1st dose, 0.58/100000 after 2nd dose over a 10-d period, all were men aged 20-32 yr. The IRR of myocarditis = 0.38 after 1st dose and 2.7 after 2nd dose
Nygaard *et al* [19], Denmark	Pfizer-BioNTech	15/261334 (12-17 yr)	5.74/100000	Clinical presentation, ECG, ECHO, MRI, Troponin	Myocarditis = 3.06/100000 after 1st dose, 2.68/100000 after 2nd dose mostly in male (M:F = 6:1)
Husby *et al* [20], Denmark	Pfizer-BioNTech/Moderna	269/4931775 (Age ≥ 12 yr)	5.45/100000	Danish Vaccination Register	HR of myocarditis/pericarditis = 1.34, 3.92 within 28 d from the vaccination of Pfizer-BioNTech, Moderna respectively. Myocarditis or pericarditis occurred at 1.4/100000 for Pfizer-BioNTech and 4.2/100000 for Moderna. Vaccination with Moderna vaccine was associated with an increased risk of myocarditis or pericarditis, especially in aged 12-39 yr
Diaz *et al*[21], United States	Pfizer-BioNTech/Moderna/Janssen	57/2000287 (26-70 yr)	2.85/100000	Clinical presentation, ECG,	Myocarditis = 1.0/100000 and pericarditis = 1.8/100000. Myocarditis and pericarditis

				ECHO, Troponin	were observed after the COVID-19 vaccination. Myocarditis developed rapidly in younger patients, mostly after the 2nd dose. Pericarditis affected older patients later, after either the 1st or 2nd dose
Chouchana *et al*[22], WHO	Pfizer-BioNTech/Moderna	2277/716576 reports	NA	VigiBase	Over all myocarditis = 3.57/100000 with 12–17 yr = 3.69/100000, 18–29 yr = 1.97/100000, and ≥ 30 yr = 0.21/100000. Younger male aged 12–17 yr were more prone to report myocarditis or pericarditis with 22.3/100000. The median time to onset for myocarditis was 3 d after vaccine injection
Barda *et al* [23], Israel	Pfizer-BioNTech	21/938812	2.23/100000	Clinical presentation, ECG, ECHO, Troponin	Vaccination was most strongly associated with an elevated risk of myocarditis [risk ratio, 3.24 (1.55-12.44)]. Alternatively, SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis [risk ratio, 18.28 (3.95-25.12)]. The BNT162b2-mRNA vaccine increased the incidence of a few adverse events over a 42-d follow-up period

ECG: Electrocardiography; ECHO: Echocardiography; HR: Hazard ratio; IRR: Incidence rate ratio; KPSC: Kaiser Permanente Southern California; M:F: Male to female; MRI: Magnetic resonance imaging; NA: Not available; NIMS: The English National Immunisation; ROR: Reporting odds ratio; VAERS: Vaccine Adverse Events Reporting System; VigiBase: World Health Organization (WHO) global safety database; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

(275-2075). One patient's cardiac biopsy revealed perivascular lymphocyte and eosinophil infiltration. On admission, ECG findings (48 cases) showed 71% normal LV function. Fourteen patients (29%) showed some degree of LV dysfunction. Seventeen percent presented with mild symptom, four percent had mild symptom, four percent had moderate symptom, two percent had moderate-to-severe symptom, and two percent had severe symptom. Fifteen patients underwent cardiac magnetic resonance imaging (MRI) and showed normal LV function (Table 2). They concluded that the highest incidence of myocarditis after BNT162b2 mRNA vaccination was among male patients aged 16-29 years. The majority of myocarditis cases were mild to moderate in severity.

Mevorach *et al*[12] retrospectively reviewed data regarding myocarditis cases. During the surveillance period, 9289765 Israeli residents were included. Of those, 5442696 individuals received the 1st dose and 5125635 received two BNT162b2 mRNA vaccines. They found that 136 cases were confirmed as diagnoses of myocarditis. In most cases, the clinical presentations in 129 cases were mild with a resolution of myocarditis. The overall incidence of myocarditis *per* 100000 vaccinated people was 1.46. A comparison of risks 21 d after the 1st and 2nd doses based on age and gender revealed a risk difference of 1.76 *per* 100000 people. Male recipients had a risk difference of 3.19, while female recipients had a risk difference of 0.39. The highest difference was observed among male patients aged 16 and 19, at 13.73 *per* 100000 people. These findings pointed out that the 1st wk after the 2nd dose of vaccination was the leading risk period.

Myocarditis symptoms usually appear within a few days of receiving the 2nd dose of the vaccine. After the 2nd dose of vaccine, they estimated that definite cases of myocarditis occurred at a rate of 1 in 26000 males and 1 in 218000 females in the general Israeli population. The majority of the patients had normal or mildly reduced ejection fraction (EF), but the EF in 4 patients was severely reduced. MRIs were performed on 48 people who had a positive result from a T2-based sequence or a T1-based sequence that indicated myocarditis. They concluded that the myocarditis incidence that occurred after 2 doses of the mRNA vaccine was very low, although the incidence was higher than in unvaccinated people. Myocarditis was mostly discovered in young male recipients after the second dose of the vaccine.

Montgomery *et al*[13] retrospectively studied a United States Military Health System case series that experienced myocarditis after COVID-19 vaccination (BNT162b2-mRNA and mRNA-1273 vaccines). The authors found that 23 male patients aged 20-51 years were evaluated for acute-onset chest pain following 2810000 mRNA COVID-19 vaccinations and confirmed acute myocarditis. The overall incidence was 0.82 *per* 100000 doses of vaccination. Myocarditis was reported at 1.88 *per* 100000 vaccinations after the 1st dose, at 3.49 *per* 100000 vaccinations after the 2nd dose, and at 4.36 *per* 100000 vaccinations in males after the 2nd dose. T-wave inversions, ST-segment elevations, and nonspecific ST changes were reported in 83% of patients as abnormal ECG findings. In 17% of the recipients, echocardiography (ECHO) demonstrated reduced LVEFs (40% to 50%). They concluded that the number of cases of myocarditis observed in the Military Health System exceeded some estimates of expected numbers, particularly when considering the subset of the population who received the 2nd dose of the mRNA vaccine. It's time to pay more attention to myocarditis as a potential side effect of the mRNA COVID-19

Table 2 Characteristic of acute myocarditis patients after coronavirus disease 2019 mRNA vaccination

Ref.	Type of vaccine	No. of myocarditiscases	Male/Female (%)	Median age in yr (IQR)	Myocarditis after 1st dose (%)	Myocarditis after 2nd dose (%)	Clinical severity F/I/M
Witberg *et al*[11], Israel	Pfizer-BioNTech	54	51/3 (94/6)	27 (21–35)	17 (31.48)	37 (68.52)	1/12/41
Mevorach *et al* [12], Israel	Pfizer-BioNTech	136	118/18 (87/13)	- (16-> 30)	19 (13.97)	117 (86.03)	1/6/129
Montgomery *et al* [13], United States	Pfizer-BioNTech/Moderna	23	23/0 (100/0)	25 (20-51)	3 (13.04)	20 (86.96)	0/7/16
Perez *et al*[14], United States	Pfizer-BioNTech/Moderna	7	6/1 (86/14)	44 (22-71)	1 (14.29)	6 (85.71)	0/6/1
Das *et al*[15], United States	Pfizer-BioNTech	25	22/3 (88/12)	15 (12-17)	3 (12.00)	22 (88.00)	0/22/3
Simone *et al*[18], United States	Pfizer-BioNTech/Moderna	15	15/0 (100/0)	25 (20-32)	2 (13.33)	13 (86.67)	0/15/0
Nygaard *et al*[19], Denmark	Pfizer-BioNTech	15	13/2 (87/12)	17 (13-17)	8 (53.33)	7 (46.67)	0/1/14
Diaz *et al*[21], United States	Pfizer-BioNTech/Moderna	20	15/5 (75/25)	36 (26-48)	4 (20.00)	16 (80.00)	2/17/1

F/I/M: Fulminant/intermediate/mild; IQR: Interquartile range.

vaccination.

Perez *et al*[14] used the Mayo Clinic COVID-19 Vaccine Registry to conduct a retrospective case series study to assess post-immunization myocarditis. They discovered that a total of 7 people were diagnosed with myocarditis after receiving at least one dose of a COVID-19 mRNA vaccine (BNT162b2-mRNA and mRNA-1273 vaccines). The COVID-19 registry contained 175472 individuals (aged 12 years to 106 years), of whom 718 (0.4%) were adolescents aged 12 years to 15 years. Myocarditis was found to be 55.35 *per* 100000 person-years in the two weeks following a dose of COVID-19 mRNA vaccination. The incidence rate ratio (IRR) of myocarditis after mRNA vaccinations in males was 6.69 (2.35–15.52) which was higher than the Rochester Epidemiology Project during the years 2016–2020. However, the myocarditis IRR in females was 1.41 (0.03–8.45) which was not statistically significant. The most common presenting symptoms were chest pain, dyspnea, and fatigue, with a baseline troponin T of 486.5 ng/L (222.5–965.0). Seventy one percent of the patients had ECG abnormalities, including ST-segment changes. On ECHO examination, 3 patients (60%) were noted to have a reduced LVEF. Cardiac MRI was performed in 6 patients (86%) and showed myocardial delayed enhancement. Pericardial involvement was seen in 3 (50%) patients. Myocarditis is a rare side effect of COVID-19 mRNA vaccines, according to the authors. It affects adult males at a significantly higher rate than the general population.

Das *et al*[15] performed a study of 25 cases aged between 12 and 18 years who developed myopericarditis following the mRNA vaccine in 7735017 children and adolescents. The incidence of myopericarditis after COVID-19 mRNA vaccination was 0.32 *per* 100000 people. Myopericarditis has occurred in 0.04 *per* 100000 people after the 1st dose, 0.28 *per* 100000 persons following the 2nd dose, and 0.26 *per* 100000 males following the 2nd dose. The most common presenting symptom was chest pain. Sixty percent and seventy-two percent of patients reported the development of symptoms within 2 and 3 d of getting the second dosage of the vaccine, respectively. All 25 patients had elevated plasma troponin concentrations. Abnormal ECG was found in 84% of the patients, including 60% of the elevation of ST-segment, 24% of the isolation of nonspecific ST-segment changes, 4% of the depression of ST-segment, and 4% of the depression of PR interval. An ECHO was performed in all patients and showed normal LV function in 92% of the individuals. Cardiac MRI was done on 16 of 25 patients (64%) and revealed late gadolinium enhancement in 94% of cases. Myocardial edema on T2 mapping was found in 37.5% of the patients, and a small pericardial effusion was found in 19% of the patients. They concluded that the complication of mRNA vaccine-related myopericarditis has been observed primarily in men. It has not been thoroughly investigated if hormonal or other variables have a role in the manifestation of this disease.

Li *et al*[16] employed the Vaccination Adverse Event Reporting System, a nationwide early warning system that monitors potential vaccine safety issues, as the major data source. The COVID-19 mRNA vaccines and viral vector vaccinations were the vaccines studied in this study. They found that the incidence rate of myocarditis or pericarditis following COVID-19 vaccination was 0.598 (0.573–0.624) *per* 100000 doses of vaccinations. The incidence rate was highest in adolescents aged 12-17 years, with an incidence rate of 2.09 (1.90–2.30) *per* 100000 vaccinations. It decreased with increasing age to 0.59

(0.56–0.62) *per* 100000 in adults aged 18-64, and 0.19 (0.16–0.22) *per* 100000 aged 65 years and over. The incidence rate was higher for different vaccine types in the mRNA vaccines, at 0.59 (0.57–0.62) *per* 100000, than for a viral vector vaccine, at 0.56 (0.44–0.70) *per* 100000 vaccinations. Among mRNA vaccines, BNT162b2-mRNA vaccines had a higher incidence rate of 0.67 (0.63–0.70) cases *per* 100000 than the rate of 0.49 (0.46–0.53) cases *per* 100000 of the mRNA-1273 vaccine. Moreover, the incidence rate after the 2nd dose was twice that of the 1st dose of mRNA vaccinations. Fifty percent of myocarditis or pericarditis cases were reported 2 to 7 d after vaccinations, with 58.67% of cases having chest pain symptoms. They also found that reporting odds ratios (RORs) of the mRNA-1273 vaccine were 2.91 (2.21–3.83) compared with the RORs of the BNT162b2-mRNA vaccine at 5.37 (4.10–7.04). They concluded that the BNT162b2-mRNA vaccine was associated with significant risks of myocarditis or pericarditis in adolescents aged 12 to 17, with RORs ranging from 8.19 (4.37–15.36). A viral vector vaccine may be an alternative for consideration for individuals with myocardial injuries after mRNA vaccination.

Patone *et al*[17] conducted the study to find out the incidence of myocarditis or pericarditis after COVID-19 vaccinations in the United Kingdom using the English National Immunisation Database of COVID-19 vaccinations. During that period, 38615491 individuals received one dose of a viral vector vaccine ChAdOx1 (n = 20615911), an mRNA vaccine BNT162b2 (n = 16993389), or an mRNA vaccine 1273 (n = 1006191). Results showed an increased myocarditis risk at 1–7 d after the 1st dose of ChAdOx1-viral vector vaccine as an IRR of 1.76 (1.29-2.42), of BNT162b2-mRNA vaccine as an IRR of 1.45 (0.97-2.12), and of mRNA-1273 vaccine as an IRR of 8.38 (3.53-19.91). For the 2nd dose of the BNT162b2-mRNA vaccine, the IRR was 1.75 (1.13-2.70), the IRR of the mRNA-1273 vaccine was 23.10 (6.46-82.56). Over the 1–28 d post-vaccination, they observed an association with the 1st dose of ChAdOx1-viral vector vaccine, whose IRR was 1.29 (1.05-1.58), with BNT162b2-mRNA vaccine, whose IRR was 1.31 (1.03-1.66) and with mRNA-1273 vaccine, whose IRR was 2.97 (1.34-6.58). After a 2nd dose, the mRNA vaccine 1273 had higher risk [IRR = 9.84 (2.69–36.03)] compared with the BNT162b2-mRNA vaccine [IRR = 1.30 (0.98–1.72)]. They observed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunization in adults was linked with a low myocarditis risk after 1 wk of getting the 1st immunization of a viral vector vaccine and a mRNA vaccine, as well as after receiving the 2nd dose of both mRNA vaccines. COVID-19, on the other hand, was linked to an increased risk of hospitalization or mortality from myocarditis, pericarditis, and cardiac arrhythmia.

Simone *et al*[18] performed a study using Kaiser Permanente Southern California (KPSC) as a case study. The KPSC members' database (2392924) was used to evaluate acute myocarditis incidence and clinical outcomes among adults following mRNA vaccinations. In the vaccinated group, the authors discovered 15 cases of confirmed myocarditis (2 after the 1st dose and 13 after the 2nd dose). Over a 10-d observation period, the observed incidence after the 1st dosage was 0.08 cases *per* 100000 and 0.58 cases *per* 100000 after the 2nd dose. The IRR for myocarditis was 0.38 (0.05–1.40) after the 1st dose and 2.7 (1.4–4.8) after the 2nd dose. The most common clinical manifestation was chest pain (93%), which occurred between 1 and 5 d after vaccination. They determined that acute myocarditis following COVID-19 immunization was uncommon, with a prevalence of 5.8 occurrences in 1000000 people following the 2nd immunization (1 occurrence in 172414 fully immunized people). They proposed that the higher risk of myocarditis in adolescence males needs more research.

Nygaard *et al*[19] performed a prospective population-based cohort study to evaluate the incidence of myopericarditis after COVID-19 vaccination in Danish adolescents. They discovered that among 133477 males and 127857 females aged 12–17 years who got the first dose of the BNT162b2-mRNA vaccination, the incidence of myopericarditis was 97 and 16, respectively, *per* 1000000, corresponding to 1 in 10000 males and 1 in 63000 females. In contrast, 16900 males and 16044 females aged 12–17 years old infected with SARS-CoV-2 showed multisystem inflammatory syndrome in children, including myocarditis at an incidence of 1 in 2800 men and 1 in 5300 women, which was substantially more than the prevalence of myopericarditis following the immunization of the COVID-19 vaccine in both men and women. They determined that the frequency of myopericarditis in male adolescents following BNT162b2-mRNA immunization is greater than previously reported, and that more severe cases are more common.

Husby *et al*[20] conducted a study using the Danish Vaccination Register to evaluate the incidence of myocarditis or myopericarditis after BNT162b2-mRNA and mRNA-1273 vaccinations in Denmark. Among the cohort participants, 3482295 were vaccinated with BNT162b2-mRNA vaccines, whereas 498814 were immunized with mRNA-1273. Individuals who received the BNT162b2-mRNA vaccine exhibited a non-substantially higher risk of myocarditis in the 28-d following immunization compared to unvaccinated follow-up [hazard ratio (HR) = 1.34 (0.90–2.00)]. Individuals aged 12–39 years had a non-significantly higher rate in the 28-d following vaccination compared non-immunization people [HR = 1.48 (0.74–2.98)]. Individuals vaccinated with mRNA-1273, on the other hand, exhibited a substantially higher risk of myocarditis or myopericarditis compared to unvaccinated follow-up [HR = 3.92 (2.30–6.68)]. Furthermore, people aged 12–39 years had substantially higher rates of myocarditis or myopericarditis when compared to unvaccinated controls [HR = 5.24 (2.47–11.12)]. Myocarditis occurred at a rate of 1.7 (1.3-2.2) *per* 100000 vaccinated people. Within 28 d, the incidence rate of myocarditis following BNT162b2-mRNA vaccination or mRNA-1273 immunization was 1.4 (1.0–1.8) and 4.2 (2.6–6.4), respectively. Within 28 d of immunization, the equivalent rates of myocarditis from BNT162b2 vaccination was 1.6 (1.0-2.6) *per* 100000 people compared with mRNA-1273 vaccination was

5.7 (3.3-9.3) *per* 100000 people. The authors found that mRNA-1273 immunization was linked with a higher risk of myocarditis or myopericarditis compared to uninfected people, whereas BNT162b2-mRNA vaccination was related to a higher rate of myocarditis or myopericarditis among females. Furthermore, clinical outcomes following myocarditis or myopericarditis episodes were mostly modest, lending credence to the general safety of COVID-19 mRNA vaccinations.

Diaz *et al*[21] conducted a retrospective study to evaluate the incidence of myocarditis and pericarditis after COVID-19 vaccinations among 2000287 individuals who received at least one COVID-19 vaccination (52.6% received the BNT162b2-mRNA vaccine, 44.1% were given the mRNA-1273 vaccine, while 3.1% were given the Ad26.COV2.S vaccine). They found that 20 individuals had vaccine-related myocarditis [1.0 (0.61-1.54)] *per* 100000 vaccinations, and 37 individuals had pericarditis [1.8 (1.30-2.55)] *per* 100000 vaccinations, which occurred 3.5 d after being vaccinated. They concluded that mRNA vaccination was linked to myocarditis, particularly in adolescence males, within 3 d following the 2nd dose of immunization. Additionally, pericarditis may be more common than myocarditis among older patients.

Chouchana *et al*[22] conducted an observational retrospective analysis on inflammatory cardiac events that were reported regarding mRNA immunizations in the global safety database of the World Health Organization using a case–non-case methodology (VigiBase). Among the 26258646 reports in the VigiBase, 716576 were associated with the mRNA COVID-19 vaccination as a suspected medication, with 2277 cases of inflammatory heart responses identified as 1241 (54.5%) myocarditis, 851 (37.3%) pericarditis, and 167 (7.3%) myopericarditis. The majority of myocarditis cases have been observed in male patients aged between 12 and 29. Overall, the median duration from the beginning of myocarditis following immunization was 3 (2–14) d. When compared to myocarditis, a median onset of pericarditis was delayed to be 8 (3–21) d. Most of the myocarditis (81.8%) and pericarditis (57.8%) reported cases that required hospitalization, and 21.5% of myocarditis and 20.5% of pericarditis were life threatening. The overall incidence rate of myocarditis or pericarditis was 0.61 (0.57–0.65) *per* 100000 fully vaccinated individuals. In 2 doses of immunization, they found a significant increase in incidence rates in 12–17–year–old patients [3.69 (3.25–4.18) *per* 100000 people] and 18–29–year–old patients [1.97 (1.80–2.16) *per* 100000 people], while patients older than 30 years were 0.21 (0.19–0.24) *per* 100000 patients. Male patients had an elevated chance of reporting myocarditis with RORs = 9.4 (8.3–10.6) and diagnosed pericarditis with RORs = 3.7 (3.2–4.2). Age category analysis revealed a significant decrease in myocarditis reporting after mRNA immunizations in 12- to 17-year-olds [RORs = 22.3 (19.2–25.9)] and 18–to–29-year-olds [RORs = 6.6 (5.9–7.5)] individuals when compared to individuals older than 30 years. Across all age groups, this increased reporting was more significant in male patients than in female patients. While there was a considerable disproportionate reporting of myocarditis in teens and young adults, particularly in male patients, and it was an uncommon event, they discovered that it did not appear to compromise the vaccines' favorable benefit-risk balance.

Barda *et al*[23] evaluated the safety of the BNT162b2-mRNA COVID-19 vaccine using the largest health care organization in Israel. They discovered that the vaccinated and control groups each had an average of 884828 people. Vaccination was the strongest predictor of an increased risk of myocarditis [risk ratio, 3.24 (1.55–12.44)]. By contrast, infection with SARS-CoV-2 was linked to a significantly higher myocarditis rate [risk ratio, 18.28 (3.95–25.12)]. They concluded that the BNT162b2-mRNA vaccine increased the occurrence of a few side effects over a 42-d period of follow-up. Whereas the majority of these incidents were minor, myocarditis has the potential to be life-threatening. According to the findings, SARS-CoV-2 infection is a significant risk factor for myocarditis, as well as a number of other adverse outcomes.

Table 2 summarizes the characteristics of acute myocarditis patients, such as sex, age, occurrence after the 1st or 2nd dose of mRNA COVID-19 vaccination, and clinical severity. Many investigators' data indicated the same result: Acute myocarditis was more prevalent in younger males, and over 90% occurred after the 2nd dose of immunization. Furthermore, practically all patients had mild to moderate clinical presentation and prognosis. Figure 1 shows the number of acute myocarditis cases after the 1st and 2nd doses of the Pfizer-BioNTech mRNA COVID-19 vaccine. According to these data, the majority of the cases occurred shortly after the 2nd dose of immunization, generally within 5 d. Close observation and monitoring of vaccination recipients are critical during this period.

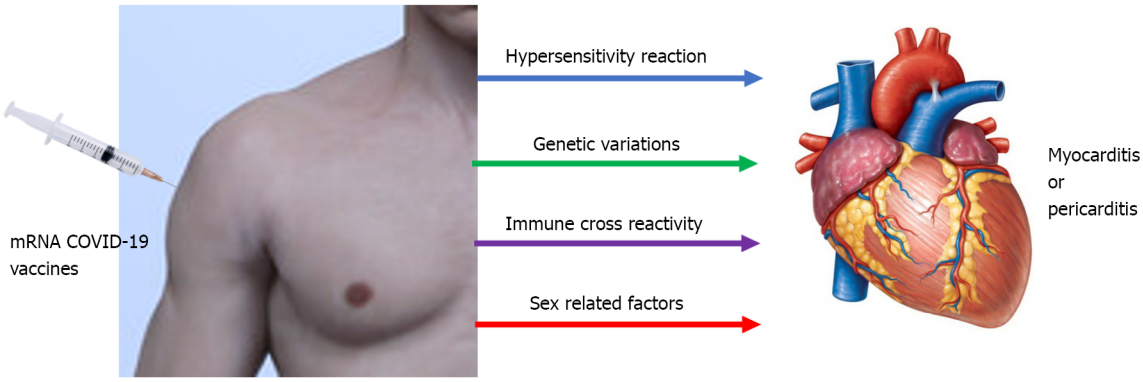
Table 3 shows the clinical presentation of the patients with acute myocarditis after mRNA COVID-19 vaccinations, which usually included chest pain, myalgia, fatigue, and fever. The common ECG abnormalities were ST-elevation, non-specific ST/T changes, PR depression, T-wave inversion, and ventricular fibrillation. ECHO showed the reduction of LVEF. Laboratory findings demonstrated the elevation of cardiac troponin and C-reactive protein. The imaging studies of acute myocarditis patients after mRNA COVID-19 vaccination showed myocardial inflammation, myocardial edema, and delayed iodine enhancement.

Despite the fact that the majority of the findings of various studies demonstrated the occurrence of acute myocarditis following mRNA COVID-19 immunization, the incidence was quite low. Furthermore, there were significant disparities across these trials in terms of ethnicity, age, underlying disorders, inherent immunity to the SARS-CoV-2 virus, and other genetic variables. More research should be conducted to understand this problem.

Table 3 Clinical presentation of the patients with acute myocarditis after coronavirus disease 2019 mRNA vaccination

	Clinical presentation of acute myocarditis
1	Chest pain, Myalgia, Fatigue, Fever
2	Abnormal ECG: ST-elevation, Non-specific ST/T changes, PR depression, T-wave inversion, Ventricular fibrillation
3	Elevation of cardiac troponin
4	Elevation of CRP
5	Abnormal ECHO: LVEF reduction
6	Abnormal cardiac MRI: Myocardial inflammation, Myocardial edema
7	Abnormal cardiac spectral CT: Delayed iodine enhancement

CRP: C-reactive protein; CT: Computerized tomography; ECG: Electrocardiogram; ECHO: Echocardiogram; LVEF: Left ventricular ejection fraction; MRI: Magnetic resonance imaging.



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Figure 1 Timelines of acute myocarditis occurrence after Pfizer-BioNTech and Moderna mRNA coronavirus disease 2019 vaccination. COVID-19: Coronavirus disease 2019.

HISTOPATHOLOGICAL FINDINGS OF MYOCARDITIS AFTER MRNA COVID-19 VACCINATION

Ameratunga *et al*[24] reported a 57-year-old woman who died of fulminant necrotizing myocarditis after receiving the first dose of the BNT162b2 mRNA vaccine. The clinical manifestations were lethargy, fatigue, breathlessness, stiff neck, and upper limb pain. After that, she complained of back pain, a sore throat, and hematuria without palpitation or chest pain. The autopsy findings showed that the heart was normal without pericardial effusion and intra-cardiac thrombosis. There was a large thymoma mass (710 g) in the left pleural cavity. The histopathology demonstrated fulminant necrotizing eosinophilic myocarditis. Multifocal aggregates of lymphoid cells, histiocytes, and many eosinophils with isolated myocyte necrosis were seen in the free walls of both ventricles, the interventricular septum, and throughout the conduction system (sinoatrial and atrioventricular nodes) (Table 4). They concluded that the danger of myocarditis and other deadly consequences of COVID-19 infection outweighed the risk of these uncommon vaccine-related side effects. The advantages of immunization substantially outweigh the hazards of COVID-19 infection. Choi *et al*[25] published the autopsy results of a 22-year-old man who had chest discomfort 5 d after receiving the 1st dose of the BNT162b2-mRNA vaccination and died 7 h later. He developed ventricular fibrillation on ECG before cardiopulmonary resuscitation in the emergency department. The autopsy findings showed the heart weighed 470 g with multiple petechial hemorrhages on its surface.

There was no fibrin buildup or exudate in the pericardium. The coronary arteries were patent, and the cardiac valves were in good condition. Within the heart, histology revealed a diffuse inflammatory infiltrate with neutrophils and histiocyte predominance. Inflammatory infiltrates were more common in the atria and around the sinoatrial and atrioventricular nodes, but there were few or no inflammatory cells in the ventricular area. They concluded that the major cause of mortality was myocarditis, which was linked to the BNT162b2-mRNA vaccination. Schneider *et al*[26] conducted an autopsy of 18 deceased people after COVID-19 vaccinations and found that only 1 case was related to the BNT162b2-mRNA vaccine. The autopsy findings showed severe coronary sclerosis, massive cardiac hypertrophy,

Table 4 Gross and histopathological findings of the heart after coronavirus disease 2019 mRNA vaccination

Ref.	No. of cases (age, sex)/vaccine	Gross findings	Histopathological findings
Ameratunga *et al*[24]	1 (57, F)/Pfizer-BioNTech	The heart was normal without pericardial effusion and intra-cardiac thrombosis. There was a large thymoma mass (710 g) in the left pleural cavity	The heart sections showed fulminant necrotizing eosinophilic myocarditis. There were multifocal aggregates of lymphoid cells, histiocytes, and abundant eosinophils with focal myocyte necrosis in the free walls of both ventricles, interventricular septum, and around the conduction system (sino-atrial and atrioventricular nodes)
Choi *et al*[25]	1 (22, M)/Pfizer-BioNTech	The heart weighed 470 g with multiple petechial hemorrhages on its surface. The pericardium was smooth with no fibrin deposition or exudate. The coronary arteries were patent, and the heart valves were unremarkable	The myocardial sections showed a diffuse inflammatory infiltration with neutrophils and histiocytes predominance. The inflammatory infiltrates dominant in the atria and around the sinoatrial and atrioventricular nodes with no inflammatory cells in the ventricular muscles
Schneider *et al*[26]	1 (65, M)/Pfizer-BioNTech	The heart showed severe coronary sclerosis, massive cardiac hypertrophy, myocardial infarction scars	The myocardial sections showed myocarditis with lymphocytic and plasmacytoid infiltration of the perivascular space and the myocardium

F: Female; M: Male.

and myocardial infarction scars. The histopathology showed myocarditis with lymphocytic and plasmacytoid infiltration of the perivascular space and the myocardium.

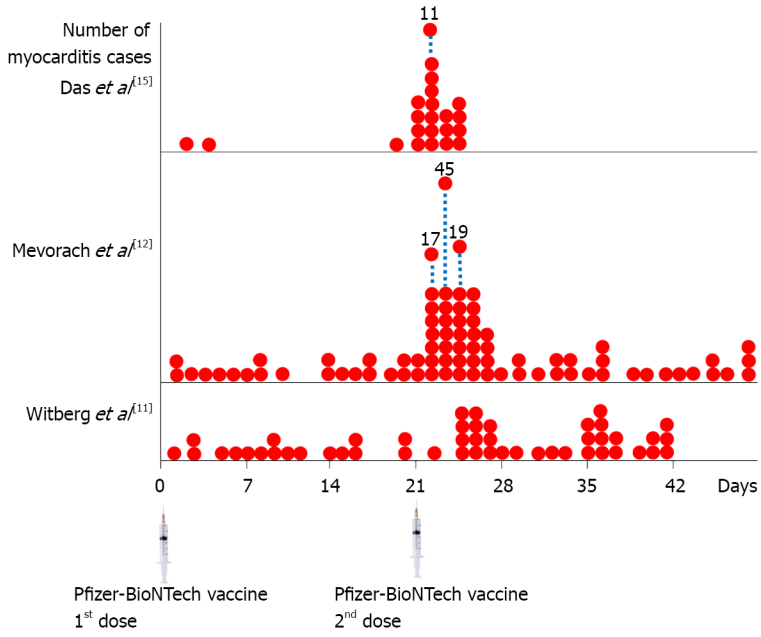
PATHOPHYSIOLOGY OF CARDIAC DYSFUNCTION AFTER MRNA COVID-19 VACCINATIONS

The mRNA COVID-19 vaccines are made up of the mRNA which was modified with nucleosides that codes for the spike protein of SARS-CoV-2 and is enclosed in nanoparticles of lipid that do not have live virus particles or DNA of virus. When the spike protein of a virus is created on the cell surface during the entry of mRNA-vaccine, it activates an adaptive immune response that detects and kills viruses expressing the spike protein. SARS-CoV-2 attachment to the host cell is blocked by vaccine-induced spike-protein IgG antibodies, which bind to the angiotensin-converting enzyme 2 receptor and destroy the virus[27].

Myocarditis caused by enterovirus or human herpesvirus infection is often severe in young adolescents and adult males. Genetic polymorphisms in genes producing HLA factors and, in a minority of individuals, genetic variants in genes encoding cytoskeletal, desmosomal, or sarcomeric proteins are related to this kind of myocarditis, which raises the chance of developing acute myocarditis following viral infection[28]. Myocarditis and pericarditis have previously been documented following immunization, particularly with smallpox and influenza vaccinations with shallow incidence rates[5]. There are sex-specific hormone alterations in COVID-19 mRNA-vaccination-related myocarditis and non-COVID-19 viral myocarditis[29].

Although potential processes are unclear, various ideas may be possible. mRNA immune reactivity, cross reactivity with cardiac proteins, SARS-CoV-2 spike protein antibodies, and hormonal alterations are the four main mechanisms by which COVID-19 mRNA vaccines might induce hyper-immunity. Immune–genetic background, age, and sex can all impact these processes. The immune system may detect the vaccine's mRNA as an antigen, triggering immunological pathways and pro-inflammatory cascades in the heart. Despite the fact that nucleotide changes to mRNA diminish its innate immunogenicity, the mRNA immune response could induce an abnormal innate and acquired immunity, explaining why mRNA vaccinations induce a stronger immune response than other COVID-19 immunization approaches[30]. Another proposed mechanism is molecular mimicry between the SARS-CoV-2 spike protein and cardiac self-antigen presentation. Antibodies against SARS-CoV-2 spike proteins may cross-react with myocardial-myosin heavy chain. These autoantibodies might be inadvertent bystanders that cause myocardial inflammation and damage (Figure 2).

Moreover, they could represent a specific immune–genetic background that predisposes to hyper-immunity and myocarditis in response to any stimulus[31,32]. Furthermore, while COVID-19 mRNA-vaccination-related myocarditis is more common in men, changes in hormone signaling may play a role in its etiology. Testosterone has the capacity to reduce anti-inflammatory immune cells while increasing the aggressiveness of T helper cell-type immune responses. On the other hand, estrogen suppresses pro-inflammatory T cells, leading to a reduction in cell-mediated immune response. As a result, testosterone may still promote an abnormal acquired and innate immune response, which may explain why mRNA immunizations produce a larger immunological response than other methods of COVID-19



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Figure 2 Coronavirus disease 2019 mRNA vaccine associated with myocarditis.

immunization in males than females[33-36].

CONCLUSION

Post-mRNA vaccination myocarditis is most common in young boys under 21 years old. The majority of instances appear within a few days of receiving the 2nd immunization dose. The most common symptom is chest pain, followed by fever or myalgia. The majority of patients have an abnormal ECG. Elevated cardiac troponin and inflammatory markers are mainly laboratory abnormalities. On cardiac MRI, most individuals have evidence of myocardial edema, or inflammation of the cardiac muscles. Possible causes of myocarditis or pericarditis following mRNA COVID-19 vaccines include antibodies to SARS-CoV-2 spike proteins, immune response to mRNA, cross reaction with cardiac proteins, and alteration in hormones. A more rigorous investigation was required to resolve this issue. Despite a few incidences of self-limited myocarditis, the risk-benefit evaluation for COVID-19 vaccination shows a positive balance for all age and gender categories; hence, COVID-19 vaccination is now recommended for all people aged 12 and above.

FOOTNOTES

Author contributions: Leowattana W wrote the paper; Leowattana T collected the data.

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MINIREVIEWS

Takotsubo cardiomyopathy: A comprehensive review

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Abstract

Takotsubo cardiomyopathy (TCM), also known as stress cardiomyopathy, occurs in the setting of catecholamine surge from an acute stressor. This cardiomyopathy mimics acute myocardial infarction in the absence of coronary disease. The classic feature of TCM is regional wall motion abnormalities with characteristic ballooning of the left ventricle. The etiology of the stressor is often physical or emotional stress, however iatrogenic causes of TCM have been reported in the literature. In our review, we discuss medications, primarily the exogenous administration of catecholamines, and a wide array of procedures with subsequent development of iatrogenic cardiomyopathy. TCM is unique in that it is transient and has favorable outcomes in most individuals. Classically, beta-blockers and ACE-inhibitors have been prescribed in individuals with cardiomyopathy; however, unique to TCM, no specific treatment is required other than temporary supportive measures as this process is transient. Additionally, no improvement in mortality or recurrence have been reported in patients on these drugs. The aim of this review is to elucidate on the iatrogenic causes of TCM, allowing for prompt recognition and management by clinicians.

Key Words: Takotsubo; Cardiomyopathy; Iatrogenic; Heart Failure; Myocardial Infarction

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Core Tip: The aim of this review is to elucidate on the iatrogenic causes of Takotsubo cardiomyopathy (TCM). To date, there are individual case reports of iatrogenic TCM but there is not a comprehensive review article. In this review article, we discuss medication and procedure-induced TCM as well as an in-depth review of the current pathophysiology behind TCM.

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INTRODUCTION

Takotsubo cardiomyopathy (TCM) was first identified in Japan in 1991. The term "Takotsubo" originates from the Japanese word for octopus trap as cardiac morphology in this disease process often resembles the shape of these traps. Since its identification, TCM has also been referred to as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome. This complex disease mimics acute myocardial infarction in the absence of obstructive coronary disease and is characterized by transient left ventricular dysfunction. The main feature of TCM is regional wall motion abnormalities with a characteristic ballooning of the left ventricle during systole. The wall motion abnormalities are unique as they extend beyond a single vascular territory and are usually localized to the apex of the left ventricle; however, non-apical variants exist[1]. Although TCM itself is often underdiagnosed, its clinical relevance, recognition, and understanding have progressively accelerated in the recent years. The cardiomyopathy occurs in the setting of a catecholamine surge from an acute stress leading to cardiac dysfunction. The etiology of the stressor is often physical or emotional stress; however, less commonly iatrogenic causes of TCM have been reported as well. Iatrogenic TCM can classified as either medication or procedure related. The aim of this review article is to focus on the reported iatrogenic causes of TCM and to make clinicians aware of this disease process and its complications, allowing for prompt recognition and possibly reducing morbidity and mortality from this rare process.

CLINICAL PRESENTATION

Before discussing iatrogenic causes of TCM, it is important to review the clinical presentation of TCM. Patients frequently present with chest pain, dyspnea, and syncope, and less commonly with arrhythmias, cardiogenic shock, and cardiac arrest. These symptoms are triggered most often by acute physical or emotional stress and infrequently by medical procedures and medication administration. Patients may have elevated cardiac biomarkers (NT-proBNP, troponin T), which complicates differentiating TCM from acute myocardial infarction. High NT-proBNP/troponin T ratio has a sensitivity of 91% and specificity of 95%, is suggestive of TCM, and is helpful in differentiating TCM from ST-elevation myocardial infarction[2]. Typical electrocardiographic findings in TCM include ST-elevation, ST depression, QTc prolongation, and T-wave inversions[3]. On the echocardiogram, left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) can be observed as apical ballooning or midventricular, basal, or focal wall motion abnormalities[4]. TCM predominantly affects the apex; however, non-apical variants may occur. The incidence of such non-apical variants ranges from 8%-40%, with the mid-ventricular variant accounting for approximately 20%, and the basal form for approximately 3%[1]. This cardiomyopathy is unique because it is associated with a nonischemic etiology of acute, but transiently decreased, systolic function with wall motion abnormalities extending beyond a single vascular territory. Angiography often reveals the absence of coronary atherosclerotic disease without dissection, plaque rupture or thrombus formulation. If ventriculography is performed, an apical nipple sign (Figure 1) may be visualized with regional wall motion abnormalities. Lastly, on cardiac magnetic resonance imaging these patients often have reveal wall motion abnormalities, apical ballooning (Figure 2A), late gadolinium enhancement and edema (Figure 2B) on T2 weighted imaging in the dysfunctional left ventricle (LV) regions[1]. Therefore, given that its presentation can mimic that of an acute myocardial infarction, it is critical to diagnose and treat this disease appropriately to allow for rapid recovery and improve long term outcomes in patients.

PATHOPHYSIOLOGY

The pathophysiology of TCM is not completely understood. One of the most well-known and accepted hypotheses concerning the etiology of ventricular dysfunction in this condition is the catecholamine theory[5]. Amariles and Cifuentes suggested that acute stressors lead to an increase in the concentration of neuropeptides and catecholamines (dopamine, epinephrine, norepinephrine) during the acute phase of TCM, contributing to LV dysfunction[6]. These elevated levels of catecholamines contribute not only to myocardial dysfunction, but also cause coronary microvascular vasospasm, increasing cardiac workload and leading to a supply-demand mismatch. This acute mismatch is followed by post-ischemic stunning of the myocardium, resulting in the typical apical ballooning the left ventricle. However, the



Figure 1 Ventriculogram with apical ballooning with presence of apical nipple sign[31]. Citation: Walter Desmet, Johan Bennett, Bert Ferdinande, Dries De Cock, Tom Adriaenssens, Mark Coosemans, Peter Sinnaeve, Peter Kayaert, Christophe Dubois. The apical nipple sign: a useful tool for discriminating between anterior infarction and transient left ventricular ballooning syndrome. *Eur Heart J Acute Cardiovasc Care* 2013; 3: 264-267. Copyright The European Society of Cardiology 2013. Published by Oxford University Press.

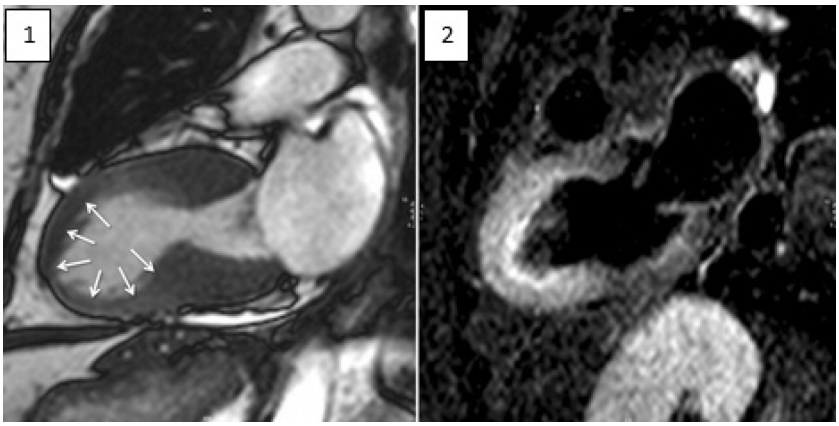


Figure 2 Cardiac magnetic imaging noting (1) apical ballooning (2) myocardial edema in the mid-apical region of the left ventricle[36]. Citation: Plácido R, Cunha Lopes B, Almeida AG. The role of cardiovascular magnetic resonance in takotsubo syndrome. *J Cardiovasc Magn Reson* 2017; 18: 68. Copyright The Authors 2017. Published by Springer Nature.

stunning is temporary and the transient ballooning and is typically followed by complete recovery of the left ventricular contractility after a short period of time in most cases.

In TCM, stress leads to an acute increase in primarily two catecholamines, norepinephrine and epinephrine. Most of the norepinephrine and all of the epinephrine is released from the adrenal medulla [7]. Interestingly, only some of these secreted catecholamines are released into the circulation; most is released directly by the sympathetic nerve endings into the nerve terminals and is presented directly to the adrenoreceptors in the myocardium. This direct release of catecholamines into the myocytes leads to decreased myocardial viability through cAMP mediated calcium overload resulting in myocardial toxicity and myocardial contraction band necrosis[8]. Similar toxicity and necrosis is seen in acute neurovascular events such as subarachnoid hemorrhage as well as in patients with pheochromocytoma, and those dying from violent assaults, or drowning, thus confirming the link between acute stress and cardiac injury[8]. The pattern of contraction band necrosis is considered one of the hallmark signs of TCM[9].

A protective method that the myocardium implements against excessive catecholamines to prevent myocardial necrosis and LV dysfunction is "stimulus-trafficking". During a catecholamine surge, myocardial adrenoreceptors undergo a switch from Gs to Gi coupling leading to a negative inotropic response[10]. If not for this switch, the catecholamine surge would activate the Gs protein pathway, causing increased myocardial contractility and workload, ultimately leading to myocardial injury and toxicity as described earlier. Additionally, the characteristic apical ballooning pattern can be explained by the regional differences in the presence of adrenoreceptors in the myocardium. B2-adrenoreceptors are more densely distributed in the apical region than the basal segment of the LV, whereas B1-adrenoreceptors are expressed more at the base than the apex[11]. Therefore, with high levels of catecholamines, the classic pattern of enhanced basal contraction and reduced apical contractility is seen. This theory was confirmed in rat models in which a bolus of epinephrine to mimic a catecholamine surge resulted in reversible depression of apical contraction and basal hypercontractility[12].

In addition to activation of negative inotropic signaling, catecholamines have been shown to cause epicardial coronary vasospasm and microvascular coronary dysfunction. Decreased radioactive tracer uptake during positron emission tomography perfusion scans in the acute phase of TCM confirms the involvement of microvascular coronary dysfunction as a trigger for myocardial dysfunction[5]. Additionally, Angelini performed acetylcholine testing of the coronaries which led to transient LV dysfunction, confirming a potential role of vasospasm in TCM[13].

Lastly, estrogen deficiency has also been identified as a contributing factor to TCM. In menopause, there is an increased sympathetic drive noted from the lack of estrogen in the circulation. This increases the risk of post-menopausal females to TCM and explains the high incidence of (approximately 89.8%) of TCM in elderly women[14]. Similar to post-menopausal females, the lack of estrogen in males places them at a higher risk of developing TCM and they are noted to have worse outcomes than their female counterparts. To further support estrogen's role in TCM, animal models have demonstrated that estrogen pre-treatment prevents stress-induced LV apical ballooning[5].

CASE REPORTS: MEDICATION-INDUCED TCM

TCM has been widely reported following medication administration with a much higher incidence occurring after catecholamine administration[15-18]. Most of the case reports listed in Table 1, with the exception of Teixeria *et al*[19], discuss an acquired TCM after receiving a prolonged administration of catecholamines. Laínez *et al*[16] present the case of a 61-year-old female who was to undergo resection of a urinary neoplasm. Following anesthesia induction, she experienced fictitious hypotension that was initially believed to be anaphylactic shock. High-dose epinephrine and norepinephrine were administered, and she was found to have a new left bundle branch block on ECG. Further evaluation revealed septal, lateral, and apical dyskinesia with subsequent angiogram revealing non obstructive coronary artery disease. These findings were consistent with TCM, and she had full ventricular recovery over the following four d. As mentioned, Teixeria *et al*[19] stands alone from other case reports listed in Table 1 in that the offending agent was a beta-blocker and not a catecholamine. This case involved a 47-year-old female presenting with severe gastrointestinal symptoms who was given a beta blocker (esmolol) for sinus tachycardia and shortly thereafter developed cardiogenic shock in the setting of elevated cardiac biomarkers. Subsequent evaluation revealed nonobstructive coronaries, preserved apical contractility, and basal akinesis consistent with a non-apical TCM variant. She had full ventricular recovery over the next two d, and her clinical course is unique as it was likely the result of sympathetic stimulation from severe gastrointestinal illness and exacerbated by esmolol administration, likely mimicking the switch from Gs to Gi as seen in "stimulus-trafficking". Additional cases have been reported in the literature involving medication induced TCM following catecholamine administration and can be found in Table 1.

CASE REPORTS: PROCEDURE-INDUCED TCM

In addition to medication induced TCM, there are several cases documenting post-procedural TCM. With the exception of a patient incidentally receiving undiluted norepinephrine, Table 2 lists post-procedural development of TCM in patients who did not receive catecholamines prior to or during a procedure[20]. Table 2 highlights a wide range of procedures associated with TCM including electroconvulsive therapy, endoscopy, valve replacement and bronchoscopy. In one case report, Narayanan *et al* presented the case of a middle-aged female with refractory depression who developed TCM after receiving electroconvulsive therapy[21]. She had been receiving long term therapy with a beta-blocker (bisoprolol) and an ace-inhibitor (lisinopril), both of which were believed at that time to offer protection against the development of TCM[22]. However, Brunettii *et al*[23] subsequently reanalyzed and ultimately refuted this assertion. Most of the cases presented in Table 2 involved anesthetic induction which may have been a contributing factor in the subsequent development of TCM in these patients.

RISK FACTORS, TREATMENT AND PREVENTION

TCM is transient and has favorable outcomes in the large majority of patients. Significant adverse events such as free wall rupture, or cardiac arrest occurs infrequently. Therefore, no specific treatment is recommended. TCM has been known to have a relatively low recurrence rate, at 4% per El-battrawy *et al* [24] Beta-blockers and ACE-inhibitors (ACEi) are commonly used in patients with LV dysfunction given their cardioprotective nature; however, no consensus is available for their use in TCM. Isogai *et al*[25] established that early introduction of beta-blockers in individuals with TCM did not lower their 30-day inpatient mortality. However, lower rates of cardiac rupture were noted in patients with TCM on beta-blockers by Kumar *et al*[26].

Table 1 Medication-induced takotsubo cardiomyopathy case reports

	Sundbøll *et al*[15], 2014	Laínez *et al*[16], 2009	Azouzi *et al*[17], 2019	Ward *et al*[18], 2019	Teixeira *et al*[19], 2014
Electrocardiogram findings	STE II, III, I, aVL, V2-6	New LBBB	Anterolateral STE	TWI	QTc prolongation (479ms)
Peak troponin I (μg/L)	0.773	N/A	0.08	N/A	8.2
Echocardiogram	Apical ballooning	Septal, apical, lateral akinesia	40%; apical hypokinesis	Basal hypokinesis	Mid-to base akinesis w/severe systolic dysfunction; preserved apical contractility
Angiography	Nonobstructive	Nonobstructive	Nonobstructive	Nonobstructive	Nonobstructive
Administered medication	Mucosal E, cocaine	NE, E	E gtt(BB overdose)	NE	Esmolol
LV Recovery Time	4 d	5 d	[a]	[a]	2 d

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle.

Table 2 Iatrogenic-takotsubo cardiomyopathy after procedure case reports

	Narayanan *et al*[21], 2014	Yeow *et al*[27], 2020	Chen *et al*[20], 2011	Kim *et al*[32], 2011	Yu *et al*[33], 2016	Blázquez *et al*[4], 2010	Hui *et al*[34], 2019	Tori *et al*[35], 2008
Procedure	ECT	ECT	Percutaneous coronary intervention	Upper, lower endoscopy	Upper endoscopy	Mitral valve replacement	Bronchoscopy	cholecystectomy and choledocholithotomy
Procedure medication	Propofol, succinyl choline	N/A	Undiluted NE	Pentazocine, Midazolam	Lidocaine spray, Midazolam	N/A	N/A	N/A
Electrocardiogram findings	ST depression and TWI V5-V6	Left anterior fascicular block, TWI III	STE V2-V6	STE V2-3	normal	TWI V1-6	Anterior TWI	TWI V2-5
Peak troponin I (ng/mL)	2.847	N/A	15.11	2.0	3.79	N/A	N/A	normal
Echocardiogram	52%, mid-segment and apical hypokinesia with ballooning	Mid-ventricular and apical akinesis	20-40%, severe apical and septal hypokinesis	Hyperkinetic basal LV; rest of LV akinetic	45%, Hypokinetic mid-LV	15-20%; severe mid-ventricular dysfunction, apical akinesis, with hyperdynamic basal segments	10-15%, apical ballooning and hypokinesis	apical akinesis, basal hyperkinesis
Angiography	NOB	NOB	NOB.	NOB.	NOB.	NOB.	NOB.	N/A
LV recovery time	[a]	3 wk d	2 d	2 mo	6 d	11 d	[a]	14 d

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle; NOB: Nonobstructive.

Singh *et al*[22] performed a meta-analysis evaluating the efficacy of beta-blockers and ACEi in preventing recurrent TCM. They concluded that ACEi were superior to beta-blocker in recurrent TCM. A case report by Yeow *et al*[27] supports the use of both ACEi and beta-blockers. It involves a 61-year-old male who was admitted suicidal ideation and underwent ECT with subsequent development of TCM. This patient was started on a beta-blocker (metoprolol succinate) and ACEi (lisinopril) while hospitalized and re-evaluated in the outpatient setting three weeks later. He was found to have full ventricular recovery and underwent ECT four additional times over the following six mo without recurrence of TCM, which supports the findings of Singh *et al*[22]. However, Brunetti *et al*[23] reanalyzed the data of Singh *et al*[22] a year later, and suggested that the lower rates of TCM were noted in patients treated with ACEi than beta-blockers; however, this difference was not secondary to the drugs' cardioprotective effect, but rather due to the fact that the patients in the ACEi cohort were

prescribed the drug at a higher rate and these patients had closer follow-up than patients in the beta-blocker cohort. Lastly, a recent study by Kim *et al*[28] failed to show a survival benefit or prevent recurrence in patients with TCM treated with ACE inhibitors or beta-blockers.

A recent study by Deshmukh *et al*[29] collected data from the Nationwide Inpatient Sample database in order to analyze potential risk factors for TCM. They identified that age, gender, tobacco or alcohol use, dyslipidemia, hypertension, and external stressors, such as physical or emotional stress, contributed to an increased risk in the development of TCM[29]. Age and gender appear to the be the strongest risk factors as Deshmukh *et al*[29] revealed that women over the age of fifty-five had 4.8 times higher odds of developing TCM when compared to younger women. This increased risk is likely due to decreased circulating levels of estrogen levels and resultant increased sympathetic drive as noted previously in the findings of Templin *et al*[14].

LIMTATIONS

Although iatrogenic medication-induced TCM is likely related to excessive catecholamine administration based on the case reports listed in Table 1, procedure-induced TCM appears to be an associated but rare complication. It is likely that the patients involved in Table 2 experienced an endogenous catecholamine surge that resulted in transient cardiac dysfunction. With the exception of Chen *et al*[20], the case reports in Table 2 did not involve pre-procedural catecholamine administration; however, all patients experienced post-procedural TCM. Case reports listed in Table 2 did not elucidate on potential complications during procedures, such as transient hypotension or the administration of vasopressor support resulting in a catecholamine surge causing iatrogenic TCM. In addition, case reports did not consistently include their home medications. Withdrawal of certain medications could theoretically precipitate a catecholamine surge (*i.e.*, clonidine[30]) or render the patient more susceptible to the endogenous effects of catecholamines.

CONCLUSION

Although Takotsubo cardiomyopathy was first described in 1991, this specific type of cardiomyopathy has only recently gained increased recognition throughout the medical community. TCM is largely provoked by extreme, acute physical or emotional distress but there are now several iatrogenic cases involving catecholamine administration and post-procedural complications highlighted in Table 1 and Table 2. There are many aspects of TCM that are still not completely understood; however, future research should increase our understanding of this disease. It is important to acknowledge this clinical syndrome and its association with medications and procedures in order to better predict complications and potentially prevent further iatrogenic cases of Takotsubo cardiomyopathy.

FOOTNOTES

Author contributions: Barmore W, Patel H and Harrell S performed the majority of the writing, prepared the figures and tables; Barmore W and Patel H performed data accusation and writing; Barmore W, Patel H, Harrell S and Garcia D performed the majority of literature review; Calkins Jr JB provided the input in writing the paper; Harrell S designed the outline and coordinated the writing of the paper.

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ORIGINAL ARTICLE

Observational Study

Association of obesity anthropometric indices with hypertension, diabetes mellitus and hypertriglyceridemia in apparently healthy adult Nigerian population

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Abstract

BACKGROUND

Hypertension, hyperglycemia and hypertriglyceridemia are chronic conditions associated with cardiometabolic diseases. Certain anthropometric indices are known to predict them.

AIM

To investigate the association of anthropometric indices with these chronic diseases and which anthropometric index predicts them best.

METHODS

In this study, 221 apparently healthy individuals who never received treatments for cardiovascular disease (CVD), diabetes or other chronic diseases participated. The age of the participants ranged from 20-75 years with mean age of 36.9 ± 11.4 years. The risk factors of these diseases namely systolic blood pressures (SBP) and diastolic blood pressures (DBP), fasting blood glucose (FBG) and triglycerides (TG) were determined for all the participants using standard clinical procedures. The obesity anthropometric indices, waist circumference, waist-to-height ratio, waist-to-hip ratio and body mass index as well as abdominal height (AH) and body surface index were determined. The association between each of them with the risk factors were determined by the Pearson correlation method.

RESULTS

From the results, it was found that AH showed superiority over the rest for SBP (r = 0.301, P < 0.01), DBP (r = 0.370, P < 0.01), FBG (r = 0.297, P < 0.01) and TG (r = 0.380, P < 0.01). Using the receiver operating characteristic curves, cut-off values of AH for SBP, DBP, FBG and TG were determined to be 24.75 cm, 24.75 cm, 25.25 cm and 24.75 cm respectively.

CONCLUSION
The indices of anthropometry used in this study correlated significantly with the studied CVD risk factors, with AH emerging as the most predictive.

Key Words: Hypertension; Hyperglycemia; Hypertriglyceridemia; Abdominal height; Anthropometric indices

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Core Tip: In this work, we used common anthropometric indices and some novel ones to correlate with cardiometabolic diseases in an attempt to identify the best anthropometric index that accurately predicts risk of cardiometabolic diseases in apparently normal individuals.

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INTRODUCTION

It has been identified that chronic disease conditions such as hypertension, hyperglycemia and hypertriglyceridemia are important public health challenges often encountered in Sub-Saharan Africa and worldwide with hypertension considered a major risk factor leading to stroke, myocardial infarction, heart failure and even ultimate death[1,2]. Metabolic conditions associated with abdominal obesity such as elevated blood pressure, impaired glucose tolerance, insulin resistance and elevated triglycerides (TG) are all contributing factors of metabolic syndrome (MetS) and cardio-metabolic diseases (CMD)[3-5]. For a long time, excess adiposity, especially the visceral fat is identified as one of the major risk factors of these chronic diseases[6]. Moreover, visceral fat has a more significant impact on diabetes and other related conditions than subcutaneous fat[7]. The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. An increased intake of energy-dense food high in fat; and an increase in physical inactivity due to the increasingly sedentary lifestyle is responsible for this energy imbalance[8]. In most population based cardiovascular risk evaluation studies found in the literature, researchers have chosen two or more of traditional obesity anthropometric indices among waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR) and body mass index (BMI) to establish the risk level of cardiovascular disease (CVD). This is because they are simple, non-invasive and cost effective measuring procedures. However, as shown in the literature, none of these adiposity anthropometric indices has been found to be systematically better than the others in the discriminatory power of CVDs[9] because, they can have some inherent clinical deficiencies associated with them in getting accurate diagnosis. For decades, BMI has been the most widely accepted index of adiposity and most commonly used for defining obesity recommended by the WHO[10] but it can be affected by age, gender, and ethnicity[11]. Some studies found statistical evidence that supports the superiority of measures of abdominal obesity (WC, WHR, or WHtR) over BMI, for discriminating cardiovascular risk factors in both genders[12,13]. Moreover, it has been shown that BMI cannot distinguish between visceral (abdominal) adiposity and overall (general) adiposity and therefore, found to be incapable of differentiating body fat and lean body mass[14]. Although WC takes abdominal obesity into account but it includes both visceral and transcutaneous fat in its measurements. Some studies have proposed WHtR and WHR as the better anthropometric parameters than BMI for predicting cardiometabolic risk[15-17]. Another study showed that although WC and WHR could indicate relative abdominal shape more clearly, they still provided limited information on the fat distribution and can lead to inaccurate diagnosis[17]. Moreover, the predictive power of different anthropometric indices also depends on the ethnic origin of the studied population[18] and this suggests the need for regional studies to be carried out in order to determine the best adiposity discriminators unique to each of these population groups for more accurate community risk evaluations of cardiometabolic diseases. In this study, two other adiposity indices abdominal height (AH)[19] and body surface index (BSI)[20] were included along with BMI, WC, WHtR and WHR. The purpose of this study is to identify the best anthropometric index for each of the disease conditions; hypertension, diabetes mellitus (DM) and hypertriglyceridemia for our chosen cross-sectional population study group and to determine their respective cut-off values.

MATERIALS AND METHODS

Materials

After signing the consent form, the participants were given a questionnaire to fill indicating their sex, age, state of origin, smoking status (Yes or No), alcohol use (Yes or No), physical inactivity (Yes or No) and the family history of CVD (Yes or No). For the measurements to determine the anthropometric indices, Hana bathroom scale, a stadiometer, a non-flexible measuring tape and an abdominometer were used. The blood pressures were measured with an Omron M2 basic automatic digital blood pressure monitor while fasting blood glucose (FBG) and TG were determined with an SD lipidocare dual analyzer.

Methods

Study design: A cross-section of apparently healthy adult Nigerians of multiple ethnicity participated in this study. All participants recruited for this study reside in Jos, which is the capital of Plateau State of Nigeria. By "apparently healthy" we meant people who assume themselves to be healthy because they feel no symptoms although they had never done routine medical check-ups or taken any type of medications for chronic diseases such as hypertension, DM and MetS in their life time. They may well be in some form of cardiometabolic disease incubation depending on their age, physical attributes and lifestyle. The minimum sample population size was determined statistically by using the formula, $N = (Z^2\ p\ q)/X^2$ to be 196. The prevalence of cardiometabolic diseases in Nigeria as reported in a previous literature was taken to be 15%[21]. This study was carried out at the Jos University Teaching Hospital, Jos, Nigeria after obtaining the ethical clearance from the hospital's ethical committee. Informed and written consents were obtained from each of the participants of this study. Demographic, behavioral and other risk factor information needed in this study were obtained by administering a questionnaire.

Inclusion criteria: Only the apparently healthy staff and students in Jos University Teaching Hospital who never received treatments for CVD, Diabetes or other chronic diseases were included in this study. The minimum age to qualify for this study was 18 years.

Exclusion criteria: Pregnant women and children were excluded from this study.

Ethical consideration: The study design and protocols were duly approved by the Ethical Committee of the Jos University Teaching Hospital, Jos; and the study lasted between August 2015 to January 2016.

Measurements of anthropometric indices: The body mass was measured using a Hana bathroom scale to the nearest 0.5 kg with subjects wearing light clothes as much as possible with empty pockets standing erect on the scale with both legs well placed on it without shoes. The height measurement was taken as the subject stands erect without shoes on a stadiometer in centimeters. Waist and hip circumferences were measured using a non-flexible tape in centimeters to the nearest 0.1 cm. WC was measured at the end of a normal expiration with arms relaxed at the sides over the light clothing in standing position at the mid-point between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured with tape wrapped around the maximum circumference of the buttocks with the subjects standing with their feet together with body weight evenly distributed over the feet. WHR was determined by the ratio between the waist and the hip circumferences. Similarly, WHtR was determined by the ratio between the WC and height. The BMI and BSI were computed by dividing the body mass (kg) by the square of height (m^2) and dividing the body mass (kg) by the body surface area (m^2)[20]. The AH was measured using a locally constructed wooden instrument 'abdominometer' in centimeters with an accuracy of 0.5 cm by placing the instrument at the level of iliac crest which corresponds to the space between 4th and 5th lumber vertebrate and the anterior abdominal wall at the level of umbilicus as the subject stands erect[19].

Measurements of blood pressures: Both systolic and diastolic blood pressures (DBP) were measured using an Omron M2 Basic automatic digital blood pressure monitor. The subjects were asked to sit without crossing legs on a chair quietly and place his/her hands on the table after resting in a sitting position for about 15 min. The inflating cuff was fixed tightly on the upper left arm making sure that the lower edge of the cuff was placed about 2 cm above the inner side of the elbow joint. The measurements were taken 3 times within a 5-min interval and the average of both systolic and DBP of the last two measurements were recorded according to WHO guidelines[22].

Measurements of TG and FBG: SD lipidocare dual analyzer was used to determine the TG and FBG levels.

High risk cut-off values of risk factors: In clinical practice, hypertension is diagnosed when systolic blood pressure (SBP) ≥ 140 mmHg and DBP ≥ 90 mmHg[21]. Hyperglycemia which is also known as DM is clinically established when FBG level ≥ 7.0 mmol/L[23]. Hypertriglyceridemia is also diagnosed from the fasting blood serum when the level of TG ≥ 1.7 mmol/L[24].

Statistical analysis: In this study, all statistical analysis were carried out with IBM SPSS Version 22 software package. Correlations between risk parameters (SBP, DBP, FBG and TG) and obesity anthropometric indices (AH, WC, WHR, BSI, WHtR and BMI) were carried out using Pearson correlation method. Also, the correlation between AH and the rest of the anthropometric indices was determined. The receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of AH for all the risk parameters including obesity.

RESULTS

In this study, 221 consenting subjects (82 males and 139 females) of aged between 18-75 years with a mean age of 36.9 ± 11.4 years participated. Out of this, 67% were indigenes of Plateau state (Central Nigeria) while the rest of the 33% were from 18 other different states representing the North, South, East and West geographical regions of Nigeria.

From the questionnaires, the percentages of traditional risk factors such as status of smoking, alcohol use, physical inactivity and family history of CVD were found to be 2.3%, 17.2%, 31.7% and 24.4% respectively.

Table 1 shows the number of subjects from the study population and the percentage risk for each of the risk parameters considered in this study including the risk of obesity (BMI ≥ 30.0 kg/m^2).

Figure 1 shows the correlations between SBP, DBP, FBG and TG respectively with the selected obesity anthropometric indices.

Table 2 shows the order of correlation coefficients of the anthropometric indices from the highest to the lowest for each of the four risk parameters SBP, DBP, FBG and TG.

Table 3 shows the Pearson Correlation coefficients and *P* values between AH and other anthropometric indices used in this study.

Table 4 shows the ROC curve analysis with cut-off values of AH for all the risk parameters including obesity.

DISCUSSION

Table 1 shows the summary of the prevalence of risk levels of chronic diseases among the apparently healthy cross section of adult Nigerians chosen in this study. Unknown to them, a significant percentage of these participants were at high risk for CMD. We found that 16.3% of the participants had SBP greater or equal to 140 mmHg while 10.0% had DBP greater or equal to 90 mmHg. However, only 2.7% had hyperglycemia but 19.0% had hypertriglyceridemia. Interestingly, 28.1% of these participants who claimed to be healthy were obese. Correlation coefficients of anthropometric indices WC, AH, BMI, BSI, WHtR and WHR with risk parameters SBP, DBP, FBG and TG were illustrated in Figure 1 and all the correlations were significant at $P < 0.01$ and showed a positive association between the anthropometric indices and risk parameters. Table 2 shows the order of correlation with each risk parameter from highest to lowest values. It was found that AH is superior to all the other obesity anthropometric indices considered in this study to discriminate hypertension (SBP and DBP), hyperglycemia (FBG) and hypertriglyceridemia (TG). This confirms the findings of an earlier pilot study by Okeahialam *et al*[25] that AH was superior to BMI in predicting hypertension and diabetes. This present study shows that even for hypertriglyceridemia AH is a better predictive anthropometric index. Although both WHO and American Heart Association recommend the use of WC in screening for cardiometabolic risk[26], in our study WC is positioned as the second best discriminator for SBP, DBP and FBG except for TG where BSI proved to be better. Previous studies also showed that AH, also known as sagittal abdominal diameter (SAD) correlates better with cardiovascular risk factors than WC and BMI[27-29]. However, in these studies SAD was measured with a subject lying in a supine position to allow loose subcutaneous fat to fall to the sides of the subject on the couch and more rigid visceral fat to remain in place to be measured using a caliper instrument. They also reported that the ability of SAD to index abdominal fat and high risk obesity more accurately is greater than that of the WC and BMI. We also noticed that BSI is superior to BMI in discriminating all the risk parameters considered in this study. The other two anthropometric indices WHtR and WHR can also be used as good discriminators of CMD. However, some inaccuracies can occur especially in finding the best anatomical site for WHR measurement[30]. Although all these six anthropometric indices are statistically found suitable for the risk evaluation studies of adult Nigerians, some uncertainties involved in differentiating of visceral fat from subcutaneous fat and abdominal obesity from general obesity can hinder the accuracy of these traditional anthropometric indices in diagnosing cardiometabolic diseases. Therefore, we propose AH to be the best discriminator of CMD for adult Nigerians in this locality taking into consideration both statistical superiority and clinical acceptability due to its ability to measure visceral fat more accurately. Table 3 shows the association of AH with the other five anthropometric indices. Incidentally, AH also shows very strong and positive correlations with all the other indices: WC (0.944), WHtR (0.905), BSI (0.892), BMI (0.872)

Table 1 Number of risk subjects and percentage risk for study parameters

Risk cut-off of parameter	Number of subjects	Percentage risk
SBP ≥ 140 mmHg	36/221	16.3
DBP ≥ 90 mmHg	22/221	10.0
FBG ≥ 7.0 mmol/L	06/221	2.7
TG ≥ 1.7 mmol/L	42/221	19.0
BMI ≥ 30.0 kg/m^2	62/221	28.1

SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; BMI: Body mass index; TG: Triglycerides.

Table 2 The order of correlation of the anthropometric indices with risk parameters

Risk-parameter	Order of correlation with anthropometric indices, highest (1) to lowest (6)					
	1	2	3	4	5	6
SBP	AH	WC	WHR	BSI	WHtR	BMI
DBP	AH	WC	BSI	WHtR	BMI	WHR
FBG	AH	WC	WHtR	WHR	BSI	BMI
Triglycerides	AH	BSI	WC	BMI	WHtR	WHR

AH: Abdominal height; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; BMI: Body mass index; WC: Waist circumference; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; BSI: Body surface index.

Table 3 Correlation between abdominal height and other anthropometric indices

	WC	BMI	WHtR	WHR	BSI
AH	0.944	0.872	0.905	0.682	0.892
P value	0.000	0.000	0.000	0.000	0.000

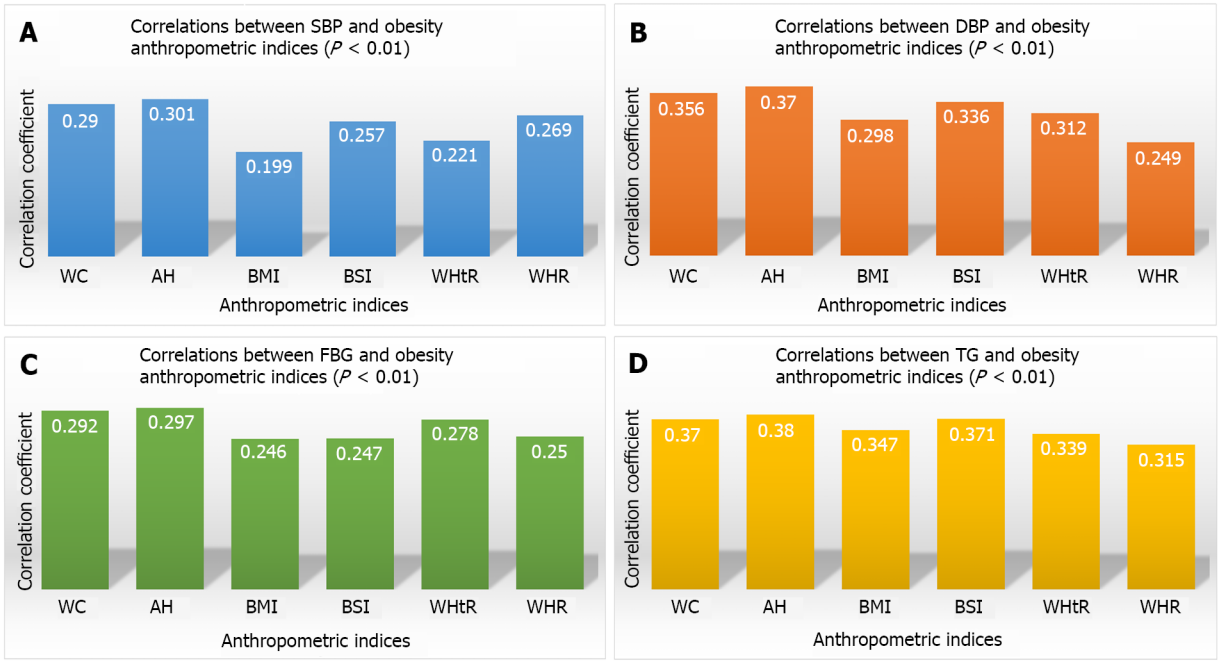
AH: Abdominal height; BMI: Body mass index; WC: Waist circumference; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; BSI: Body surface index.

Table 4 Receiver operating characteristic curve analysis with cut-off values of abdominal height for risk parameters

Disease condition	Risk value	AH cut-off (cm)	Sensitivity, %	Specificity, %	AUC	95%CI
Hypertension (SBP)	≥ 140 mmHg	24.75	66.7	56.8	0.638	0.544-0.730
Hypertension (DBP)	≥ 90 mmHg	24.75	77.3	56.3	0.664	0.551-0.778
Hyperglycemia (FBG)	≥ 7.0 mmol/L	25.25	66.7	58.6	0.621	0.344-0.899
Hypertriglyceridemia (TG)	≥ 1.7 mmol/L	24.75	83.3	61.5	0.751	0.675-0.827
Obesity (BMI)	≥ 30.0 kg/m^2	25.75	85.5	79.2	0.923	0.889-0.957

AH: Abdominal height; TG: Triglycerides; BMI: Body mass index; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; AUC: Area under the curve; CI: Confidence interval.

and WHR (0.682). This shows the strong relationship of AH over the other anthropometric indices considered in this study for risk evaluations of CMD. From the ROC curve analysis, we found the cut-off values, area under the curve, 95% confidence interval of AH for all the risk parameters SBP, DBP, FBG, TG and obesity (using the BMI scale) as shown in Table 4. We established that the risk cut-off value of AH ≥ 24.75 cm for both hypertension and hypertriglyceridemia and AH ≥ 25.25 cm for hyperglycemia. Using BMI ≥ 30.0 kg/m^2 as the risk value of obesity, the cut-off value of obesity is found to be AH ≥ 25.75 cm. This means that, going by our findings, cardiometabolic disease risk can occur



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Figure 1 Correlation between each index and obesity anthropometric index. A: Correlations between systolic blood pressures and obesity anthropometric indices; B: Correlations between diastolic blood pressures and obesity anthropometric indices; C: Correlations between fasting blood glucose and obesity anthropometric indices; D: Correlations between triglycerides and obesity anthropometric indices. AH: Abdominal height; WC: Waist circumference; BMI: Body mass index; BSI: Body surface index; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; TG: Triglycerides.

without a person being classified as obese going by WHO BMI values.

CONCLUSION

From this study, we have attempted to establish the clinical and statistical significance of the AH measured when a subject is standing in erect position at ease with our abdominometer in risk evaluation of cardiometabolic diseases over the other existing traditional obesity anthropometric indices such as WC, WHtR, WHR and BMI. Moreover, we also found that the BSI can be a better index than the BMI for cardiometabolic risk evaluations as a general obesity anthropometric index.

Recommendations

Using this simple AH measurements, large scale community based population studies were recommended to predict and separate high risk individuals for possible life style modification procedures, clinical interventions and treatments to minimize the mortality and morbidity rates of cardiometabolic diseases as preventive measures. This is necessary given the relatively small size of our sample and the convenience approach to sampling; in order to improve external validity.

ARTICLE HIGHLIGHTS

Research background

For decades, body mass index (BMI) has been the most widely accepted index of adiposity and most commonly used for defining obesity recommended by the WHO but it can be affected by age, gender, and ethnicity.

Research motivation

In most population-based cardiovascular risk assessment studies found in the literature, researchers selected two or more of traditional obesity among waist circumference, waist-to-height ratio, waist-to-hip ratio, and body mass index. Anthropometric measures (BMI) to determine the level of cardiovascular disease (CVD) risk. This is because they are simple, non-invasive and cost-effective measurement procedures. However, as shown in the literature, these anthropometric measures of

obesity have not been found to be systematically superior to others in terms of their discriminative power for CVD, as they may have some inherent clinical pitfalls associated with them in obtaining an accurate diagnosis.

Research objectives

We sought to identify the best anthropometric index predictive of each of the disease conditions; hypertension, diabetes mellitus and hypertriglyceridemia for our chosen cross-sectional population study group and to determine their respective cut-off values.

Research methods

This was a cross-sectional study that included 221 consenting apparently healthy adult Nigerians 18 years and above who were not pregnant at enrolment. After signing the consent form, the participants were given a questionnaire to fill indicating their sex, age, state of origin, smoking status (Yes or No), alcohol use (Yes or No), physical inactivity (Yes or No) and the family history of CVD (Yes or No). Height and weight were measured as well as the other anthropometric indices using a measuring tape and an abdominometer. The blood pressures were measured with an Omron M2 basic automatic digital blood pressure monitor while fasting blood glucose and triglycerides were determined with an SD lipidocare dual analyzer.

Research results

In this study, 221 consenting subjects (82 males and 139 females) of aged between 18-75 years with a mean age of 36.9 ± 11.4 years participated. From the questionnaires, the percentages of traditional risk factors such as status of smoking, alcohol use, physical inactivity and family history of CVD were found to be 2.3%, 17.2%, 31.7% and 24.4% respectively.

Research conclusions

Anthropometric measures used in this study were significantly associated with the CVD risk factors studied, with abdominal height (AH) emerging as the most predictive measure.

Research perspectives

Using this simple measure of AH, large-scale community population studies are recommended to predict and differentiate high-risk individuals for possible lifestyle modification procedures, clinical interventions, and treatments to minimize cardiometabolic mortality and mortality. Morbidity as a preventive measure. This is necessary given our relatively small sample size and convenient sampling method.

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FOOTNOTES

Author contributions: Sirisena A generated data, analyzed data and contributed to write up; Okeahialam B conceptualized and supervised project, wrote up the paper.

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ORIGINAL ARTICLE

Observational Study

Study of coronary sinus anatomy during levophase of coronary angiography

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Abstract

BACKGROUND

Coronary sinus (CS) imaging has recently gained importance due to increasing need for mapping and ablation of electrophysiological arrhythmias and left ventricular (LV) pacing during cardiac resynchronization therapy (CRT). Retrograde venogram is the current standard for imaging CS and its tributaries.

AIM

To evaluate CS anatomy during levophase of routine coronary angiography to aid LV lead implantation during CRT.

METHODS

In this prospective observational study, 164 patients undergoing routine coronary angiography for various indications (Chronic stable angina-44.5%, acute coronary syndrome- 39.5%, Dilated cardiomyopathy-11%, atypical chest pain-5%) were included. Venous phase (levophase) of left coronary injection was recorded in left anterior oblique - cranial and right anterior oblique -cranial views. Visibility of coronary veins, width and shape of CS ostium, angulations of proximal CS with body of CS were noted. Presence, size, take-off angle and tortuosity of postero-lateral vein (PLV), anterior interventricular veins (AIV) and middle cardiac vein (MCV) were also noted.

RESULTS

During levophase, visibility grade (Muhlenbruch grade) for coronary veins was 3 in 74% and 2 in 26% of cases. Visibility of CS did not correlate with body mass index. The diameter of CS ostium was < 10 mm, 10-15 mm and > 15 mm in 48%, 42% and 10% of patients respectively. Proximal CS was tubular in 136 (83%)

patients and funnel-shaped in 28 (17%) patients. Sharp take-off angulation between ostium and body of CS was seen in 16 (10%) patients. Two or more PLV were present in 8 patients while PLV was absent in 52 (32%) patients. Angle of take-off of PLV with body of CS was favourable (0°-45°) in 65 (40%) patients. The angle was 45°-90° in 36 patients and difficult take-off angle (> 90°) was seen in 8 patients. Length of PLV reached distal third of myocardium in 84 cases and middle third in 11 cases. There was no tortuosity in 79 cases, a single bend in 29 cases and more than 2 bends in 4 cases. Thirty nine (24%) patients had other veins supplying posterior/Lateral wall of LV. There was a single vein supplying lateral/posterior wall in 31 (19%) patients. Diameter of MCV and AIV was significantly larger in patients with absent PLV as compared to patients with a PLV.

CONCLUSION

Levophase study of left coronary injection is effective in visualization of the CS in almost all patients undergoing coronary angiography and may be an effective alternative to retrograde venogram in patients with LV dysfunction or LBBB.

Key Words: Posterolateral vein; Ostium; Angiography; Sharp take off; Favourable angulation

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Core Tip: In this prospective, observational study, we assessed venous phase of coronary angiogram (n = 164) with the intent to evaluate coronary sinus anatomy for purpose of left ventricular (LV) lead placement during cardiac resynchronization therapy. Levophase analysis showed excellent visibility of coronary sinus and its tributaries irrespective of body mass index. Shape of ostium & angulations within body of coronary sinus could be delineated reliably. Number, size, take off angle and any tortuosity within postero-lateral vein could be well identified. We found levophase study of coronary angiography an acceptable alternative to retrograde venography for LV lead placement assessment.

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INTRODUCTION

Imaging of the coronary venous system is usually overshadowed by that of the coronary arteries. However, imaging of coronary venous system has gained importance in recent past, as many cardiac interventions currently use the coronary sinus *e.g.*, mapping and ablation of various arrhythmias, left ventricular (LV) pacing, targeted drug delivery, and stem cell therapy. The coronary sinus (CS) is the largest cardiac venous structure and is frequently cannulated during electrophysiologic and interventional procedures. Thus, detailed knowledge of its normal anatomy and anomalies is of paramount importance to avoid any complications[1,2].

The cardiac veins are classified, according to the region they drain viz. the CS and its tributaries, the anterior cardiac veins, and the thebesian veins[3-6]. The anterior cardiac veins are the primary venous return for the anterior wall of the right ventricle. They include three or four small veins which drain directly into the right atrium either separately or after forming a common venous trunk before emptying into the right atrium[5]. The right marginal vein is a relatively constant vein which ascends along the right margin of the heart. The right marginal vein can also drain into the small cardiac vein, which runs in the right atrioventricular groove which eventually terminates by draining into the CS or directly into the right atrium[5]. The thebesian veins (venae cordis minimae) are several small veins that drain the subendocardium.

The major tributaries of the CS include: (1) The anterior interventricular vein; (2) The great cardiac vein (GCV); (3) The left marginal vein and posterior vein; and (4) the middle cardiac vein or posterior interventricular vein. The CS is variable in size. It varies 45 to 63 mm in length, and the size of the ostium ranges from 4 mm × 5 mm to 9 mm × 16 mm[7-10].

Cardiac resynchronization therapy (CRT) involves LV pacing in patients with LV systolic dysfunction to improve synchronization of LV conduction. It yields the best results when the LV lead is implanted in area of latest mechanical activation, with the lateral and posterior branches being the usual target veins for this procedure[3]. Hence, CS imaging can play an important role in planning LV lead implantation

strategy and help identify suitable veins in area of interest. The most co mmonly employed technique to visualize CS anatomy is occlusive retrograde venography. In this study, we evaluated venous phase (levophase) of coronary angiography to assess its utility in studying CS anatomy.

MATERIALS AND METHODS

All patients above 18 years of age undergoing coronary angiography for various indications between November 2017 and October 2018 were considered for inclusion. Patients who were in cardiogenic shock, had congestive heart failure, had eGFR < 50 mL/min, those having severe left main disease or complex congenital heart disease were excluded from the study.

Our study included patients who were undergoing invasive coronary angiography for different reasons such as acute coronary syndromes or stable angina. A written informed consent was taken from all patients in our study. Baseline characteristics were recorded in all patients which included age, sex, height, weight, NYHA functional class, cardiovascular risk factors like diabetes mellitus, hypertension, smoking, prior history of coronary artery disease (CAD) and left ventricular ejection fraction (LVEF).

Patients underwent a coronary angiogram from either the radial route using a 5F tiger catheter or femoral route with a 5F/6F Judkins left diagnostic catheter. A non-ionic, low osmolarity, iodide contrast medium - Iohexol (Omnipaque, GE Healthcare, Chicago, Illinois, United States) was used through manual injection in all cases. After canulating the left coronary ostium, a left anterior oblique (LAO) caudal view was recorded to detect patients with severe left main disease or any abnormality affecting the safety of the procedure. Further coronary angiogram was done with necessary angiographic view as per detected lesions. LAO with cranial angulation (LAO 40 degrees, cranial 30 degrees) and right anterior oblique (RAO) with cranial angulation (RAO 30 degrees, cranial 30 degrees) views were recorded for all patients. These are the views in which venous anatomy was studied. Venous phase (levo-phase) of injection was recorded beyond the initial 5-10 seconds to visualise the coronary venous anatomy in these LAO- cranial and RAO-cranial views. Recording was done on cine mode at rate of 15 frames per second. The rest of the coronary angiogram and all other procedure including intervention, post-procedure care was done as per routine. In some cases, the coronary venous anatomy could also be seen in other views taken during the study. When this revealed additional information, they were also included in our analysis.

Analysis of coronary venogram

Visibility of the coronary veins was classified on the 0-3 point scale described by Muhlenbruch *et al*[10] (Table 1).

Measurements were taken on the CAAS QCA software based on pixel size and comparison with the catheter diameter. Width of the coronary sinus ostia was measured. Shape of the coronary sinus: tubular, funnel-shaped or other was recorded (Figure 1). The proximal portion of the coronary sinus was studied subjectively for factors that affect sheath selection such as angulation and presence of a thebesian valve. Superior angulation of the proximal portion of the coronary sinus with the body of the coronary sinus was measured in the LAO cranial view and classified into 3 groups: (Figure 2) Group 1: 0°-30°; Group 2: 31°-60° and Group 3: > 60°. The presence of posterior angulation of the coronary sinus ostia with the body of the coronary sinus was recorded in the RAO cranial view. LAO cranial view was studied for the presence of a Thebesian valve. A Thebesian valve was detected by noting an upward direction of outflow into the right atrium (RA) from the coronary sinus, and by a smooth inferior border of the outflow jet.

Other anomalies in venous anatomy such as posterior lateral vein (PLV) draining near the coronary sinus ostia or directly into the RA, left superior vena cava (SVC) were also recorded when relevant. Number of suitable (> 2 mm diameter) PLVs were noted. Veins with a diameter of > 2 mm measured 2cms distal to its ostium were considered favourable. Veins tapering or dividing into venules of less than 2 mm size before running 2 cms as seen in two recorded views were classified as unfavourable. The diameter of the PLV, measured at 2 cms distal to its ostia with the coronary sinus was noted. In cases with > 1 PLV, the diameter of the largest PLV was recorded. The angle made by the PLV with body of CS was also noted in the LAO cranial view and classified into 3 groups: (Figure 3) - Easy take-off: (0° to 45°); Medium difficulty: 45° to 90°; Difficult take-off: > 90°.

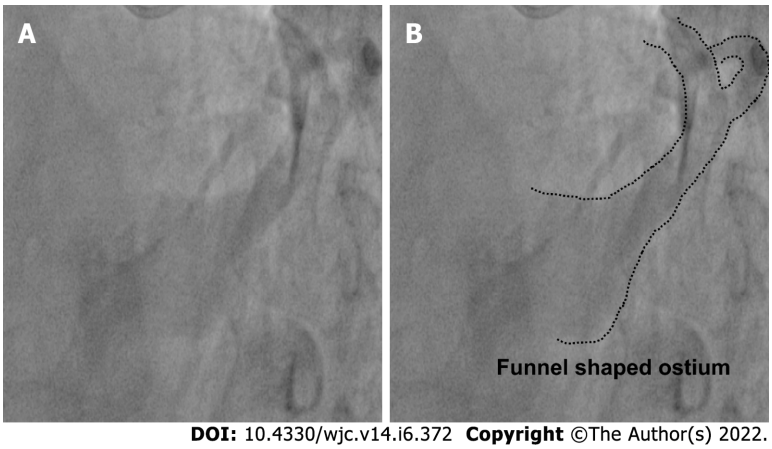
When a PLV was absent, the incidence of other tributaries draining the posterior-lateral part of the LV was studied. Diameter of the anterior interventricular vein (AIV) and the middle cardiac vein (MCV) was recorded in all cases. Comparisons were made of the diameters of the AIV and MCV in patients with and without a PLV. Tortuosity of the PLV most suitable for the purpose of CRT LV lead was studied, and the number of bends were also recorded.

Statistical analysis

Demographic data were reported as percentages, mean and median were calculated when applicable. Chi square test and the student t-test were used for statistical analysis. *P* value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences (IBM

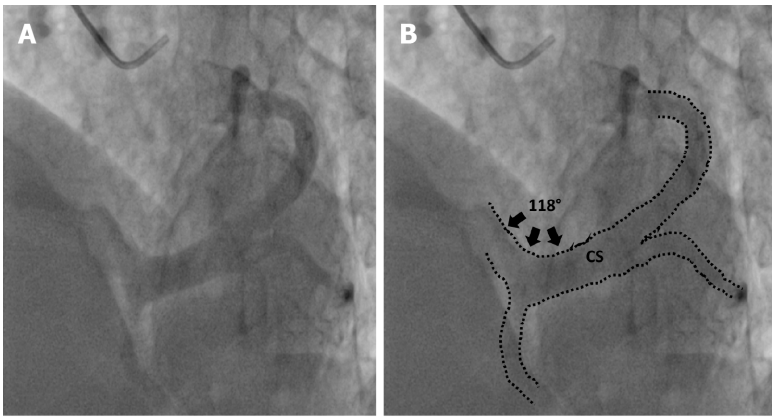
Table 1 Visibility of the coronary veins was classified on the 0-3 point scale

Grade	Visibility
0	Not visible
1	Visible but with discontinuities
2	Visible but with irregular borders
3	Visible with vascular borders perfectly defined



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Figure 1 Funnel Shaped Ostium as seen in left anterior oblique cranial view. A: Fluoroscopic image; B: Rendered image with dotted lines outlining coronary sinus morphology.



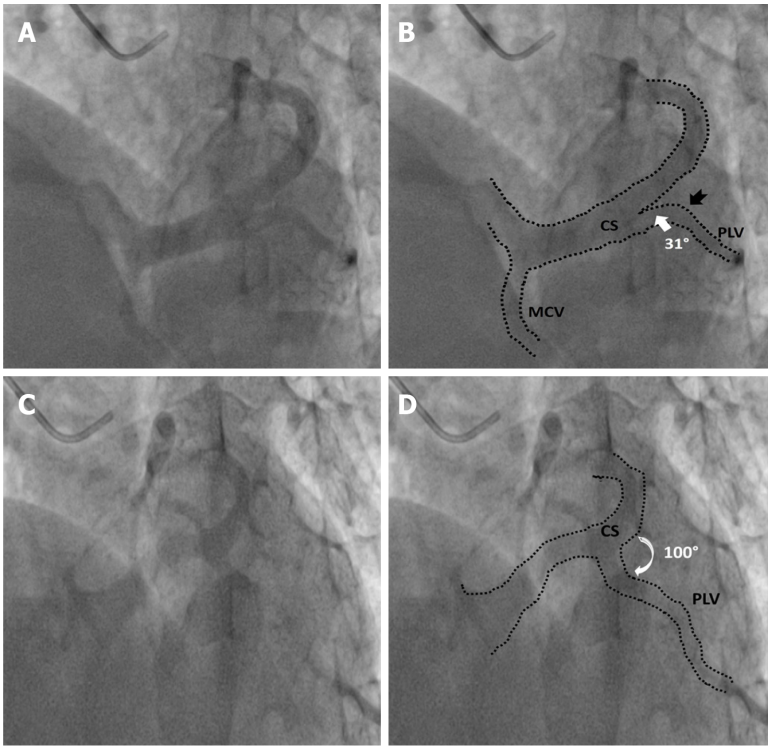
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Figure 2 Superior angulation made by the proximal portion of the coronary sinus with the body of the coronary sinus in left anterior oblique cranial view. A: Fluoroscopic image; B: Rendered image with dotted lines outlining coronary sinus anatomy, black arrows represent angle subtended.

SPSS; Chicago, IL, United States) program, version 20.

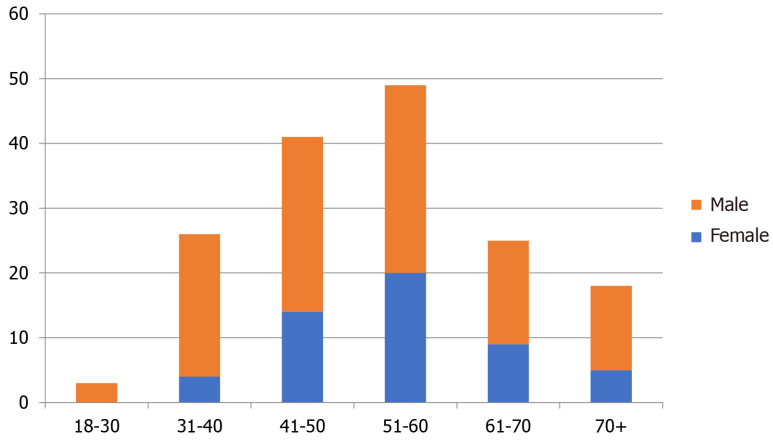
RESULTS

A total of 168 patients undergoing coronary angiography for various indications between November 2017 and October 2018 were included in our study. Coronary sinus could not be assessed in four patients due to a suboptimal study (inadequate volume of dye given, too short cine time) and were excluded from analysis. Data of the remaining 164 patients was analysed. 116 (72%) were male and the mean age of the study population was 53.3 years (Figure 4). The various indications for coronary angiography were Chronic Stable Angina in 73 (44.5%) cases, Acute Coronary Syndrome in 65 (39.5%) patients [43 with Non-ST elevation Myocardial infarction, 22 With ST-elevation myocardial infarction], Dilated cardiomyopathy/ischemic cardiomyopathy was present in 11 (7%) patients. Angiography was



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Figure 3 Favourable and unfavourable take off angles of posterolateral vein. A: Example of posterolateral vein (PLV) with favourable angle-fluoroscopic image; B: Corresponding rendered image with dotted lines outlining coronary sinus (CS) morphology, white arrow denoting narrow angle between body of CS and PLV, black notched arrow represents single bend in PLV; C: Example of unfavourable angle PLV-fluoroscopic image; D: Corresponding rendered image with dotted lines outlining CS morphology, white curved arrow denoting wide angle between PLV and CS body.



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Figure 4 Demographic profile of study population.

performed for the evaluation of atypical chest pain in 09 (5%) patients, 2 patients had VT in a structurally normal heart, 3 patients underwent routine angiography prior to valve replacement, and 1 patient had PSVT with angina. The LVEF of patients ranged from 22%-76%. Eleven patients (7%) had an EF of less than 35%. 93 patients (57%) had an EF of 50% and above. The body mass index (BMI) in 53% of patients ranged from 18-24, 6% had a BMI of 30 or above and 14% had a BMI of less than 18. The visibility of CS did not correlate with BMI ($P = 0.69$). The visibility score was 3 in 121 (74%) cases, 2 in 43 (26%) cases, < 2 in 0 cases. Access was *via* right radial artery in 134 (89%) patients, right femoral artery in 16 (11%) patients. The mean contrast medium volume used was 65.2 ± 26.6 mL. Among complications, two patients developed grade 1 radial hematoma, and none had any complications related to femoral arterial access. No contrast-induced nephropathy was seen in our study.

Coronary venous anatomy

The diameter of CS ostia ranged from 2 mm-18 mm.The diameter was < 10 mm in 80 (48%) of the patients, 10-15 mm in 74 (42%) of patients and > 15 mm in 10% patients. Ostial stenosis (diameter < 2 mm) was present in 1 case with a co-existing left SVC. The shape of proximal portion of CS was tubular in 136 (83%) patients and funnel-shaped in 28 (17%) patients (Figure 1). The superior Angle between body of CS and ostia (take-off angle) in LAO cranial view was 0°-30° (horizontal) in 102 (63%) patients, 31°-60° (intermediate) in 45 (27%) patients and > 60° (sharp angulation) in 16 (10%) patients (Figure 2). Significant posterior indentation in RAO cranial view was seen in 5 patients. Presence of a thebesian valve (directing inferior border of flow into RA superiorly as seen in LAO cranial view) was present in 21 cases. Two or more PLV were present in 8 patients while PLV was absent in 52 (32%) patients. The diameter of the largest PLV was 4.1 mm. Angle of take-off of PLV with body of CS was favourable in 65 (40%) patients (0°-45°). The angle was 45°-90° in 36 patients and difficult take-off angle (> 90°) was seen in 8 patients. Extension or length of largest PLV (from base to apex) was assessed in RAO cranial view. Base to apex length was equally divided into 3 equal parts-proximal, mid and distal one third. It reached distal third in 84 patients, up to mid third in 11 patients and remained in proximal third in 5 patients. No bends were seen in PLV in 79 cases. There was single bend in 29 cases and more than 2 bends in 4 cases. 39 (24%) patients had other veins supplying posterior/lateral wall of LV. There was a single vein supplying lateral/posterior wall in 31 (19%) patients.

Diameter of the middle cardiac vein (MCV) was significantly larger in patients with absent PLV, compared to patients with a PLV. The mean diameter of MCV in patients without a PLV (n = 52) was 4.9 mm (SD 1.7), the mean diameter of patients with a PLV (n = 112) was 3.3 mm (SD 1.5), P = 0.000291. Similarly, diameter of the anterior inter-ventricular vein (AIV) was larger in patients with absent PLV compared to patients with a PLV. Mean diameter of AIV in patients without PLV was 3.3 mm (SD 1.2), the mean diameter of AIV in patients with a PLV was 2.6 mm (SD 1.3). However, the difference did not reach statistical significance (P = 0.076).

Of the 13 cases in which no suitable vein was visible, aberrant origin of left circumflex coronary artery (LCX) *via* the right sinus was detected in retrospect in 1 patient. Five patients had severe CAD involving the LCX, one patient had severe disease involving both the distal right coronary artery (RCA) and the LCX. The MCV was larger than 6 mm in 3 patients, The AIV was > 5 mm in 1 patient. No cause could be found in 2 patients.

Severe CAD involving the arterial supply of the posterior lateral wall of LV was present in 23 out of 50 (46%) patients with an absence of PLV, compared to 18 out of 100 (18%) patients with a PLV (Relative Risk (RR) = 2.55; P value 0.0086). Other findings included separate opening of the PLV into the RA in 1 patient. PLV opening near the ostia of the coronary sinus seen in 6 patients.

DISCUSSION

In our observational study of levophase of coronary angiograms, we analysed coronary venous anatomy for the purpose of cardiac resynchronization therapy (CRT) LV lead placement. Coronary sinus lead placement for resynchronisation therapy is required at all ages, and younger patients of dilated cardiomyopathy are a common subgroup. There is no sex predilection for dilated cardiomyopathy. In our study the median age was 56 years. Sex ratio was 2.5:1 (male:female). Age and sex distribution of the study is characteristic of the patient population seeking treatment at our tertiary care centre. This phenomenon is known to skew data of studies conducted in developing countries. There is a strong referral bias; female patients are more likely not to reach a tertiary care centre for treatment. The sex ratio in similar studies carried out in the western countries were 0.8:1 in a study of retrograde balloon occlusion venography by Mischke *et al*, and 1.2:1 in a study of levo-phase coronary angiograpy by Gilard *et al*[11,12]. Similarly there was no gender bias in anatomical studies of the coronary venous anatomy on human cadavers.

Nearly all cases in our study underwent coronary angiography for the evaluation and treatment of coronary artery disease. Only 11 patients had severe LV dysfunction which is present in all cases requiring CRT. Although the branching pattern can be assumed to be unaffected by the development of cardiomyopathy, there can be significant change in angle of opening of coronary ostium in cases with significant enlargement of left heart and normal sized RA and RV. Our study had too few cases of cardiomyopathy to be able to detect such a difference. The coronary sinus was adequately visualized in all cases. The borders were sharply delineated in a majority (visibility scale 3 in 74%). In the rest of the cases the borders were hazy but sufficient for the purpose of guiding the planning of LV lead implantation. Surprisingly, obesity (BMI) did not affect visibility. Because we obtained the CS anatomy in levophase in patients undergoing coronary angiography only in two views without any extreme angulation, insignificant amount of additional radiation exposure was anticipated.

The visibility of the venous system in our study was comparable to that attained by 360 slice CT study conducted by Chunjuan Sun *et al*[13]. In our study we identified a separate opening of the PLV into the RA in 1 case, and a suitable PLV opening close to the CS ostia in 6 cases. These are visualized better antegrade than retrograde as selective hooking will cause them not to be opacified. Meisel *et al*[14]

in their study on retrograde CS venography obtained optimum anatomical information in 67% of cases, compared to 92% in our study.

It is believed that retrograde occlusive venography better visualises the CS anatomy but it has its own lacunae. Some physicians use hyperaemic agents to aid visualization of CS in levophase. Arbelo E *et al* [15] compared occlusive retrograde venography with hyperaemic venous return angiography (levophase of coronary angiography). They used 200 µg of intracoronary Nitroglycerine or 60 µg of Adenosine to increase the coronary flow and thus the venous return in coronary sinus. The anatomical information obtained by both methods was adequate (100% *vs* 97.5%, respectively). Although occlusive retrograde venography is the most co mmonly employed technique, it has its own drawbacks. First, in the absence of venous anastamoses, veins with a posterior origin may not be visualized. Sometimes balloon does not provide a completely occlusive barrier, and 2 injections (distal and proximal) are then required to highlight the venous anatomy. In addition, for the opacification of the AIV, contrast medium has to be injected with the balloon inflated more distally in the GCV. This may lead to complications such as dissection of CS and heart blocks[15].

Levo-phase radiological anatomy

We utilized 2 orthogonal views viz. LAO Cranial (40°, 30°), and RAO Cranial (30°, 30°) to view the Coronary Sinus. The LAO Cranial view showed the coronary ostia clearly. This view visualizes the proximal portion of CS without foreshortening and we can also see its angulation with main body of CS. Posterior vein, PLV, lateral vein were also well differentiated in this view along with the take-off angle of the PLV with the body of the CS. However, the distal portion of the Coronary Sinus was foreshortened in this view, making it hard to differentiate an anterolateral vein from an AIV. Presence of a thebesian valve was detected by noting an upward direction of the outflow jet into the RA. The inferior border of the outflow is smooth. We found evidence of a thebesian valve in 21 cases. An obstructive thebesian valve may require an Amplatz guiding catheter to cannulate the CS ostium. Mischke K *et al*[11] in their study of coronary venous anatomy found evidence of a thebesian valve in 11 out of 100 cases. These figures are much less than those found in anatomical studies carried out by Randhawa *et al*[16] (thebesian valves seen in 50 dissections) and by Noheria *et al*[17] (309 valves seen in 643 dissections). Small sized valves visible on direct examination are of little clinical significance[15,16].

RAO cranial view showed the ostia and the proximal portion of the CS end on. The proximal portion was however foreshortened. Posterior indentation of the proximal portion of the CS before joining the main CS body was studied in this view. We found this in 5 (3%) of 164 cases. This view was most useful for showing the length of the vein, from the base of the heart (AV groove) to the apex. In our study, we divided this base to apex distance into 3 equal lengths: Proximal, mid, and distal; 81% of the PLVs extended upto the distal one third.

In some cases, the coronary venous anatomy could also be seen in other views taken during the study. The RAO caudal view was very useful in showing the branches of the MCV, which were not visible in our 2 cranial views. Having more views also helped in showing the PLV in greater detail. More bends could be seen when more views were available.

The optimal site for LV lead placement is the posterior lateral wall of the LV. Of the 164 patients in our study, 151 (92%) had a suitable vein draining the posterior lateral wall of the LV. In 112 cases this was the PLV; in another 39, other veins drained this area. A critically stenosed LCX or a super-dominant RCA were strongly associated with failure to visualize an adequate vein. In one case in which the PLV was not visualized, the patient was found to have an anomalous LCX. If dye had been injected into this anomalous vein (instead of into the LAD) a PLV would probably be seen. The PLV opacifies if dye is injected into the region (posterior lateral wall of the LV) that it drains. In most cases the artery supplying the area drained by the PLV is the LCX, in some it is a super-dominant RCA. If the LCX has flow limiting stenosis, an anomalous origin, or if there is a super-dominant RCA, the posterior lateral part of the LV does not recieve enough dye and likely remains hidden.

We found 4 cases with a very large MCV or AIV (6 mm). Patients without a PLV were found to have on an average 1.5 mm larger MCV than patients with a visible PLV ($P > 0.05$). The AIV was found to be on an average 0.7 mm larger in cases without a PLV, compared to cases with a PLV; but this did not reach statistical significance. An absent PLV was found in 52 cases in our study. In 39 of these cases, there was another vein supplying the posterior-lateral wall of the LV. The number of cases in which the PLV is absent is far greater in our study than in a similar study using levo-phase coronary angiography by Gilard *et al*[12] or in the anatomical studies on human cadavers by Randhawa *et al*[16] and by Noheria *et al*[17]. We did not count small veins (unsuited for CRT LV lead placement) in our study. Veins with a diameter of > 2 mm measured 2cms distal to its ostium were considered favourable. The larger number of cases with no PLV seen in our study, is explained when this is considered. When a PLV was present, it was generally straight with 62% having no bends. The take-off angle was generally favourable, with an unfavourable take-off seen in only 7% patients.

Non availability of a suitable branch draining the lateral or posterior LV wall is an indication for epicardial lead placement by thoracotomy. In our study, we were unable to visualize an adequate vein in 13/164 cases, although the number of cases in which it is truly absent may be lower.

We evaluated only 2 levo-phase views of left coronary angiograms in our study. Use of more views may better identify the venous anatomy. We did not study the venous tree in right coronary angiograms. Although this is not required in most cases, our study shows that visualization from left injections is poor when circumflex territory is not perfused by the left coronary artery. The technique increases total quantity of dye, and radiation during coronary angiogram, and this may be significant in very sick patients in poor general condition. We excluded such patients from our study.

We did not compare our results with retrograde occlusive venography because it may increase the contrast and radiation dose. We also did not use a hyperaemic agent (*e.g.*, nitroglycerine or adenosine) to increase coronary flow and resultant venous return in CS as used in some studies because it might cause hypotension and/or bradycardia in some patients. In addition, adenosine use may not be feasible in patients with bronchial asthma and severe obstructive pulmonary disease.

CONCLUSION

Levo-phase study of left coronary injection is effective in visualization of the coronary sinus in almost all patients undergoing coronary angiography. Visualization of postero-lateral veins is usually adequate in LAO cranial view, but the veins of interest are not well visualized in patients with occluded left circumflex artery and also in cases with very large right coronary and small left coronary artery. These patients may require levo-phase study of RCA or selective coronary sinus ostium cannulation. But broadly talking, levo-phase study of left coronary angiogram in LAO cranial view may be an useful extension of the standard coronary angiogram protocol, especially in patients with LV dysfunction or LBBB.

ARTICLE HIGHLIGHTS

Research background

Coronary sinus imaging is gaining importance due to improvement in electrophysiology techniques and wide spread use of left ventricular lead as a part of Cardiac resynchronization therapy.

Research motivation

Although standard technique is retrograde venogram, it has its own challenges.

Research objectives

To evaluate the feasibility of levophase of routine coronary angiography for studying coronary anatomy.

Research methods

We conducted a prospective observational in patients undergoing routine coronary angiography. In two angiographic views (left anterior oblique & right anterior oblique with cranial angulation), we evaluated the levophase for coronary sinus anatomy including ostial uptake, size, branches and angulation.

Research results

The levophase coronary angiography achieved good visibility in almost all patients. Most patients had a tubular coronary sinus ostia with size < 10 mm. Sharp take off between ostia and body as well tortuosity were seen only in a minority.

Research conclusions

Levophase coronary angiogram evaluation for coronary sinus anatomy is safe and highly effective.

Research perspectives

Large randomized studies are need to further substantiate the results.

FOOTNOTES

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MINIREVIEWS

COVID-19 vaccine-associated myocarditis

Michael C Morgan, Lavannya Atri, Sean Harrell, Wael Al-Jaroudi, Adam Berman

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Abstract

Myocarditis is now recognized as a rare complication of coronavirus disease 2019 (COVID-19) mRNA vaccination, particularly in adolescent and young adult males. Since the authorization of the Pfizer-BioNTech™ and Moderna™ mRNA vaccines targeting the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein, the Centers for Disease Control and Prevention (CDC) has reported 1175 confirmed cases of myocarditis after COVID-19 vaccination in individuals ages 30 years and younger as of January 2022. According to CDC data in June 2021, the incidence of vaccine-mediated myocarditis in males ages 12-29 years old was estimated to be 40.6 cases *per* million second doses of COVID-19 mRNA vaccination administered. Individuals with cases of COVID-19 vaccine-mediated myocarditis typically present with acute chest pain and elevated serum troponin levels, often within one week of receiving the second dose of mRNA COVID-19 vaccination. Most cases follow a benign clinical course with prompt resolution of symptoms. Proposed mechanisms of COVID-19 vaccine myocarditis include molecular mimicry between SARS-CoV-2 spike protein and self-antigens and the triggering of preexisting dysregulated immune pathways in predisposed individuals. The higher incidence of COVID-19 vaccine myocarditis in young males may be explained by testosterone and its role in modulating the immune response in myocarditis. There is limited data on long-term outcomes in these cases given the recency of their occurrence. The CDC continues to recommend COVID-19 vaccination for everyone 5 years of age and older given the greater risk of serious complications related to natural COVID-19 infection including hospitalization, multisystem organ dysfunction, and death. Further study is needed to better understand the immunopathology and long-term outcomes behind COVID-19 mRNA vaccine-mediated myocarditis.

Key Words: COVID-19; SARS-CoV-2; mRNA vaccine; Myocarditis; Pericarditis

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Core Tip: In this review article, we aim to synthesize the current literature surrounding coronavirus disease 2019 (COVID-19) vaccine-mediated myocarditis. COVID-19 mRNA vaccination has been associated with increased cases of myocarditis, particularly in the adolescent and young adult male population. Presentation typically occurs several days following administration of the second dose of a COVID-19 mRNA vaccination. As the world continues to vaccinate against COVID-19, understanding this vaccine-related adverse event is clinically important. Potential mechanisms are reviewed, and current clinical recommendations are discussed.

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INTRODUCTION

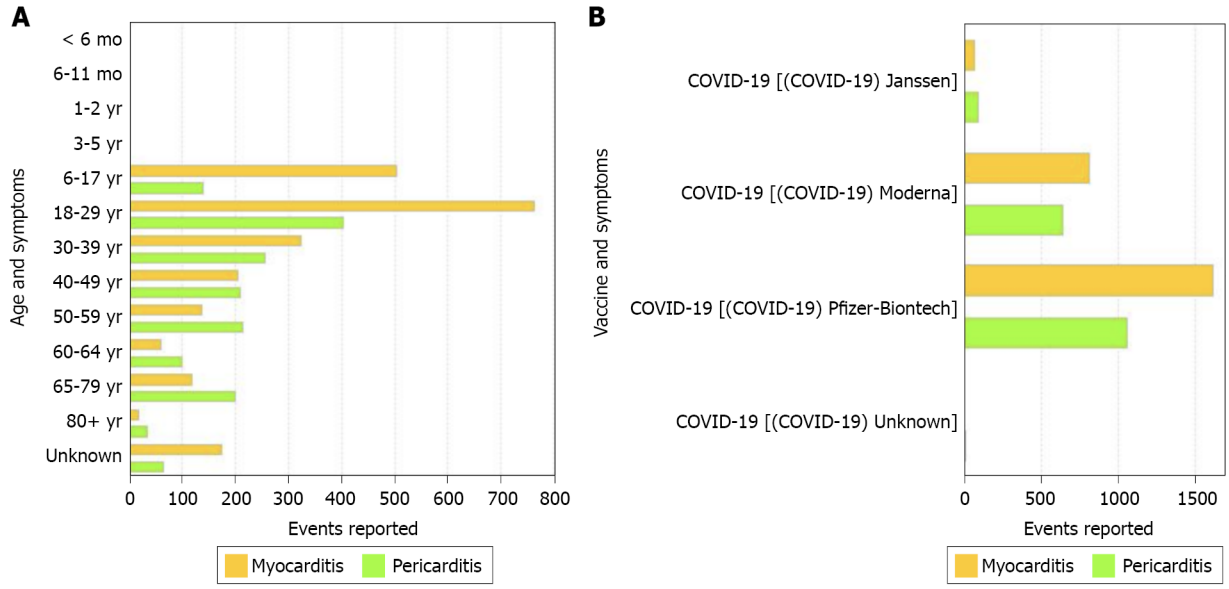
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the novel virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has impacted the entire globe and continues to spread. On December 11, 2020, the United States Food and Drug Administration granted an emergency use authorization (EUA) for the Pfizer-BioNTech™ COVID-19 vaccine in individuals 16 years of age or older. Seven days later, another EUA was released for the Moderna™ vaccine in adults 18 years of age or older[1]. Since their introduction, the mRNA vaccines against the SARS-CoV-2 virus have been highly effective in preventing both symptomatic and asymptomatic infections along with COVID-19-related hospitalizations and death[2]. Despite the great success of these vaccines, they have not come onto the public stage without controversy. In May 2021, the first case of myocarditis following mRNA vaccination was identified, and as of January 12, 2022, the Vaccine Adverse Events Reporting System (VAERS) had received 2077 reports of myocarditis or pericarditis among people ages 30 and younger who received a COVID-19 vaccine with 1175 confirmed cases[3]. This article aims to review the current literature regarding COVID-19 vaccine-related myocarditis.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

While the possibility for developing myocarditis or pericarditis following COVID-19 vaccination is concerning, it is important to emphasize that the incidence of this adverse effect is rare. Since January 2022 there have been over 502 million doses of COVID-19 mRNA vaccines administered across the United States with less than 1175 confirmed cases of myocarditis or pericarditis[3]. The primary group being impacted by this adverse event is the male adolescent and young adult population, ages 12-29[4-8]. The principal window of risk for the development of COVID-19 vaccine-mediated myocarditis appears to be within a week of receipt of the vaccine and occurs most commonly following the second dose of an mRNA vaccine[4,5,7,9]. Affected young men are predominately healthy individuals without a history of COVID-19 infection or comorbidities. Resolution of clinical symptoms usually occurs within 6 d with preservation of cardiac function, indicative of overall fast recovery with no short-term complications[4,5,8].

It is challenging to calculate the true incidence of vaccine-related myocarditis in the United States, as currently reported case series are not population-based. Based on crude data with both confirmed and unconfirmed cases reported to the VAERS, the CDC has estimated the incidence rates of myocarditis to be 40.6 cases *per* million second doses of mRNA COVID-19 vaccines administered to males between 12 and 29 years old[1]. Females in the same age group had an estimated incidence of 4.2 cases of myocarditis *per* million second doses. In adults 30 years and older, rates of myocarditis were reported as 2.4 cases *per* million second doses in males and 1.0 case *per* million second doses in females. As of December 31, 2021, VAERS has processed 4317 reported events of COVID-19 vaccine-associated myocarditis and pericarditis across all age groups with the highest number of cases reported for both myocarditis and pericarditis in the age group 18-29 (Figure 1A)[9].

Investigators from Israel queried the database of the largest Israeli healthcare organization that contains data related to 2.5 million vaccinated individuals. They determined that post-vaccine myocarditis had an estimated incidence rate of 2.13 cases [95% confidence interval (CI): 1.56-2.70] *per*



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Figure 1 Coronavirus disease 2019 vaccine-mediated myocarditis and pericarditis cases reported to Vaccine Adverse Event Reporting System. A: Age. A total of 4317 events of myocarditis and pericarditis after receiving coronavirus disease 2019 (COVID-19) vaccine were reported to Vaccine Adverse Event Reporting System (VAERS) as of December 31, 2021. Age group 18-29 had the highest number of cases reported for myocarditis (763 cases) as well as pericarditis (404 cases). Adapted from centers for disease control and prevention (CDC) WONDER and VAERS which is updated weekly for continuous updates including revisions and new reports for preceding time periods[9]; B: Vaccine manufacturer. A total of 2512 cases of myocarditis and 1805 cases pericarditis after receiving COVID-19 vaccine were reported to VAERS as of December 31, 2021. Pfizer-BioNTech™ had the highest number of cases reported for myocarditis (1615 cases) as well as pericarditis (1063 cases). Adapted from CDC WONDER and VAERS which is updated weekly for continuous updates including revisions and new reports for preceding time periods[11]. COVID-19: Coronavirus disease 2019.

100000 individuals who had received at least one dose of the Pfizer-BioNTech™ vaccine[10]. Additionally, the incidence increased to 10.69 cases *per* 100000 individuals (95%CI: 6.93-14.46) among males between 16 and 29 years old.

To compare the three types of vaccines, a systematic review of 6 case reports and 2 case series with a total of 15 patients reported that 60% of the myocarditis-related COVID-19 vaccine cases were associated with the Pfizer-BioNTech™ vaccine, 33% were associated with the Moderna™ vaccine, and 7% were associated with the Johnson & Johnson™ vaccine[5]. Similarly, as of December 31, 2021, VAERS indicated Pfizer-BioNTech™ had the highest number of cases reported for myocarditis and pericarditis, 1615 and 1063 cases respectively (Figure 1B)[11]. The clinical presentation of post-vaccine myocarditis is similar to other forms of myocarditis, most commonly featuring acute chest pain combined with other symptoms such as shortness of breath, fever, and palpitations[6,8,9,12,13]. Evidence of myocardial injury *via* serum troponin elevations was present in all cases. Electrocardiogram (EKG) findings were varied but often showed ST segment elevations. Echocardiogram findings ranged from preserved ejection fraction to varying degrees of wall motion abnormalities. When cardiac magnetic resonance imaging (MRI) was performed, findings were consistent with acute myocarditis with late gadolinium enhancement being the most commonly cited abnormality. Figure 2 displays a cardiac MRI consistent with myocarditis following COVID-19 vaccination in a 21-year-old male. Notably, most cases resulted in normalization of symptoms, troponin levels, and EKG/echocardiogram abnormalities upon discharge or at follow-up (Table 1). The CDC Vaccine Safety Technical Work Group Report on August 30, 2021, reviewed 98 cases with chest pain, pressure, and discomfort of which 56% of the cases met confirmatory criteria for myocarditis within 0-21 d of vaccination with elevated troponin, abnormal EKG findings, and abnormal MRI commonly found. It was determined that all of these included cases were discharged home, with 76% of them being discharged within 0-2 d[14].

POTENTIAL MECHANISMS OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

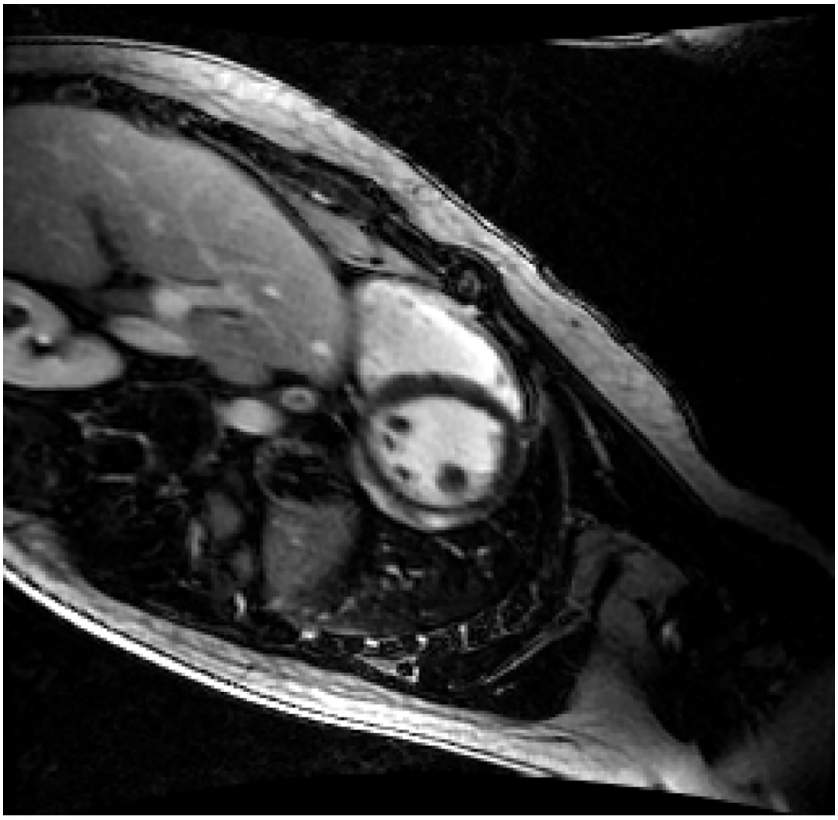
The mechanism underlying COVID-19 vaccine-mediated myocarditis is poorly understood. SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA encoding for the virus's spike protein encapsulated in lipid nanoparticles which aid in delivery of the mRNA into the cell. The cell then produces the spike protein, and a subsequent adaptive immune response ensues generating antibodies against the spike protein. The nucleoside modification of the mRNA aids in reducing the mRNA's immunogenicity, however in some individuals with an unknown genetic predisposition, exposure to

Table 1 Summary of coronavirus disease 2019 vaccine-associated myocarditis studies

Ref.	Study design	Sample size	Main findings	Analysis
Salah and Mehta[5], 2021	Systematic review of 6 case reports and 2 case series with a total of 15 patients	15 individuals who developed myocarditis following a COVID-19 vaccine, regardless of the type or dose of the vaccine	(1) 60% of the myocarditis related COVID-19 vaccine cases were associated with the Pfizer-BioNTech™ vaccine, 33% were associated with the Moderna™ vaccine, and 7% were associated with the Johnson & Johnson™ vaccine; (2) All the myocarditis related to the Moderna™ vaccine (5/5) occurred following the second dose of the vaccine, whereas 6/9 (66.7%) of the myocarditis related to the Pfizer-BioNTech™ vaccine occurred following the second dose of the vaccine; (3) Peak cardiac troponin I level (ng/mL) was reported in 13/15 patients, and it ranged between 0.37 and 51.37 ng/mL (mean 12.9 ng/mL). Peak troponin T levels were reported in the other 2/15 patients and were 854 ng/L and 1693 ng/L; (4) Transthoracic echocardiogram in all these patients showed preserved LVEF; exact LVEF value was reported in 13/15 patients with a mean LVEF of 53.5% and a range of 48% to 65%. In the other 2/15 patients, the LVEF was reported as normal with no value; (5) There were no regional wall abnormalities in 14/15 of the patients; 1 patient had subtle apical septal and apical lateral hypokinesis with a LVEF of 52%; and (6) All patients recovered within 6 d of their presentation with complications reported	(1) Myocarditis related to COVID-19 vaccines mostly occurs in young male individuals following the 2nd dose of the vaccine; (2) Myocarditis related to COVID-19 vaccines mostly occurs with mRNA vaccines (*i.e.*, Pfizer-BioNTech™ and Moderna™ COVID-19 vaccines); (3) In all the reported cases of myocarditis related to COVID-19 vaccine, clinical symptoms resolved within 6 d with preservation of the cardiac function; and (4) No complications were reported in any of these patients showing that myocarditis related to COVID-19 vaccine has an overall fast recovery with no short-term complications
Mevorach *et al*[4], 2021	Retrospective review of myocarditis cases from the Israeli Ministry of Health database between December 2020 and May 2021	142 Israeli patients diagnosed with myocarditis within 21 d of receiving the first dose of Pfizer-BioNTech™ vaccine or 30 d of receiving the second dose	(1) In the 136 cases of definite or probable myocarditis with recent vaccination, the clinical presentation in 129 was generally mild, with resolution of myocarditis in most cases, as judged by clinical symptoms and inflammatory markers and troponin elevation, electrocardiographic and echocardiographic normalization, and a relatively short length of hospital stay; one fulminant case was fatal; (2) As compared with the expected incidence of myocarditis based on historical data, the standardized incidence ratio was 5.34 (95%CI: 4.48-6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 yr (13.60; 95%CI: 9.30-19.20); and (3) Definite or probable cases of myocarditis among persons between the ages of 16 and 19 yr within 21 d after the second vaccine dose occurred in approximately 1 of 6637 male recipients and in 1 of 99853 female recipients	(1) There was a slight increase in the incidence of myocarditis after the Pfizer-BioNTech™ vaccine, particularly after the second dose among young male recipients; and (2) The incidence of myocarditis after two doses of the Pfizer-BioNTech™ mRNA vaccine was low but higher than the incidence among unvaccinated persons and among historical controls, driven primarily by young males after receiving their second dose
Rosner *et al*[6], 2021	Case series of 7 patients hospitalized for acute myocarditis-like illness after COVID-19 vaccination from 2 United States medical centers	Seven males, all < 40 years old	(1) Six patients received an mRNA vaccine (Moderna™ or Pfizer-BioNTech™), and 1 received the adenovirus vaccine (Johnson and Johnson™); (2) All patients presented 3 to 7 d after vaccination with acute onset chest pain and troponin elevations; EKG varied from normal to 1 mm ST segment elevations; Echocardiograms showed left ventricular ejection fraction ranging from 35% to 62%, with 5 of 7 having some degree of hypokinesis; (3) Multifocal subepicardial late gadolinium enhancement was present in 7 of 7 patients and additional midmyocardial late gadolinium enhancement was found in 4 of 7 patients; and (4) Treatment included β-blocker and anti-inflammatory medication. Hospital length of stay was 3 ± 1 d, and all patients' symptoms resolved by hospital discharge	(1) There is a potential causal association with vaccination given the temporal relationship, clinical presentation, and cardiac magnetic resonance imaging findings; (2) Vaccine-associated myocarditis appears to have a favorable clinical course; and (3) The benefits of vaccination outweigh the risks of vaccine-related myocarditis in younger adults given the potential morbidity of COVID-19 infection
Dionne *et al*[7], 2021	Case series of 15 adolescents at single United States center	15 adolescents ages 12-18 years old hospitalized with myocarditis after receiving Pfizer-BioNTech™ COVID-19 vaccine	(1) 14 children were male, and 1 child was female; (2) Symptoms started 1-6 d following vaccine administration (14 of 15 occurring after second dose); common symptoms included chest pain, fever, myalgia, and headache; (3) Elevated troponins found in all 15 cases; (4) Cardiac MRI findings were consistent with myocarditis in 13 patients, with 12 patients showing evidence of late gadolinium enhancement; (5) No patients required intensive care and the median length of hospital stay was 2 d (range 1-5 d); and (6) At 1-to-13-d follow-up after hospital discharge, 11 patients had full resolution, 1 patient had persistent borderline low LV systolic dysfunction (EF = 54%), 3 patients had mildly elevated troponins, 1 patient had nonsustained ventricular tachycardia on ambulatory monitor	(1) Following Pfizer-BioNTech™ vaccination, most cases of myocarditis were diagnosed in male children after the second dose; (2) All patients had a benign clinical course; and (3) Long-term risks of post-vaccine myocarditis in the child population remains unknown

COVID-19: Coronavirus disease 2019; MRI: Magnetic resonance imaging; EKG: Electrocardiogram; LVEF: Left ventricular ejection fraction.

the mRNA may result in an overactivated immune response *via* dendritic cells and Toll-like receptors of the innate immune system leading to proinflammatory immune cascades and cytokine activation[15]. This inflammatory response is thought to play a role in COVID-19 vaccine-associated myocarditis. The role of mRNA in the development of vaccine-mediated myocarditis is further supported by the evidence that the incidence of myocarditis occurs at a much higher rate following mRNA vaccination compared to the adenovirus vector vaccine of Johnson and Johnson™[4].



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Figure 2 Cardiac magnetic resonance imaging of coronavirus disease 2019 vaccine-associated myocarditis. Cardiac magnetic resonance imaging slice of a 21-year-old male six days after receiving his second dose of the Moderna™ mRNA coronavirus disease 2019 vaccination showing evidence of significant diffuse late gadolinium enhancement and myocardial edema consistent with myocarditis.

Another potential mechanism for COVID-19 vaccine myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens. Antibodies of the SARS-CoV-2 spike protein have been shown to cross-react with human proteins of similar structure including α-myosin in experimental studies[16]. It appears more likely that the immune-mediated adverse effects of mRNA vaccination are due to the triggering of preexisting dysregulated pathways in certain predisposed individuals rather than the inherent immunogenicity of the vaccine itself[15]. Polymorphisms in interleukin-6 have been suggested as an important genetic component for determining autoinflammatory dysregulation that may ensue upon exposure to SARS-CoV-2, however further study is needed to elucidate these theories [17].

Young men have been found to be most susceptible to the development of myocarditis outside the setting of COVID-19 vaccination as well. Kytö *et al*[18] have presented evidence that testosterone appears to play a major role in the pathogenesis of myocarditis identifying testosterone-mediated mechanisms such as inhibition of anti-inflammatory cell populations promoting cardiac inflammation, a preference towards a Th1 immune response, and increased transcription of cardiac fibrotic remodeling genes[18]. Conversely, estrogen appears to play a protective role *via* the preference of a Th2 immune response, stimulation of inhibitory regulatory T cells, and inhibition of proinflammatory T cells[18]. These mechanisms may contribute to why the young male population has the highest incidence of post-vaccine myocarditis.

COVID-19 VACCINE ASSOCIATED MYOCARDITIS IN CHILDREN AND ADOLESCENTS

Cases of myocarditis have also been reported in the childhood population since the Pfizer-BioNTech™ COVID-19 vaccine was authorized for emergency use on May 10, 2021, for children ages 12 and older. A case series of 15 adolescents who developed myocarditis following administration of the Pfizer-BioNTech™ vaccine found that, similar to the adult population, the most commonly affected group were young males ages 12-18 years old following administration of the second dose[7]. All patients in this study had an uncomplicated short-term clinical course, however the long-term prognosis of these adolescent patients remains unclear, emphasizing the importance of continued follow-up and monitoring.

A case series published by Marshall *et al*[19] reported myocarditis or pericarditis in 7 male adolescents ages 14-19 years old, all within 4 d of receiving the second dose of the Pfizer-BioNTech™ COVID-19 vaccine[19]. All 7 patients presented with elevated troponin levels. ST segment elevation was the most common EKG and was observed in 6/7 individuals. Echocardiogram results were normal in 5 of 7 patients; however, all patients had cardiac MRI findings consistent with acute myocarditis. Investigatory studies for other etiologies of myocarditis including respiratory pathogen panels, serum polymerase chain reaction (PCR) tests, and infectious serologies all returned negative, and multisystem inflammatory syndrome in children was excluded based on cardiac MRI findings.

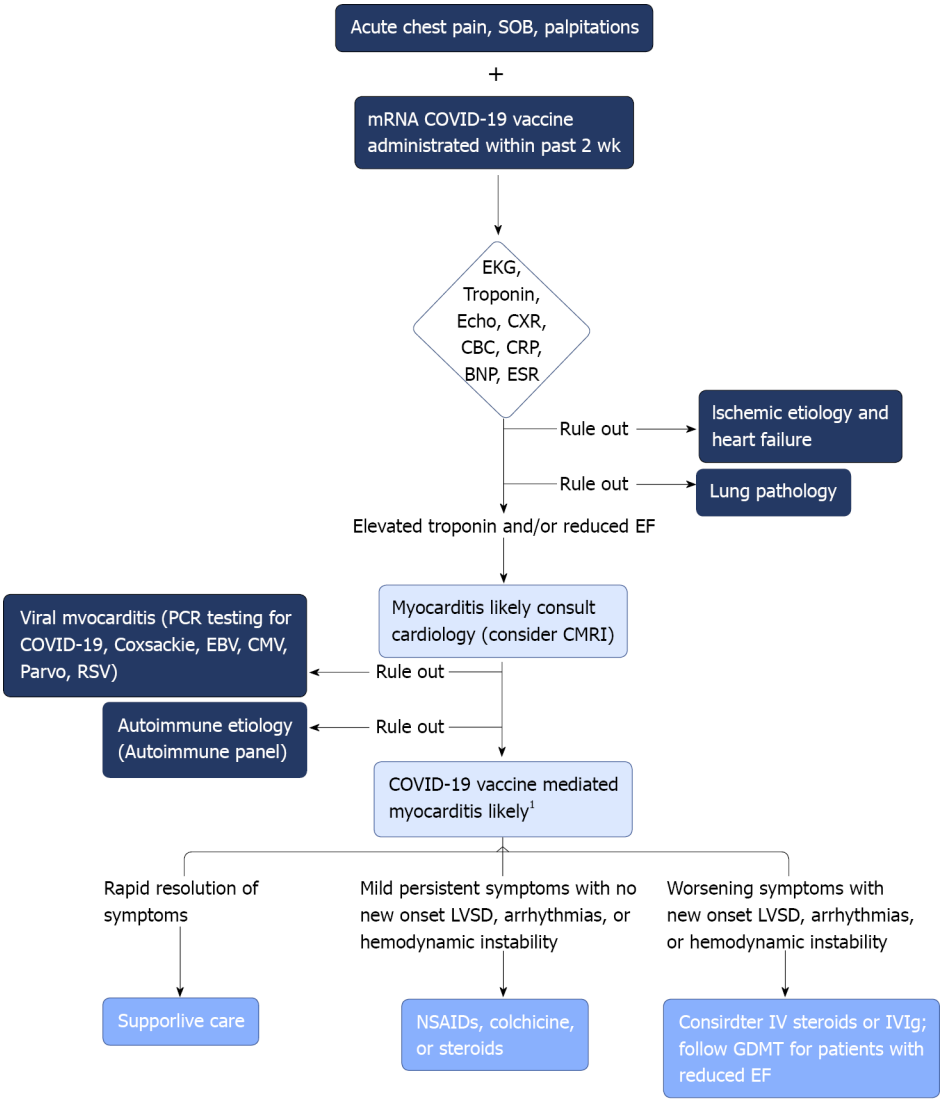
EVALUATION AND MANAGEMENT OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

Given the increased incidence of myocarditis following mRNA vaccination in adolescent and young adult males, clinicians should have a high index of suspicion for myocarditis in this demographic who present with symptoms such as acute chest pain, shortness of breath, or palpitations. Initial evaluation should include obtaining an EKG, serum troponin levels, complete blood count with differential, chest x-ray, inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate, brain natriuretic peptide, and an echocardiogram (Figure 3). If this initial workup supports a diagnosis of myocarditis, cardiology consultation should take place in conjunction with studies seeking to determine potential alternative etiologies of myocarditis. Consultation with infectious disease and/or rheumatology may also be considered to aid in this process[20]. PCR testing for acute COVID-19 infection and SARS-CoV-2 antibody testing for prior COVID-19 infection are of particular importance. Obtaining enterovirus PCR along with a respiratory pathogen panel can assist in ruling out other potential viral etiologies (*e.g*. Coxsackievirus, Epstein-Barr virus, cytomegalovirus, respiratory syncytial virus, parvovirus) and autoimmune serologies such as antinuclear antibodies may be indicated depending on clinical presentation. Cardiac MRI may be utilized to aid in diagnosing suspected myocarditis without the need for obtaining invasive endomyocardial biopsy.

The clinical management of COVID-19 vaccine-mediated myocarditis is largely supportive, and patients frequently exhibit rapid resolution of symptoms and normalization of cardiac biomarkers. Those with persistent mild symptoms and no signs of arrhythmia, left ventricular systolic dysfunction, or hemodynamic instability may benefit from therapy with nonsteroidal anti-inflammatory drugs, colchicine, or steroids. In more serious cases of myocarditis, such as those patients showing signs of hemodynamic instability, new-onset arrhythmia, or worsening systolic dysfunction, intravenous steroids or intravenous immunoglobulin may be considered[15]. Patients with reduced ejection fraction should be placed on beta-blockers and angiotensin-converting enzyme inhibitors according to guideline-directed medical therapy. The majority of cases from prior reports resulted in a resolution of symptoms and abnormal cardiac studies prior to discharge following a short hospital stay with supportive care or a short course of nonsteroidal anti-inflammatory. Close monitoring and avoidance of strenuous exercise until a complete resolution of symptoms and normalization of cardiac biomarkers, EKG, and echocardiogram is an important measure, especially in the young age group who may be eager to return to a normal exercise routine. If a patient develops myocarditis following a first dose of mRNA vaccination, the CDC recommends the second dose be delayed and reconsidered later following the complete resolution of signs and symptoms[20]. Of note, there are currently no randomized controlled trials examining the management of post-vaccine myocarditis which highlights the importance of the inclusion of cardiovascular specialists in the management and follow-up of these patients.

The concerted efforts of the biomedical community to develop safe and efficacious vaccinations in such a short time frame have been extraordinary. SARS-CoV-2 virus mRNA vaccines have been tremendously successful in curtailing the morbidity and mortality associated with COVID-19[21]. Healthy adolescents and young adults are not immune to serious complications from COVID-19 infection and rising adolescent hospitalization rates from COVID-19 infection have been observed[22]. Despite media attention regarding adverse effects of these vaccines, it is important to emphasize the low incidence in which these events occur. The benefits of vaccination to prevent both the spread and possible complications of COVID-19 infection including hospitalization, multisystem organ dysfunction, and death far outweigh the potential risk of post-vaccine myocarditis while this global pandemic persists.

The diagnosis of myocarditis is a serious one as cardiac myocytes do not regenerate, and an insult at a young age can lead to an increased risk of developing cardiac disease later on in life[23]. While myocarditis has been linked to COVID-19 mRNA vaccination, it is important to compare the risk of developing myocarditis following vaccination to the risk following natural COVID-19 infection. A large study in Israel used data from the nation's largest healthcare organization to determine the risk of myocarditis following vaccination after adequately matching vaccinated individuals to unvaccinated individuals[24]. 42 d after vaccination, they found a risk ratio of 3.24; 95%CI: 1.55-12.44, and a risk difference of 2.7 events *per* 100000 persons; 95%CI: 1.0-4.6. To put this in context, they then determined the risk of myocarditis among SARS-CoV-2 infected individuals matched to uninfected individuals.



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Figure 3 Clinical decision-making algorithm for diagnosis and management of suspected coronavirus disease 2019 vaccine-associated myocarditis. [1]All cases should have monitoring with close cardiology follow up. Initial evaluation should include a basic workup in addition to ruling out other etiologies that can present similarly. Early cardiac consultation should occur for suspected coronavirus disease 2019 vaccine myocarditis along with close cardiac monitoring and follow-up. SOB: Shortness of breath; EKG: Electrocardiogram; Echo: Echocardiogram; CXR: Chest x-ray; CBC: Complete blood count; CRP: C-reactive protein; BNP: Brain natriuretic peptide; ESR: Erythrocyte sedimentation rate; CMRI: Cardiac magnetic resonance imaging; EBV: Epstein-barr virus; CMV: Cytomegalovirus; Parvo: Parvovirus; RSV: Respiratory syncytial virus.

COVID-19 infection was associated with a much higher risk of myocarditis with a risk ratio of 18.28; 95%CI: 3.95-25.12 and a risk difference of 11.0 events *per* 100000 persons; 95%CI: 5.6-15.8[24]. This large-scale study supports the notion that the risk of myocarditis is much higher in the setting of natural COVID-19 infection compared to myocarditis following vaccination. Given the widespread transmissibility of this virus, it stands to reason that an individual should receive a vaccine to safeguard against the increased risk of myocardial injury associated with COVID-19 infection.

Underreporting of myocarditis in the adolescent and young adult male population is possible, as there may be a low index of suspicion in this relatively healthy age group. Mild cases of post-vaccine myocarditis are likely to go unreported as there is currently no routine screening protocol in place. However, as public awareness of post-vaccine myocarditis continues to grow, there may also be a potential for overreporting as well, emphasizing the need for effective surveillance systems to confirm suspected cases.

Based on the current available data, the CDC is continuing to recommend that patients aged 5 years and older be vaccinated against COVID-19, stating that the known risks and potential complications associated with COVID-19 infection far outweigh the rare chance of developing an adverse reaction to vaccination including myocarditis. Vaccine-mediated myocarditis has a low incidence, and while clinicians should be vigilant for its occurrence, this adverse effect should not deter vaccination efforts during this pandemic based on current data. Continued monitoring and reporting to the Vaccine

Adverse Event Reporting System is strongly encouraged. Additional guidance from the American Heart Association for follow-up of patients with myocarditis emphasizes the use of cardiac MRI to examine the heart *in vivo*[25].

One of the major limitations of many of the studies describing post-vaccine myocarditis is the lack of follow-up data given the recency of vaccine approval and administration. There is minimal long-term data available to date which limits our ability to interpret long-term outcomes of patients who receive a diagnosis of COVID-19 vaccine-associated myocarditis. However the availability of long-term data will accumulate with time. Additionally, many of these studies were case reports compiled *via* colleague communication rather than surveillance systems which allow for more complete diagnostic evaluation to exclude other potential etiologies of myocarditis. Many of the cases reported were presumed to be a result of the COVID-19 vaccine purely based on temporal association. While feasible, this assumption might result in the overestimation of myocarditis as a result of COVID-19 vaccination. Similarly, many studies used negative antibody tests to rule out active or prior COVID-19 infection which could be problematic due to false negatives or waning immunity.

With third dose eligibility for the Pfizer-BioNTech™ and Moderna™ mRNA vaccines recently expanding to include much of the adult general public, careful prospective observation of the rate of vaccine-mediated myocarditis following the third dose compared to rates following the second dose is needed. While there is limited data currently available, data obtained by the Israel Ministry of Health have reported lower rates of myocarditis following the third dose compared to the second dose. Proactive surveillance efforts have discovered 17 total myocarditis/perimyocarditis cases among ages 16-59 years following administration of over 2.5 million third doses of the Pfizer-BioNTech™ mRNA vaccine[26].

CONCLUSION

Vaccine-mediated myocarditis following vaccination against COVID-19 using mRNA vaccines is a rare, but potentially serious occurrence. Clinicians should be aware of the potential development of vaccine-mediated myocarditis, particularly in young males. Early consultation with cardiologists and further investigation *via* serum biomarkers and imaging with cardiac MRI may confirm the diagnosis. Long-term follow up of those patients developing vaccine-mediated myocarditis is necessary to assess the potential for chronic complications of this rare phenomenon. Despite the potential for vaccine-mediated myocarditis, vaccination continues to be recommended against COVID-19 in all eligible populations.

FOOTNOTES

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MINIREVIEWS

Heart failure in general and cardiac transplant patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is primarily an infection of the respiratory tract, but it can have multisystem manifestations. Cardiac complications of COVID-19 can range from acute myocardial injury, cardiac arrhythmias, or heart failure, amongst others. Heart failure (HF) in COVID-19 can be a de novo process or due to worsening of pre-existing cardiovascular ailment. HF in a patient with COVID-19 not only poses challenges in clinical presentation and management of COVID-19 but also affect prognosis of the patient. This article aims to succinctly revisit the implications of this pandemic regarding pre-existing HF or new-onset HF based on prevailing data. It also focuses on the management and special recommendations from prior studies and guidelines.

Key Words: COVID-19; Coronavirus; Cardiomyopathy; Heart failure; Cardiomyopathy

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Core Tip: The mini-review is composed of assimilation of guidelines and current literature recommendations for managing heart failure in coronavirus disease 2019 (COVID-19) patients. We discuss many important aspects of heart-failure in COVID-19 from epidemiology to post recovery rehabilitation.

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INTRODUCTION

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected all continents. The case count of coronavirus disease 2019 (COVID-19) continues to soar to-date, as evident by more than 300 million global caseloads[1]. COVID-19 typically presents as a respiratory tract infection, but we have witnessed it herald a multisystem disorder in a lot of patients, including but not limited to the cardiovascular system. Cardiac manifestations of COVID-19 can be broad, and symptoms generally stem from myocardial injury, cardiac arrhythmias, cardiogenic shock, heart failure (HF), or sudden cardiac death[2-5]. This article attempts to provide a brief review of all the major topics related to heart failure and covid-19 from epidemiology, diagnostic tools to the important management options, and post-recovery rehabilitation. It gives insights on breakthrough vaccination and cardiac complications post COVID-19. It attempts to touch on treatment options in various situations encountered while treating heart failure patients.

EPIDEMIOLOGY

An accurate incidence of HF in COVID-19 is difficult to determine as there are not abundant definitive data on it. HF in COVID-19 can be due to worsening of preexisting known or undiagnosed heart disease. Besides, it could also be a new onset HF due to hemodynamic stress, ischemic cardiomyopathy, or nonischemic cardiomyopathy. Available studies have not always clearly discerned a new-onset HF from worsening of chronic HF. As evident in Table 1, HF was present at baseline in up to 23% of cases while up to 7% of patients with COVID-19 had a new-onset HF as a complication of the infection[6-9]. However, we must bear in mind that there seems to be a wider range in these data reported. The other caveat is that not all studies have clearly demarcated the incidence and acuity of pure right heart failure from left heart failure to biventricular loss. Creel-Bulos C *et al*[10], described five patients with acute right HF in their case series from March 23 to April 4, 2020, in an intensive care unit in Georgia, United States. With the progression of the pandemic, Corica *et al*[11] conducted a combined pooled analysis of 3813 patients and found to have right HF in as high as 20.4% of patients with COVID-19.

ETIOPATHOLOGY

Two types of mechanisms for myocardial injury are described in prior literature. ie direct or specific and indirect effects[24].

SARS-CoV-2 directly attaches to the ACE2 on the myocardium and causes cell damage and death. It also decreases the protective and anti-inflammatory properties of ACE2 on the myocardium through its downregulation.

Sympathetic activity causing Tachycardia from underlying infection, prolonged immobility causing coagulopathy, hypoxemia, hemodynamic changes are indirect effects worsening the cardiac status[24]. Severe inflammatory response causing surge of cytokines like Interleukins, Tumor necrosis factor, interferons' play a major role in the pathogenesis of pulmonary and myocardial damage leading to acute respiratory distress syndrome (ARDS) and various cardiac complications[25]. It can precipitate new cardiac failure and worsen the course in underlying failure patients[25].

Pre-existing HF can exacerbate during COVID-19, as evident in other viral illnesses such as Influenza [15]. Stress cardiomyopathy, vasculitis, thrombosis of coronary arteries, fissuring, and rupture of atheromatous plaque leading to acute myocardial ischemia can be some of the ischemic and nonischemic causes of acute cardiomyopathy and subsequent HF[16,17]. One study evaluated that cardiogenic shock resulting from myocardial injury occurred in up to 10% of patients in shock and can result in worse prognosis compared to hypovolemic or distributive shock in COVID-19 patients[26]. 48% of patients had normal Ejection fraction and low cardiac index shock from low end diastolic volumes which was

Table 1 It shows data on incidences of acute, chronic heart failure, and acute heart failure

Ref.	Study type	Country of origin	Incidences
Zhou *et al*[6], 2020	Retrospective cohort study	China	Total patients 191. deceased 54 patients (28 had chronic hf exacerbation, *i.e.*, 52%) survived 137 patients (16 had chronic hf exacerbation, *i.e.*, 12%) $P < 0.0001$
Arentz *et al*[7], 2020	Case series	United states	Total patients 21. nine patients (42.9%) acute on chronic hf
Ruan *et al*[8], 2020	Multicenter retrospective analysis	China	Total patients 150. death 68 acute on chronic hf 5 (7%)
Shis *et al*[9], 2020	Single-center cohort jan 2020 - feb 2020	China	Total patients 416. new-onset heart failure 4.1%
Chen *et al*[12], 2020	Retrospective study	China	Total patients 274. acute on chronic hf 1 (< 1%) new-onset hf 21 (7.7%). 1 recovered and 20 died
Inciardi *et al* [13], 2020	Retrospective study	Italy	Total patients 99. acute on chronic hf 21 (21%)

due to use of Peak end expiratory pressures and mechanical ventilation causing decreased venous return. Cytokine storm detailed above can result in distributive shock[26]. Pulmonary embolism from coagulopathy and pericardial tamponade can cause obstructive shock which are reported in COVID-19. Worsening of chronic kidney disease or onset of acute kidney injury leading to volume overload has been reported in up to 29% of patients with COVID-19 and chronic HF[6,18].

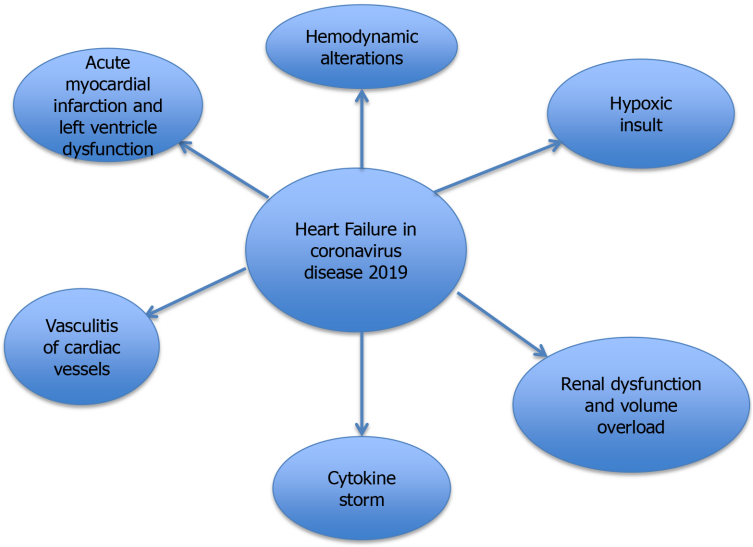
Acute right heart failure (RHF) in COVID-19 has been primarily thought to be due to ARDS and severe hypoxemia. RHF due to acute pulmonary embolism has also been reported in 5%-22% of cases by different authors[19,20]. High clot burden was also found in patients with right heart strain from pulmonary embolism[21]. Patients with COVID-19 are several times at higher risk of pulmonary embolism compared to non-COVID-19 patients and is also associated with higher mortality[20]. Severe Acute Respiratory distress syndrome may lead to pulmonary hypertension and cause right-sided heart failure. Myocardial injury and myocarditis can also weaken the right heart ventricle in COVID-19. Right heart failure in COVID-19 is associated with increased mortality[22,23] Etiopathology of HF in COVID-19 has been summarized in inline diagrams in Figures 1 and 2.

Clinical evaluation and utility of diagnostic tools

Symptoms of HF, in general, can be due to reduced cardiac output causing fatigue and weakness. It could also be due to excessive fluid accumulation resulting in dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, and edema. Patients in cardiogenic shock could have a low cardiac output state. Overall, it can be difficult to accurately distinguish most of the symptoms of HF from COVID-19 itself, so careful examination and use of diagnostic tools are imperative. Signs of fluid overload like weight gain, Jugular venous distension, fine crackles at lung bases, wheezing, third heart sound, abdominal distension, ascites, and pitting pedal edema can be used as important clues at the bedside to determine new-onset or exacerbation of HF in COVID-19 patients.

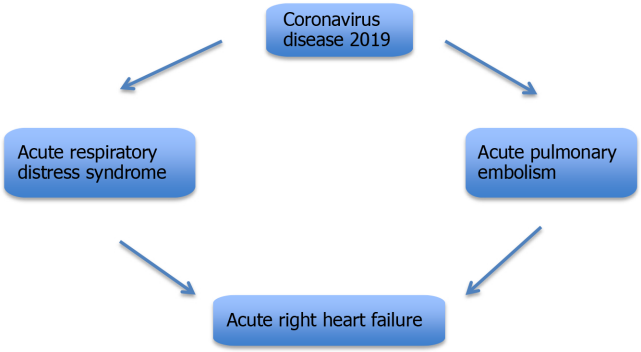
Plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro BNP) are useful laboratory markers in suspected HF. High sensitivity troponins (hs-cTn) are often elevated as a marker of myocardial inflammation[16]. BNP less than 100 pg/mL and NT-proBNP less than 450 pg/mL have high negative predictive for HF[27]. Elevated plasma BNP and NT-proBNP also indicate poor prognosis in general, and this relationship holds true for HF in COVID-19 as well[28]. Elevated NT-proBNP level was detected in 12.9% of 3219 patients in a study from Wuhan, China. The adjusted hazard ratio for NT-proBNP was 5.71 (95%CI 3.50-7.47)[29]. In another study conducted on 397 patients with COVID-19 in Milan, Italy, 14.9% had elevated BNP levels, and the mortality rate was higher by 33.9% in these patients [30]. Elevation of BNP, NT-Pro BNP or troponin, hs-cTn should be interpreted with caution. It should not trigger evaluation for heart failure or Myocardial infarction unless patients have accompanying signs and symptoms or EKG changes to suggest diagnosis.

Electrocardiogram (EKG) may not receive ample attention in the diagnosis of HF beyond the milieu of a cardiologist. Perhaps, it is highly unlikely that a patient with a normal EKG will have a dysfunctional left ventricle (LV). Atrial fibrillation, old myocardial infarction, left ventricular hypertrophy, axis deviation, bundle branch block, and ST-T wave abnormalities may hint towards underlying acute or chronic HF in patients with COVID-19[16]. EKG changes commonly observed in COVID-19 patients were atrial fibrillation or flutter, Premature atrial (APCs) and ventricular contractions, Bundle branch block, interventricular conduction delay, and repolarization abnormalities[31]. Abnormal EKGs changes like APCs, Right BBB/Intraventricular block, Ischemic T wave inversions, and non-specific repolarization abnormalities were associated with an increased risk of adverse cardiac events or death in patients with underlying comorbidities like cardiovascular or renal diseases[31,32].



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Figure 1 Pathogenesis of heart failure in coronavirus disease 2019.



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Figure 2 Causes of acute right heart failure in coronavirus disease 2019.

An echocardiogram is one of the most important diagnostic tools for HF. There have been some studies utilizing echocardiograms in patients with COVID-19. Szekely *et al*[33], performed an echocardiogram in 100 patients within 24 h of hospitalization with COVID-19. 32% of patients had a normal echocardiogram, 39% had right ventricle (RV) dilatation and dysfunction, 16% had LV diastolic dysfunction, and 10% had LV systolic abnormality. Reassessment with echocardiogram due to deterioration during hospital course showed worsening of RV failure in 12 patients and LV systolic failure in 5 patients[33]. In a prospective international study of 1216 patients from 69 countries, 667 patients (55%) were found to have an abnormal echocardiogram. 479 (39%) had LV dysfunction while 397 (33%) had RV dysfunction. Echocardiography findings changed management in 33% of these patients[34]. In an International multicenter study of 305 patients admitted with COVID-19, RV dysfunction was found in 26.3%, LV diastolic dysfunction in 13.2%, and LV global systolic dysfunction in 18.4% of patients. Moreover, multivariate adjustments showed that myocardial injury with abnormal echocardiograms represented higher mortality in comparison to normal echocardiograms[35]. Hence, an echocardiogram is a vital diagnostic tool that should be used by clinicians taking care of COVID-19 patients in a timely and appropriate manner. The Trans-thoracic echocardiogram has also been performed successfully among COVID-19 patients with ARDS who were in prone position by temporarily deflating the lower thoracic portion of the air mattress. This helps in placing the probe between the thorax and the mattress surface[36].

The role of cardiac magnetic resonance imaging (MRI) has been so far more relevant in patients that are on the road to recovery from acute COVID-19 illness. Because of inflammatory cardiomyopathy, some of these patients can develop HF as a sequela. In a German study of 100 patients that were in the recovery phase from acute COVID-19 illness, cardiac MRI was abnormal in 78% of patients at an average of 71 days from initial diagnosis. Compared to the control group, these patients had lower LV and RV ejection fractions. Furthermore, endomyocardial biopsy in three patients with elevated T1/T2 signal, late gadolinium enhancement, and LV ejection fraction less than 50% revealed lymphocytic infilt-

ration with no detection of the viral genome[37]. In another study of 148 patients with severe COVID-19 infection, cardiac MRI was done at a median of 68 days post-discharge from the hospital. The myocarditis-like scar was seen in 26%, and infarction was found in 54%, but 89% of these patients had normal LV function[38]. Thus, cardiac MRI and endomyocardial biopsy in selected COVID-19 patients may be of value in timely diagnosis and initiation of goal-directed medical therapy where HF arises as a late complication in subacute and chronic recovery phases (Table 2).

MANAGEMENT

Management of HF exacerbation during COVID-19 should be based on the volume status, the previous history of heart failure, and vital signs. Patients with heart failure and COVID-19 have worse hospitalization and in-hospital mortality outcomes in a systematic review and meta-analysis of 18 studies[39].

Shared decision-making among consultants is necessary to guide clinical management regarding immunosuppression, multiple treatments, multiorgan involvement, and associated complications in COVID-19.

Chronic heart failure patients have a higher risk of in-hospital complications like acute heart failure, acute renal failure, sepsis and length of stay, and in-hospital mortality[40,41].

Medications should be initiated per Guideline-directed medical therapy and continued. Special considerations exist for each class of drugs which are discussed below.

Diuretics

Diuretics in heart failure and COVID-19 help to decongest the lungs. Prior to starting diuretics, they require careful monitoring of the volume status by physical examination, BNP, and bedside ultrasound assessment for the IVC (inferior vena cava) collapsibility[42]. Pulmonary artery catheter, Echocardiography, and cardiac output monitoring are other methods for advanced hemodynamic monitoring in patients with complex hemodynamics. Conservative fluid strategy with judicious initiation or up-titration of diuretics with daily weights is recommended[43]. Aiming for a negative fluid balance is necessary for these patients. Watching for signs of hypotension and over diuresis which can result in kidney injury is necessary. Nephrotoxic medications should be used carefully along with diuretics, *i.e.*, NSAIDs, Remdesivir, or nephrotoxic antibiotics like vancomycin[42,44]. If there is diuretic resistance, then ultrafiltration can be considered to treat heart failure and AKI[42].

It was hypothesized that medications associated with upregulation of ACE2 receptors could worsen the COVID-19 infection, which was not proven in further studies. Outcomes among heart failure patients were similar regardless of ACE inhibitor or ARB use[40].

Heart failure society of America/American College of Cardiology/American Heart Association guidelines recommends against adding or discontinuing these medications beyond the standard of practice in patients with preexisting heart failure, hypertension, or ischemic heart disease. However, careful decision-making and medication discontinuation should be done in acute kidney injury, hypotension, hyperkalemia, and shock on a patient-to-patient basis[45].

Beta-blockers

Carvedilol is the recommended beta-blocker in patients with heart failure and COVID-19 due to its anti-cytokine action[46,47]. However, these medications should not be started for COVID-19 and HF beyond the standard of practice. Assessment of hemodynamic stability is necessary before the initiation of beta-blockers[42]. Patients previously on beta-blockers can have inappropriate bradycardia with COVID-19. Dose changes should be made if patients develop a low output state[45]. Betablockers also help patients with sinus tachycardia and tachyarrhythmias[45]. Antiviral medications like Remdesivir and Tocilizumab can influence the pharmacokinetics of cardiovascular medications, increasing the risk of toxicities and arrhythmias.

Digoxin

Most of the indications for digoxin in HF with reduced ejection fraction are as a rate control agent in those with low blood pressure and atrial fibrillation[48]. Digoxin has antiviral and anti-inflammatory properties per prior literature[46]. Again, there is no recommendation to start patients with new-onset HF and COVID-19 on these medications beyond clinical practice. Digoxin levels should be closely monitored when given anti-viral medications and immunomodulators that may interact with it[42].

Anticoagulation therapy

Consideration should be given for interaction between anticoagulants' current and emerging COVID-19 therapies. Monitoring the liver and kidney function is also necessary. Unfractionated Heparin or Low molecular weight heparin (LMWH) is the preferred anticoagulant in hospitalized patients with prior anticoagulation for other causes. It is particularly preferred in sick patients due to drug interactions with oral anticoagulants[45]. If oral anticoagulants are needed in less sick patients, switching to direct oral anticoagulants is preferred over Vitamin K antagonists. Prophylactic Anticoagulation with LMWH can

Table 2 A late complication in subacute and chronic recovery phases

Diagnostic tools	Likely heart failure	Likely COVID/ARDS
BNP/NT-Pro BNP and clinical findings	BNP > 100 pg/mL or NT-Pro BNP > 450 pg/mL Signs and symptoms of right and left heart failure	< 450 pg/mL Absence of signs and symptoms of volume overload
EKG	Abnormal ekg findings of LVH, LAE, Sinus tachycardia, LAD, RAD, AF, PVCs, BBB	Nonspecific findings or symptoms of pulmonary embolism, Right heart strain or myocardial ischemia
ECHO	Ejection Fraction%, RV dilatation and dysfunction, LV Diastolic dysfunction, LV global systolic dysfunction	Findings of pulmonary arterial hypertension; RV dysfunction, enlargement and abnormal contraction, septal dyskinesia. Acute Cor pulmonale
CMRI	Establishes ischemic *vs* nonischemic heart failure, quantification of ventricular function and scar burden	Distinguishes pulmonary *vs* extrapulmonary causes for acute respiratory distress syndrome

LVH: Left ventricular hypertrophy; LAE: Left atrial Enlargement; LAD: Left axis deviation; RAD: Right axis deviation; AF: Atrial fibrillation; PVCs: Premature ventricular complexes; BBB: Bundle branch blocks.

be considered in all inpatients if there is no hemorrhagic risk[49].

Mineralocorticoid receptor antagonists

Careful use in heart failure patients based on volume status and kidney function. Electrolytes should also be monitored.

Recommendations regarding guideline-directed medical therapy

Stopping GDMT, *i.e.*, Beta-blockers, ACE/ARB, and mineralocorticoid receptor antagonists in patients with chronic heart failure with COVID, are associated with increased in-hospital mortality per prior studies[50]. If GDMT therapy has been discontinued inpatient for AKI or hemodynamic instability, during discharge of patients post heart failure exacerbation, they should be restarted as they have favorable outcomes in heart failure patients[50].They should follow up with the cardiologist or physician for heart failure to review and adjust the dose of GDMT.

Ionotropic/ vasopressor medications and respiratory support

Patients with heart failure have pulmonary edema superimposed on COVID-19 pneumonia. High BNP levels elevation in patients with ARDS indicates cardiogenic shock and pulmonary edema. Use of non-invasive ventilation and prone ventilation help to decrease pulmonary edema. Heart Failure patients are susceptible to hypoxia and ARDS and therefore may require intubation and lung-protective ventilation. These methods also help to manage right heart failure from ARDS[51].

The shock from sepsis and heart failure can develop. Dehydration and hypoperfusion can worsen symptoms. Clinical assessment, bedside echo, and monitoring of hemodynamics help in assessing the pathophysiology of shock. Volume status assessment, careful use of diuretics, and intravenous fluid repletion are needed. The greatest benefit of fluid resuscitation was seen in patients with signs of hypoperfusion who are in hypovolemic shock[26]. In patients with Mixed shock (cardiogenic and septic), vasopressors or inotropes should be started.

Norepinephrine is the preferred vasopressor agent for septic and cardiogenic shock, especially in hypotensive patients[51].If there are signs of low organ perfusion or severe decreased cardiac output, inotropes such as dobutamine and epinephrine can be added[51].Cardiac output monitoring helps in the selection and titration of inotropes and vasopressors.

Bedside, Intra-aortic balloon pump should be considered in severe cardiogenic shock refractory to vasopressors or inotropes[52]. ECMO as mechanical circulatory support is used in the setting of ARDS/hypoxemia with refractory cardiogenic shock in available centers[45,51].

Myocarditis in COVID-19: Patients can present with Heart failure symptoms. Inotropes and vasopressors, mechanical circulatory support, and mechanical ventilation can be used in severe cases.

COVID-19 with HF in heart and lung transplant recipients

Heart Transplant and Heart and lung transplant recipients are on immunosuppression with medications like calcineurin inhibitors, prednisone, and antimetabolites. They are prone to COVID-19 infection from immunosuppression and can have severe symptoms and outcomes[53,54]. For patients with mild symptoms, supportive treatment with the continuation of immunosuppression is recommended.

In patients with moderate to severe illness, anti-metabolites such as azathioprine and mycophenolate mofetil can be held inpatient per the international society of heart and lung transplantation recommendations[55].

Table 3 Summary of management

Management of heart failure
We should know that the development of heart failure in COVID-19 patients can complicate management and worsen the prognosis; Chronic heart failure patients have adverse outcomes compared to new-onset heart failure patients; GDMT guided medical therapy should be used in heart failure with individualized patient decision making based on hemodynamic status and development of complications; Avoiding over diuresis to prevent kidney injury and hypoperfusion is necessary; Watching for signs of deterioration and shock with early initiation of vasopressors in mixed shock should be practiced; Cardiac arrhythmias and acute myocardial infarction are some major complications to look out for.; Advanced hemodynamic monitoring helps to guide management in these patients; Post-recovery cardiac, pulmonary rehabilitation with psychological support and nutritional interventions is necessary

COVID-19: Coronavirus disease 2019.

These patients should be treated at a heart transplant center. After the infection resolves, careful monitoring is required when restarting immunosuppression in these patients due to effects from the allograft[53].

Breakthrough infection

Breakthrough infections after the COVID-19 vaccination have been frequently observed in older patients and those with comorbidities. One study described close to 12% of breakthrough infections after vaccination[56]. In another study of 700 breakthrough cases close to 49% of the patients were symptomatic[57]. Despite increased breakthrough infection in this patient population, they did not develop disease severe enough to require supplemental oxygen or ICU admission[56,58].

Vaccinated people have a shorter duration of virus transmission, short symptom duration, and restricted tissue dissemination[59].

Chronic heart failure patients with breakthrough infections who are stable can be treated as outpatients with GDMT.

Rehabilitation post-recovery

In the Post-Acute phase, exercise training should be done in these patients, considering oxygen saturation, heart rate, systolic blood pressure, and symptoms[60]. Cardiac rehabilitation includes a variety of programs such as aerobic endurance training, interval training (IT), High intensity IT and resistance training done around 2-5 times per week[60].Thoracic expansion exercises to increase lung ventilation and airway clearance are some of the recommended methods for respiratory rehabilitation in these patients. Home-based cardiac telerehabilitation- is another alternative strategy to follow for these patients. Psychological support and nutritional interventions should also be a part of rehabilitation programs[60].

Complications

Direct viral infection of the myocardium can cause myocardial injury and complications such as myocarditis and myocardial interstitial fibrosis[61,62]. System-wide inflammatory response and release of pro-inflammatory markers like Tumor necrosis factor, interleukin-6, and interleukin-1β are associated with direct myocardial injury and can cause myocardial infarction[24,63]. The prothrombotic state can result in acute coronary events[61,62]. Cardiac Arrhythmias such as atrial arrhythmias, bradyarrhythmia, and non-sustained ventricular tachycardia can occur due to inflammation of the myocardium, fibrosis, edema of interstitial tissues, medication side-effects, and myocarditis[61,62]. Atrial fibrillation can predispose patients to cardiogenic shock[62].

Patients who recover after severe COVID-19 are at high risk of Pulmonary hypertension, Diastolic dysfunction, and right heart failure[9,64]. Stress-induced cardiomyopathy or Takutsubo cardiomyopathy can develop from microvascular dysfunction and inflammatory response[65,66]. The summary of management is illustrated in Table 3.

CONCLUSION

Heart Failure can occur as a complication in patients with COVID-19 infection. It can worsen the course of COVID-19 and is associated with poor outcomes. It requires early diagnosis and appropriate management on a patient-to-patient basis. Continuing Guideline Directed medical therapy is recommended. We need to watch out for complications during its management. Post the acute phase of COVID physical, psychological and nutritional rehabilitation for these individuals is necessary to aid in recovery.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Is there a window of opportunity to optimize trastuzumab cardiac monitoring?

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Abstract

BACKGROUND

It remains unclear whether the current arbitrary screening recommendations of trastuzumab-related cardiotoxicity provides an adequate balance between preventing heart damage and curtailing a curative treatment.

AIM

To determine the incidence rate and consequences of trastuzumab-induced cardiotoxicity as adjuvant treatment in a real-world scenario.

METHODS

We present a retrospective analysis of cardiac function measured by echocardiogram at baseline and every 3 mo during trastuzumab treatment. Cardiotoxicity was defined as a drop in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and/or any drop < 50%.

RESULTS

Between January 2011 and December 2014, 407 patients were selected. Most (93.6%) were treated with an anthracycline followed by a taxane-based regimen and trastuzumab for 12 mo. Forty patients (9.8%) had cardiotoxicity. None of

them were symptomatic, and 28 (72.5%) completely recovered LVEF. Cardiotoxicity happened early as shown by LVEF measured on echocardiogram 2 to 4 as compared to 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). There were 54 deaths (13.3%) during the 70-mo follow-up period; 1 (0.2%) was attributed to late cardiotoxicity (4 years after treatment). The absence of symptomatic cardiotoxicity during trastuzumab treatment and moreover the early occurrence on the treatment period may translate into a strategy to evaluate less frequently.

CONCLUSION

We observed a 10% rate of asymptomatic cardiotoxicity, which mirrors the results from the large adjuvant trials. Despite being transient, an LVEF drop led to frequent treatment delays and interruptions. It remains unclear whether LVEF decline is predictive of late cardiotoxicity, and treatment efficacy is compromised.

Key Words: Cardiac toxicity; Ventricular Dysfunction; Heart failure; Trastuzumab; Breast cancer

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Core Tip: It remains unclear whether the current arbitrary screening recommendations for trastuzumab-related cardiotoxicity in early-stage HER2-positive breast cancer provides an adequate balance between preventing heart damage and curtailing a curative treatment. Real world data showed that despite a low rate of mainly early, asymptomatic and transient cardiotoxicity, treatment delays and interruptions occur due to these findings. The study results suggest optimization of cardiac monitoring after an initial period without a decrease in cardiac function.

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INTRODUCTION

Trastuzumab, a monoclonal antibody targeting HER2, represents a milestone in breast cancer treatment. The drug improves the progression-free and overall survival in metastatic and localized HER2-positive breast cancer[1,2]. Cardiotoxicity remains the most compromising side effect[3]. Myocardial HER2 receptors are associated with cardiac function protection physiologically[4]. Therefore, the drug administration could lead to a decrease in left ventricular ejection fraction (LVEF), usually reversible, although a few patients need to delay or permanently stop their ongoing treatment[4,5]. The incidence is around a quarter of patients receiving the drug, with a small percentage experiencing heart failure (1%-4%)[6]. Several factors can contribute, such as the chemotherapy regimen, particularly anthracycline, patient characteristics such as age, previous cardiovascular disease and low ejection fraction prior to treatment initiation[7].

Cardiotoxicity of anti-cancer treatment includes any toxicity affecting the heart[8] and suggested by biomarkers, such as decrease of LVEF or signs of heart failure[9]. Guidelines suggest a baseline pre-treatment evaluation and risk stratification, during treatment monitoring and post-treatment surveillance[2,10]. Although these recommendations mimic the schedules used in the clinical trials, the cardiac assessment was not supported by prospective data. Our study aimed to evaluate the cardiac function during trastuzumab treatment for early-stage breast cancer in a real-world scenario.

MATERIALS AND METHODS

Materials and methods

A retrospective chart review was performed using patient medical files from January 2010 to December 2014, at the Instituto Nacional de Cancer, Brazil. Patients had tissue confirmation of HER2-positive breast cancer, stage I to III, treatment with chemotherapy combined with and followed by trastuzumab. Exclusion criteria included loss to follow-up in less than 3 mo after treatment initiation.

Echocardiogram was performed at baseline and every 3 mo during trastuzumab treatment. It was performed by the same examiner and device [Siemens SONOLINE G 60, with P 4-2 cardiac probe (4.0-2.0 MHz)]. The analyses performed included the M-mode, 2D-mode, spectral doppler, color Doppler

and tissue doppler imaging. The cavities dimensions were obtained according to the recommendation of the American Society of Echocardiography[11]. LVEF was calculated though the Teichholz Formulae. Cardiotoxicity was defined as: a 10% drop in LVEF from the baseline echo, a drop below 50% or symptoms according to the New York Heart Association class III or IV[12,30].

The study was approved by the institutional review board and conducted in accordance with the Good Clinical Practice Guidelines and the Helsinki declaration.

Statistical analysis

Numerical variables were reported by central tendency measures, and categorical variables were represented by absolute frequency and percentages. A bar plot containing the percentage of cardiotoxicity detected by echocardiograms at each scheduled measurement was performed to describe differences between patients that developed cardiotoxicity. A univariate analysis using the χ^2 method for categorical variables and two sample *t*-test for continuous variables were initially performed to test the association between cardiotoxicity and potential confounders in clinical practice (age, comorbidities, body mass index).

To verify statistical differences in cardiotoxicity during the follow-up time, odds ratio was calculated to show differences in cardiac event odds in the beginning *vs* end of screening period. The prevalence ratio was calculated using the Wald[13] and Score[14] methods. The R statistical software was used to calculate the odds ratio and prevalence measures using the epiR package[15].

RESULTS

From 423 eligible patients, 16 were excluded (7 with metastatic disease and 9 lost to follow-up), with 407 remaining for the final analysis. The median age was 52 years, and the body mass index was 27.54 kg/m^2. The stage at presentation was predominantly stage III: 59.47%. Most tumors were invasive ductal carcinoma (98.64%), and an anthracycline followed by taxane-based regimen was the most common treatment (93.6%). Almost all patients received trastuzumab for the whole 1-year period (97.0%) (Table 1).

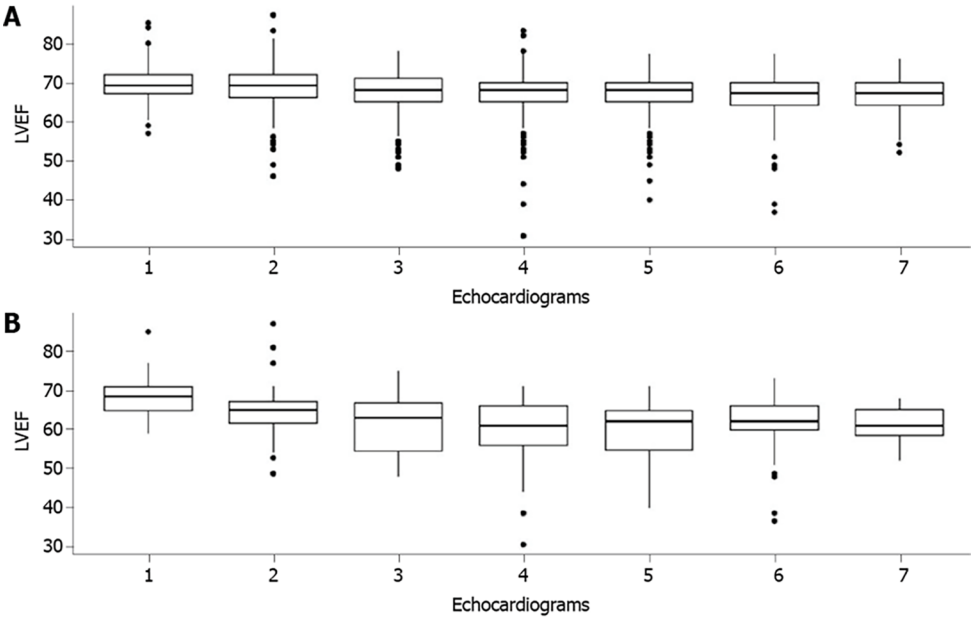
Forty patients (9.8%) had cardiotoxicity at a median time of 289 d (114-680 dc) from treatment initiation, and a wider variation of LVEF was seen in cardiotoxicity patients as shown by Figure 1. Although none of these patients were symptomatic, all of them had their treatment delayed due to the echocardiogram findings. Twenty-nine patients (72.5%) recovered the LVEF, for which the drug was restarted, and 11 (27.5%) had trastuzumab suspended. The rates of cardiotoxicity did not vary according to age (P = 0.58), comorbidities (P = 0.81) or body mass index (P = 0.64).

Cardiotoxicity occurred early, as shown in Figure 2. The prevalence in echocardiograms 2 to 4 was 2.7% against 1.1% prevalence ratio in echocardiograms 5 to 7. The odds of cardiotoxicity were 2.5 times higher when echocardiogram 2 to 4 were compared to echocardiogram 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). The median follow-up time was 70 mo, and there were 54 deaths (13.3%). Overall, survival did not vary according to cardiotoxicity (P = 0.08). One death (0.2%) was attributed to heart failure. However, it occurred 4 years after the end of trastuzumab treatment, possibly related to late anthracycline cardiotoxicity.

DISCUSSION

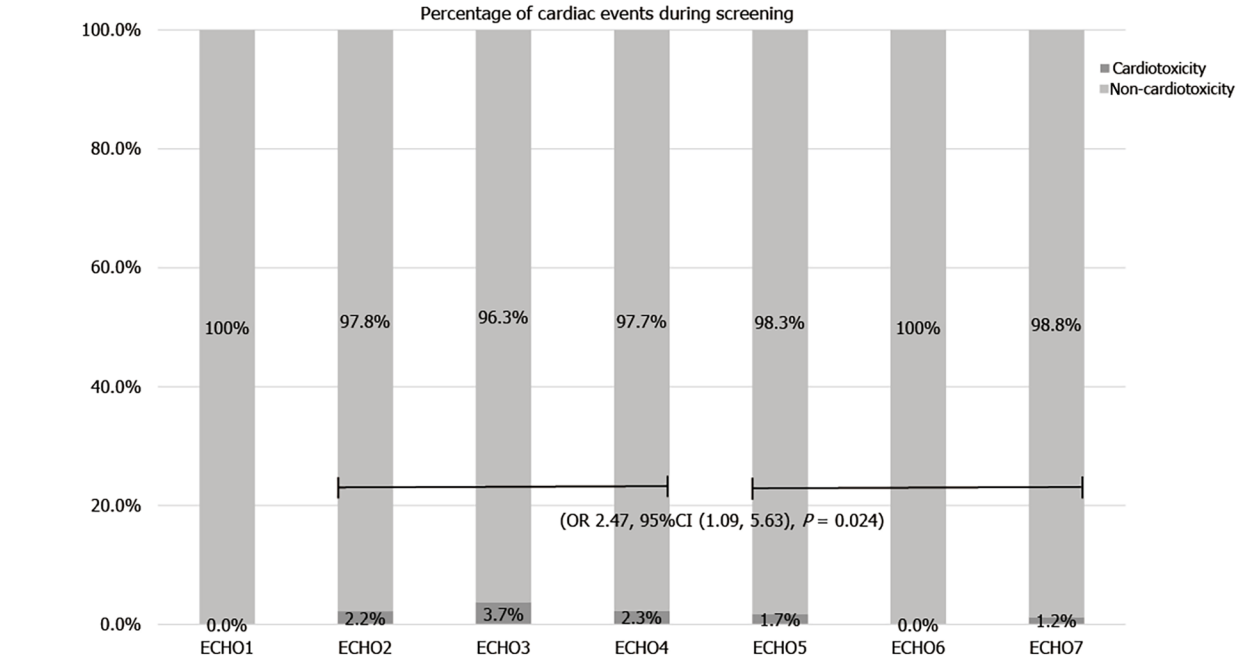
We showed a 9.8% cardiotoxicity rate detected by routine echocardiogram during trastuzumab-based treatment for early-stage breast cancer. To our knowledge, this is the largest real-world cohort reported in South America. Our results were similar to the ones presented by the large breast cancer adjuvant clinical trial 3, which varied from 6.0% to 35.4%[16,17]. This wide variation could be explained by the different chemotherapy regimens but more likely attributed to patient selection and diverse definitions of cardiotoxicity[18]. Whilst contemporary studies focus on predictive biomarkers (*i.e.* plasma levels of troponin and/or brain natriuretic peptide) and more costly imaging studies (*i.e.* cardiac magnetic resonance imaging), transthoracic echocardiogram is widely available with an affordable cost, which allows its widespread use[19]. Although the pathophysiology of cardiotoxicity is being elucidated, and players such as neuregulin[20] have been suggested. Reliable and validated biomarkers with a better cost-effectiveness than LVEF estimation are awaited[21].

Recommendations to withhold trastuzumab in Europe (absolute LVEF decrease > 20% or > 10% to < 50% or symptomatic heart failure)[22] and America (LVEF decrease ≥ 16% from baseline or LVEF below institutional limits of normality and ≥ 10% absolute LVEF decreased from baseline)[23] are roughly similar in not considering borderline asymptomatic decrease in LVEF. None of the patients in this cohort had symptoms at the time of the abnormal echocardiographic findings. Notwithstanding, it led to treatment delays and interruptions based on the guidelines available. The consequences of asymptomatic LVEF drop are unknown as well as whether early trastuzumab treatment interruption



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Figure 1 Left ventricular ejection fraction over trastuzumab cardiotoxicity monitor. A: Total sample; B: Cardiotoxicity group. LVEF: Left ventricular ejection fraction.



Status	Frist (Baseline)	Second	Third	Fourth	Third	Sixth	Seventh
Non-cardiotoxicity	407	397	392	398	348	195	80
Cardiotoxicity	0	9	15	9	6	0	1

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Figure 2 Percentage of cardiac event over time. OR: Odds ratio; CI: Confidence interval.

may compromise its efficacy[24,25]. More recent trials showed less clinical cardiac dysfunction in shorter trastuzumab treatment duration compared to longer trastuzumab treatment duration[26].

There are known risk factors associated with trastuzumab-related cardiotoxicity such as age above 65, Ile655Val HER2 polymorphism, previous cardiovascular disease, radiation therapy and the use of anthracycline, especially high cumulative doses[27,28]. In our cohort, we were unable to show such a correlation. The studies on the other hand are conflicting about other factors such as other comorbidities (diabetes or kidney function impaired) or baseline LVEF (high or low)[3]. We interpret these factors

Table 1 Patients and treatment characteristics

Variable	Absolute number	Percentage
Age		
Minimum	18	-
Median	52	-
Maximum	79	-
Body mass index		
Minimum	14.27	-
Median	27.54	-
Maximum	50.58	-
Comorbidities		
Hypertension	56	13.75
Diabetes	19	4.66
Lack of other comorbidities reported	330	81.10
Menopausal status		
Post-menopausal	304	74.69
Pre-menopausal	103	25.31
Histological subtypes		
Invasive ductal carcinoma	400	98.28
Invasive lobular carcinoma	5	1.22
Others	2	0.50
Clinical stage		
I	36	8.86
II	129	31.69
III	242	59.45
Chemotherapy regimen		
Anthracycline and taxane based	381	93.61
Non-anthracycline based	26	6.39
Chemotherapy purpose		
Neoadjuvant	204	50.12
Adjuvant	203	48.88
Adjuvant radiotherapy		
Yes	213	52.33
No	194	47.67
Trastuzumab duration		
1 yr	395	97.06
Less than 1 yr	12	2.94

with caution once the standard of care population is significantly heterogeneous and frequently differs from the subjects included in clinical trials. Moreover, specific recommendations to adapt cardiac monitoring is lacking, unless the patient has a high cardiotoxicity risk[29].

Of note, we showed an increased incidence of cardiotoxicity in the early monitoring as compared to the later cardiac function evaluation through echocardiogram. As there is a lack of prospective randomized clinical trials for optimal cardiac monitoring[30], our results provide an opportunity to such an endeavor. Our study limitations included its retrospective nature, the limited number of patients and the lack of standard reporting of comorbidities. On the other hand, similar studies suggest that a

population to optimize monitoring might exist[31].

CONCLUSION

The cardiotoxicity rates in a real-world population were similar to those reported by the large adjuvant trastuzumab trials. Most events occurred early during the initial monitoring examinations. As these findings led to treatment changes with unknown long-term consequences. These results deserve a prospective confirmation to assess the optimal way to monitor and manage trastuzumab-related cardiac events.

ARTICLE HIGHLIGHTS

Research background

It remains unclear whether the current arbitrary screening recommendations of trastuzumab-related cardiotoxicity provides an adequate balance between preventing heart damage and curtailing a curative treatment.

Research motivation

There is an urgent need to optimize monitoring of cardiotoxicity.

Research objectives

This study aimed to determine the incidence rate and consequences of trastuzumab-induced cardiotoxicity as adjuvant treatment in a real-world scenario.

Research methods

A retrospective chart review was performed using patient medical files during 5 years at a single institution in Brazil. Patients had tissue confirmation of HER2-positive breast cancer, stage I to III, treatment with chemotherapy combined with and followed by trastuzumab. Exclusion criteria included loss to follow-up in less than 3 mo after treatment initiation.

Research results

Forty patients (9.8%) had cardiotoxicity (out of 407 included). None of them were symptomatic, and 28 (72.5%) completely recovered left ventricular ejection fraction. Cardiotoxicity happened early as shown by left ventricular ejection fraction measured on echocardiogram 2 to 4 as compared to 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). There were 54 deaths (13.3%) during the 70-mo follow-up period; 1 (0.2%) was attributed to late cardiotoxicity (4 years after treatment).

Research conclusions

The absence of symptomatic cardiotoxicity during trastuzumab treatment and moreover the early occurrence on the treatment period may translate into a strategy to evaluate less frequent cardiac monitoring.

Research perspectives

This data alongside similar studies in the literature warrants a prospective evaluation of a de-escalation of cardiotoxicity monitoring in a selected population.

FOOTNOTES

Author contributions: Rala de Paula BH, Costa METF and Bines J contributed to data collection; Rala de Paula BH, de Sousa CAM and Bines J were in charge of statistical analysis; All authors participated in the study plan, paper writing and reviewing and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Vitamin d deficiency and metabolic syndrome: The joint effect on cardiovascular and all-cause mortality in the United States adults

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Abstract

BACKGROUND

The long-term impact of vitamin D deficiency and metabolic syndrome (MetS) on cardiovascular disease (CVD) and all-cause mortality are still a matter of debate.

AIM

To test the hypotheses that lower serum 25 hydroxyvitamin D [25(OH)D] concentrations (a marker of vitamin D level) and MetS have a long-term impact on the risk of CVD and all-cause mortality, and individuals with vitamin D deficiency can be identified by multiple factors.

METHODS

A sample of 9094 adults, 20 to 90 years of age, who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) were followed through December 2015 was analyzed. The associations of serum

25(OH)D concentrations and MetS with CVD and all-cause mortality were analyzed longitudinally using Cox regression models. Classification and regression tree (CART) for machine learning was applied to classify individuals with vitamin D deficiency.

RESULTS

Of 9094 participants, 30% had serum 25(OH)D concentrations < 20 ng/mL (defined as vitamin D deficiency), 39% had serum 25(OH)D concentrations between 20 to 29 ng/mL (insufficiency), and 31% had serum 25(OH)D concentrations ≥30 ng/mL (sufficiency). Prevalence of MetS was 28.4%. During a mean of 18 years follow-up, vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. Subjects with both vitamin D deficiency and MetS had the highest risk of CVD mortality (HR = 1.77, 95%CI: 1.22-2.58) and all-cause mortality (HR = 1.62, 95%CI: 1.26-2.09), followed by those with both vitamin D insufficiency and MetS for CVD mortality (HR = 1.59, 95%CI: 1.12-2.24), and all-cause mortality (HR = 1.41, 95%CI: 1.08-1.85). Meanwhile, vitamin D sufficiency significantly decreased the risk of CVD and all-cause mortality for those who even had MetS. Among the total study sample, CART analysis suggests that being non-Hispanic Black, having lower serum folate level, and being female were the first three predictors for those with serum 25(OH)D deficiency.

CONCLUSION

Vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. There was a significant joint effect of vitamin D deficiency and MetS on the risk of mortality. Findings of the CART analysis may be useful to identify individuals positioned to benefit from interventions to reduce the risk of CVD and all-cause mortality.

Key Words: Joint effect; Serum 25 hydroxyvitamin D concentration; Metabolic syndrome; Cardiovascular and all-cause mortality; Cox model and machine learning

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Core Tip: To investigate the long-term effect of vitamin D deficiency and metabolic syndrome on the risk of cardiovascular disease and all-cause mortality using a nationally representative sample. Standard measurements of the study exposures, co-variables and outcomes are processed. Multivariate Cox's proportional hazards regression analysis was used to prospectively test the associations between the exposures and outcomes. Classification and regression tree for machine learning was applied to classify subjects with higher risk of lower serum vitamin D concentrations.

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INTRODUCTION

The classical function of vitamin D is to increase the intestinal absorption of calcium for proper bone mineralization. Vitamin D can be obtained by the diet or synthesized on the skin with exposure to ultraviolet-B from the sun. The best method to determine vitamin D status is through measurement of serum 25 hydroxyvitamin D [25(OH)D] concentrations[1,2]. Recent evidence has demonstrated that individuals with vitamin D deficiency are more likely to have cardiovascular disease (CVD), and are associated with CVD risk factors, including metabolic syndrome (MetS)[3-7]. However, most studies examined the cross-sectional association of serum 25(OH)D concentrations and MetS with the prevalence of CVD. Few studies, with a longitudinal study design, estimated the causal association between vitamin D deficiency and the risk of CVD. Furthermore, the findings of the previous studies are inconsistent. For example, the Women's Health Initiative calcium-vitamin D trial, a randomized clinical trial, observed a weak association between vitamin D supplementation and CVD risk reduction among postmenopausal women[8,9]. Meanwhile, the characteristics of the population with vitamin D deficiency varied by different studies[2]. In our early report in 2012, we tested the medium-term effect of serum vitamin D deficiency and risk of heart failure and premature mortality[4]. In the present study, we aimed to examine the long-term effect of vitamin D and MetS on the risk of CVD and all-cause

mortality using data from the third National Health and Nutrition Examination Survey (NHANES III). The NHANES III started in 1988 to 1994 and is an ongoing follow-up study for the participants' vital status through the national Linked Mortality Files (LMFs). The NHANES III provides us a unique opportunity to prospectively examine the association between baseline serum 25(OH)D concentrations and risk of disease-specific and all-cause mortality among community-dwelling residents in the United States[10,11]. In this study, we aimed to test two hypotheses: (1) Serum 25(OH)D deficiency and MetS are significantly associated with risk of CVD and all-cause mortality; and (2) serum 25(OH)D deficiency varies by age, sex, race/ethnicity, poverty and key measures of serum biomarkers.

MATERIALS AND METHODS

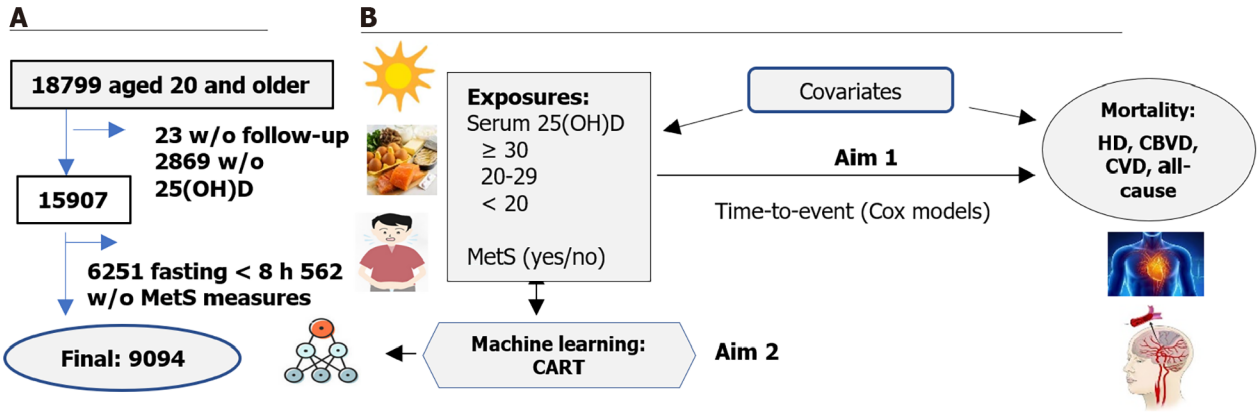
The NHANES III is a nationwide survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in the United States[10,12]. The baseline survey was conducted from October 1988 through October 1994 in two phases (phase 1: 1988-1991, and phase 2: 1991-1994) gathering information representing the health and nutritional status of the noninstitutionalized civilian United States residents ages 2 mo and older. Participants were recruited based on a nationwide probability sample across four regions of the USA (Northeast, Midwest, South, and West). The study consisted of (1) household interviews on sociodemographic factors, health behaviors, and history of medical conditions through standard survey instruments; (2) physical examinations in mobile examination centers (MEC); and (3) laboratory measures from blood and urine samples. Blood samples were obtained at the MEC for measurements of serum and urinary biomarkers. To minimize hemolysis of blood samples in the measures of serum lipid profiles and glucose concentrations, participants were asked to fast for 12 hours before a morning examination, or 6 hours before an afternoon or evening examination. All phlebotomists were certified and trained in standardized laboratory procedures. Detailed information on the NHANES III has been provided elsewhere[10,12].

Follow-up data for participants' survival status or disease-specific and all-cause mortality were extracted from the NHANES III Linked Mortality File (LMF). The LMF was linked by the NCHS working with the State's Offices of Vital Statistics to link NHANES III data with death certificate records using the National Death Index (NDI)[13]. The NDI is a central computerized index of death record information on files. This standard and technique-supported linkage process provide an opportunity to conduct longitudinal analyses between measures at baseline and outcomes through the follow-up period. In the present study, we used data from the recently available follow-up of the LMF for the NHANES III from baseline 1988-1994 through December 31, 2015. The NHANES III survey was approved by the CDC NCHS institutional review board. Data obtained from the NCHS for the present study were de-identified for participants' private information security. The study, using the deidentified NHANES III and its LMF to examine risk factors for mortality has been approved by the Drexel University Office of Institutional Review Board (#2105008546). Of 18799 participants, 23 without follow-up and 2869 without serum 25(OH)D measures were excluded. Of the rest 15907, we further excluded 6251 who had fasting blood sample < 8 hours (to assess triglycerides and glucose concentrations), and 562 who had no measurements of five MetS components. That, the final study sample size was 9094 for those who had serum 25(OH)D concentrations measured, had valid follow-up records for their vital status, and had full measurements of MetS components [waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and fasting glucose concentrations]. Figure 1A shows the sample size flowchart.

Exposures

Measurements of serum 25(OH)D concentrations were performed as part of the nutritional biomarkers of the NHANES III (1988 to 1994)[10]. Serum 25(OH)D concentrations were measured at the National Center for Environmental Health, CDC, Atlanta GA, using the DiaSorin RIA kit (Stillwater MN). In the study, we analyzed serum 25(OH)D concentrations as a categorical variable in the Cox regression models to examine hazard ratios of serum 25(OH)D concentrations for risk of mortality. We applied the commonly used cut-off points to categorize serum 25(OH)D levels into three groups: (1) Vitamin D deficiency was defined as serum 25(OH)D concentrations < 20 ng/mL (< 50 nmol/L); (2) Vitamin D insufficiency was defined as serum 25(OH)D concentration 20 to 29 ng/mL (50 to 74 nmol/L); and (3) Vitamin D sufficiency was defined as serum 25(OH)D concentrations ≥ 30 ng/mL (≥ 75 nmol/L)[1,4,14,15]

On MetS, five components are included. These are waist circumference (WC), which was measured using a standard flexible and tension-regulated tape measure. Systolic and diastolic blood pressure (SBP and DBP, respectively), were measured with an automated blood pressure monitor after five minutes of rest, with the last two of three readings, averaged and recorded. Blood samples collected at least 8 hours fasting were used to assess TG, and fasting glucose concentrations. To define MetS, we applied the cut-off criteria modified from the American Heart Association (AHA), the American Diabetes Association (ADA), and the Adult Treatment Panel III (ATP III)[16]. Individuals with MetS were defined by the presence of 3 of five MetS components: (1) Large WC (a marker of abdominal adiposity): WC > 102 cm



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Figure 1 Participant flowchart (A) and the analysis conceptual model (B) in the study. Serum 25(OH)D: Serum 25 hydroxyvitamin D (a marker of vitamin D level in blood); MetS: Metabolic syndrome; CART: Classification and regression tree; HD: Heart disease; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease.

in males and > 88 cm in females; (2) Elevated BP: SBP ≥ 130 or DBP ≥ 85 mmHg or under antihypertensive medication use; (3) Elevated TG: TG ≥ 150 mg/dL; (4) Elevated glucose: fasting glucose ≥ 100 mg/dL or use of glucose-lowering medications; and (5) Low HDL-C: HDL-C < 40 mg/dL in males and HDL-C < 50 mg/dL in females.

Outcomes

The study outcomes included mortality from (1) Heart disease (HD) (*International Classification of Disease, Tenth Revision, ICD-10* codes: I00-I09, I11, I13, I20-I51); (2) Cerebrovascular diseases (CBVD, ICD-10 codes: I60-I69); (3) CVD (included either HD and CBVD); and (4) All-cause mortality. Follow-up time (years) was calculated from the baseline interview to the end of follow-up (December 31, 2015), or until the date of death if a participant died before the end of follow-up, whichever occurred first.

Covariates

We included the following factors as covariates in the analysis. These variables are: age (years), sex (males, and females), race/ethnicity, educational attainments, smoking status, alcohol consumption, physical activity, and chronic conditions. Race/ethnicity are classified based on participants' self-reports using standard survey questionnaire. Three groups are recorded: non-Hispanic White, non-Hispanic Black (*i.e.*, African American), and the other groups (including Hispanic or Latino, Asian, native Hawaiian or other Pacific Islander). Educational attainments are classified into three groups (less than high school, high school, and colleges or higher levels), smoking status, alcohol consumption, physical activity, and chronic condition. Smoking was categorized as "never", "former", and "current smokers". Alcohol consumption was defined by a question, "Have you had at least 12 drinks in the last 12 mo?" (*i.e.*, at least once a month, "yes" or "no"). Physical activity was categorized as more activity, about the same, or less activity from a survey question: "How does the amount of activity that you reported for the past month compare with your physical activity for the past 12 mo?" Chronic conditions were self-reported diagnoses on questions: "Have you been told by a doctor that you have the following disease(s): hypertension, diabetes mellitus, coronary heart disease, heart failure or stroke?" ("yes" or "no").

Statistical analysis

We conducted a serial analysis to examine the two specific aims (Figure 1B). In the first set of analyses, we described the characteristics of the study participants across three groups of serum 25(OH)D concentrations (*i.e.*, serum 25(OH)D < 20, 20 to 29, and ≥ 30 ng/mL, respectively). Differences in MetS rates, sex, race/ethnicity, education attainment, smoking status, alcohol consumption, and history of chronic conditions at baseline were tested using the Chi-squared test. Differences in continuous variables were tested using analysis of variance. In the second-set analyses, we estimated age-sex-adjusted mortality rates (per 10000 person-years) from HD, CBVD, CVD, and all-cause mortality by serum 25(OH)D concentrations and MetS using Poisson regression models in SAS GENMOD procedure. In the third-set analyses, we estimated the hazard ratio and its 95% confidence interval of serum 25(OH)D concentrations and MetS for HD, CBVD, CVD, and all-cause mortalities using time-to-event Cox proportional hazards regression (Cox) models. In the analyses, follow-up time (years) and mortality (yes or no) were the dependent variables, and serum 25(OH)D concentrations (reference to 25(OH)D ≥ 30 ng/mL) and MetS (yes *vs* no) were the independent variables. To test Cox proportional hazard assumption, we applied plots of log(-log) survival curves and Schoenfeld residuals methods. To control potential

confounders, we performed two multivariate-adjusted models. Model 1 adjusted for age (years), sex (males and females), race/ethnicity [non-Hispanic White (NHW), non-Hispanic Black (NHB), and the others], education (< high school, high school, and > high school), and living in regions of the United Stated (Northeast, Midwest, South, and West). We included the adjustment for regions for control potential difference in the exposures to sunshine across the nation because sunshine is one of the possible resources for a human to get vitamin D. Model 2 further adjusted for covariates including smoking (never, former, and current smokers), alcohol consumption (yes or no), physical activity (more activity, about the same, or less activity) and baseline prevalence of CVD (yes or no) because these lifestyle and baseline health conditions were associated with the study exposures and outcomes. We tested the interaction effects of serum 25(OH)D and MetS on mortality risk as well. In the fourth-set analyses, because we did not observe a significant interaction effect of serum 25(OH)D and MetS on the risk of CVD and all-cause mortality, we further estimated their joint effect on the risk of HD, CBVD, CVD, and all-cause mortality.

In the fifth-set analyses, we applied classification and regression trees (CART), a predictive algorithm in machine learning techniques, to test the characteristics of participants with different serum 25(OH)D concentrations to use classification tree analysis to identify individuals who are at higher risk of vitamin D deficiency. CART analysis is a standard decision tree analysis in machine learning introduced by Breiman *et al*[17] and Bzdok *et al*[18]. CART analysis does not request data with a certain mathematical distribution (*i.e.*, distribution-free). Compared to Principal Component Analysis and Factor Analysis, CART analysis more easily handles noisy data, such as outliers from multiple variables, because CART's splitting algorithms can isolate outliers into a separate node[17]. In CART analysis, data are partitioned along the predictor axes into subsets with homogeneous values of the outcome variable. A decision tree is created, which can be used to make predictions from new observations[18]. The selection of important predictors can be assessed by mean decrease in Gini (MDG) index. MDG index is an average of a variable's total decrease in node impurity, weighted by the proportion of samples reaching that node in each decision tree in the random forest. A higher MDG index indicates higher variable importance. To valid the classification process, we used two sub-datasets: (1) 20% of the total participants were randomly selected serving as the validation dataset; and (2) The remaining 80% served as the training dataset to construct the predicting models. In the analysis, serum 25(OH)D concentrations in two and three categorical groups as the dependent variable and the other 46 variables as the independent variables (Supplementary Table 1). Serum 25(OH)D concentrations were categorized as: (1) Serum 25(OH)D ≥ 20 *vs* < 20 ng/mL; (2) Serum 25(OH)D ≥ 30, *vs* 20 to 29, *vs* < 20 ng/mL; and (3) Serum 25(OH)D ≥ 30 *vs* < 30 ng/mL.

Statistical analyses were performed using SAS 9.14 (SAS Institute, Cary, North Carolina). SAS analyses for complex sample surveys were used by taking into consideration the NHANES III's complex, multistage, probability sampling design. CART analyses were performed using R programming[19], and "rpart" package[20]. A 2-sided P value < 0.05 was considered statistically significant in all data analyses.

Finally, we conducted a sensitivity analysis by the exclusion of those who died within the first year of follow-up to avoid a potential over-estimate of the association of serum 25(OH)D concentrations and MetS with mortality risk because patients with serious health conditions might die within the first year of the follow-up.

RESULTS

Participants' characteristics

Of 9094 participants, 30% had serum 25(OH)D concentrations less than 20 ng/mL (defined as vitamin D deficiency), 39% had serum 25(OH)D concentrations in the 20 to 29 ng/mL range (insufficiency), and 31% had serum 25(OH)D concentrations ≥ 30 ng/mL (sufficiency). The total prevalence of MetS was 28.4%. Table 1 shows that across the three groups of serum 25(OH)D concentrations, the highest prevalence of MetS (35.3%) was observed among participants with serum 25(OH)D < 20 ng/mL, followed by 29.2% and 20.7%, respectively, among those with serum 25(OH)D concentrations in the 20 to 29 ng/mL range and those with serum 25(OH)D concentrations ≥ 30 ng/mL (testing for rates differences, P < 0.001). The mean ages were 45.8, 44.7, and 40.3 years older among those with serum 25(OH)D concentrations of < 20 ng/mL, 20 to 29 ng/mL, and ≥ 30 ng/mL, respectively (P < 0.001).

Participants with the lowest serum 25(OH)D concentrations had the highest mean waist circumference (WC), body mass index (BMI), SBP and DBP, serum TG, and glucose concentrations, but slightly lower HDL-C concentrations compared to those with serum 25(OH)D ≥ 30 ng/mL. Among those with serum 25(OH)D concentrations < 20 ng/mL, 61.7% were females. The proportions of race/ethnicity, education attachments, and alcohol consumption by serum 25(OH)D concentrations were significantly different (P < 0.001). Meanwhile, participants with serum 25(OH)D concentration < 20 ng/mL had a significantly higher prevalence of hypertension (36.5%), diabetes mellitus (9.3%), and CVD (6.3%) compared to those with serum 25(OH)D 20-29 ng/mL and those with serum 25(OH)D ≥30 ng/mL, respectively (P < 0.01).

Table 1 Characteristics of participants at baseline

	Serum 25(OH)D concentrations									*P* value
	< 20 ng/mL			20 to 29 ng/mL			≥ 30 ng/mL			
	No.	mean, %	(SE)	No.	mean, %	(SE)	No.	mean, %	(SE)	
MetS, %										< 0.001
No	2640	64.7		2230	70.8		1276	79.3		
Yes	1394	35.3		1089	29.2		465	20.7		
Age, yr	4034	45.8	(0.6)	3319	44.7	(0.6)	1741	40.3	(0.6)	< 0.001
Waist circumference, cm	4034	94.2	(0.4)	3319	92.2	(0.3)	1741	88.3	(0.4)	< 0.001
Body mass index, kg/m^2	4033	27.8	(0.2)	3318	26.5	(0.1)	1739	25.0	(0.1)	< 0.001
Systolic BP, mmHg	4034	123.4	(0.6)	3319	122.0	(0.6)	1741	119.0	(0.6)	<0.001
Diastolic BP, mmHg	4034	74.7	(0.3)	3317	74.1	(0.3)	1741	72.9	(0.4)	< 0.001
Triglycerides, mg/dL	4034	138.9	(4.1)	3319	136.4	(2.6)	1741	126.5	(3.8)	< 0.001
HDL-C, mg/dL	4034	51.0	(0.5)	3319	49.3	(0.4)	1741	51.5	(0.6)	< 0.001
Glucose, mg/dL	4034	100.7	(0.7)	3319	98.4	(0.5)	1741	94.7	(0.4)	< 0.001
Categorical variable, %										
Sex, male, %	1561	38.3		178	51.9		975	55.4		< 0.001
Race/ethnicity, %										< 0.001
NHW	894	55.1		1557	79.7		1213	92.0		
NHB	1788	25.8		575	6.0		139	1.9		
Others	1352	19.1		1187	14.3		389	6.1		
Region										< 0.001
Northeast	490	15.8		429	20.6		303	26.7		
Midwest	651	18.9		709	24.5		434	28.1		
South	1933	40.3		1299	33.2		685	29.1		
West	960	25.0		882	21.6		319	16.1		
Education level										0.001
< High school	930	13.1		818	11.8		355	8.2		
High school	1971	49.2		1532	45.8		788	46.1		
> High school	1113	37.7		949	42.4		592	45.6		
Smoking										0.07
Never	2562	62.1		2230	63.9		1130	62.5		
Former	193	5.5		191	6.0		105	4.0		
Current	1279	32.4		898	30.2		506	33.5		
Alcohol consumption, yes	1704	44.8		1592	55.9		910	63.7		< 0.001
Exercise, yes										0.13
More activity	559	14.1		475	16.3		287	18.4		
About the same	2433	58.3		1998	56.2		1005	52.7		
Less activity	1040	27.6		841	27.5		445	28.9		
Health conditions										
Hypertension, yes	1489	36.5		1129	29.6		565	25.5		< 0.001

Diabetes mellitus	465	9.3	312	6.7	105	3.3	< 0.001
CVD	278	6.3	252	5.3	124	3.4	0.001

Weighted mean and percentage are estimated because NHANES III applied a complex, multistage, probability sampling design. SE: Standard error; MetS: Metabolic syndrome; BP: Blood pressure; HDL-C: High-density lipoprotein cholesterol; NHW: Non-Hispanic White; NHB: Non-Hispanic Black; Others: Including all the other race/ethnicity groups; CVD: Cardiovascular disease included those with coronary heart disease, heart failure, or stroke.

Mortality rate by serum 25(OH)D concentrations and MetS status

Table 2 shows that during a mean of 18 years follow-up, participants with serum 25(OH)D concentrations < 20 ng/mL had significantly higher age-sex-adjusted mortality from HD (17.4 per 10000 person-years), CVD (21.3 per 10000 person-years), and all-cause mortality (103.9 per 10000 person-years) compared to those with serum 25(OH)D concentrations ≥ 30 ng/mL. Participants with MetS had significantly higher age-sex-adjusted mortality from HD (16.7 per 10000 person-years), CVD (22.0 per 10000 person-years), and all-cause mortality (102.4 per 10000 person-years) compared to those without MetS.

Multivariate-adjusted hazard ratios of serum 25(OH)D and MetS for mortality

Table 3 shows that, after adjusting for age, sex, race/ethnicity, and region (Model 1), and additional adjusting for health behaviors and baseline CVD (Model 2), participants with serum 25(OH)D concentrations < 20 ng/mL had a significantly higher risk of HD, CVD, and all-cause mortality compared to those with serum 25(OH)D concentrations ≥ 30 ng/mL. The corresponding hazard ratios [HRs and 95% confidence intervals (CI)] in Model 2 were 1.43 (1.07-1.91, P = 0.017) for HD, 1.36 (1.04-1.78, P = 0.028) for CVD, and 1.32 (1.10-1.58, P = 0.004) for all-cause mortality, respectively.

Participants with MetS had a significantly higher risk of CVD and all-cause mortality compared to those without MetS in Models 1 and 2. The corresponding HRs (95%CI) in Model 2 were 1.29 (1.05-1.59, P = 0.017) for CVD, and 1.20 (1.05-1.36, P = 0.01) for all-cause mortality.

No significant association of serum 25(OH)D concentrations and MetS with the risk of CBVD mortality, and no significant interaction effects of serum 25(OH)D concentrations and MetS on the risk of HD, CBVD, CVD, and all-cause mortality were observed (P > 0.05).

Joint effects of serum 25(OH)D concentrations and MetS on mortality risk

We further estimated the joint effect of those who had lower serum 25(OH)D concentrations and MetS on mortality risk. Figure 2 depicts that individuals with serum 25(OH)D concentrations < 20 ng/mL and MetS had the highest risk of CVD (HR = 1.77, 95%CI: 1.22-2.58, P < 0.01, Figure 2A) and all-cause mortality (HR = 1.62, 95%CI: 1.26-2.09, P < 0.01, Figure 2B), followed by those with serum 25(OH)D concentrations 20 to 29 ng/mL and with MetS [1.59 (1.12-2.24, P = 0.01) for CVD, and 1.41 (1.08-1.85, P = 0.01) for all-cause mortality] as compared to those with serum 25(OH)D ≥ 30 ng/mL and without MetS (the reference group). Figure 2 also shows that individuals with MetS, but with serum 25(OH)D concentrations ≥ 30 ng/mL, did not have a significantly higher risk of CVD (HR = 1.44, 95%CI: 0.96-2.22, P = 0.008) and all-cause mortality (HR = 1.30, 95%CI: 0.95-1.78, P = 0.09) compared to the reference group (shown as green bars in Figure 2), indicating a higher protective effect of serum 25(OH)D concentrations ≥30 ng/mL on CVD and all-cause mortality compared to MetS.

Identifying the main predictors for those with lower serum 25(OH)D concentrations

We used CART to identify the top 10 important predictors from 46 variables (Supplementary Table 1) for participants with serum 25(OH)D at different concentrations and by sex. Table 4 shows the overall results. Figure 3 depicts an example of CART analysis for serum 25(OH)D concentrations ≥ 20 ng/mL *vs* < 20 ng/mL among the total sample (S1 of Table 4). Racegp (race/ethnicity) is grouped as racegp = 1 for non-Hispanic White (NHW), 2 for non-Hispanic Black (NHB), and 3 for the other racial/ethnic groups. Figure 3A indicates that the classification tree starts from node 1 (also called the root) and ended in node 5 (*i.e.*, the "leaves"). Under each oval-shaped box, the values on the left-listed indicate the percentage of individuals with serum 25(OH)D concentrations ≥ 20 ng/mL [such as under node 1, 55% of individuals had serum 25(OH)D concentrations ≥20 ng/mL]. It should be noted that if the left-listed value is more than 0.5 (*i.e.*, > 50%), the oval-shaped box will be labeled as 25(OH)D ≥ 20 ng/mL, otherwise labeled as 25(OH)D < 20 ng/mL (such as 5a and 5b of node 5, *i.e.*, 0.29 and 0.38 are less than 0.50). Under each box, the value on the right-listed indicates the percentage of the participants included in the node (such as 100% in node 1). Figure 3A depicts that among the randomly selected training sample, 55% of them had serum 25(OH)D concentrations ≥20 ng/mL. In the analysis, race/ethnicity was first selected by the CART algorithm as a predictor. Of the sample, 28% (the value showing on the right-listed under box 5a of node 5) were NHB (*i.e.*, racegp = 2). Among NHB, 29% (on the left-listed value) had serum 25(OH)D concentrations ≥ 20 ng/mL (note: the oval-shaped box is labeled as 25(OH)D < 20 ng/mL because 0.29 is less than 0.5). In other words, 71% of NHB had serum 25(OH)D concentrations < 20 ng/mL. Of the total training sample, 72% were NHW and other racial/ethnic groups (*i.e.*, racegp ≠ 2), and 66% of them had

Table 2 Age-sex-adjusted mortality from heart disease, cerebrovascular disease, cardiovascular disease, and all-cause mortality

	Observed number		Weighted mortalityrate per 10000 PY		*P* value
	No. at risk	Case	Rate	(95%CI)	
Heart Disease					
25(OH)D, ng/mL					
≥ 30	1741	130	11.7	(8.2-16.6)	Ref.
20-29	3319	272	13.2	(10.3-16.9)	0.43
< 20	4034	292	17.4	(13.1-23.0)	0.012
CBVD					
25(OH)D, ng/mL					
≥ 30	1741	34	3.6	(2.0-6.6)	Ref.
20-29	3319	83	3.6	(2.5-5.1)	0.97
< 20	4034	88	4.5	(2.5-7.9)	0.53
CVD					
25(OH)D, ng/mL					
≥ 30	1741	164	15.3	(11.4-20.5)	Ref.
20-29	3319	355	16.6	(13.3-20.7)	0.56
< 20	4034	382	21.3	(16.6-27.3)	0.023
All-cause					
25(OH)D, ng/mL					
≥ 30	1741	545	75.9	(64.9-88.8)	Ref.
20-29	3319	1141	87.5	(79.4-96.3)	0.066
< 20	4034	1290	103.9	(93.2-115.8)	< 0.001
MetS status					
Heart Disease					
MetS, no	6146	327	12.5	(9.7-16.2)	Ref.
MetS, yes	2948	369	16.7	(12.9-21.7)	0.002
CBVD					
MetS, no	6146	97	3.2	(2.2-4.7)	Ref.
MetS, yes	2948	108	5.1	(2.9-8.9)	0.059
CVD					
MetS, no	6146	424	15.9	(13.0-19.5)	Ref.
MetS, yes	2948	477	22.0	(16.9-28.6)	< 0.001
All-cause					
MetS, no	6146	1490	82.5	(75.3-90.5)	Ref.
MetS, yes	2948	1486	102.4	(91.0-115.3)	< 0.001

PY: Person-years; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease; 25(OH)D: Serum 25 hydroxyvitamin D concentration; MetS: Metabolic syndrome.

serum 25(OH)D concentrations ≥20 ng/mL (these values showing under the box of node 2). Of the 72% sample (*i.e.*, racegp ≠ 2), 32% were the other race/ethnicity (*i.e.*, racegp = 3), and 54% of them had serum 25(OH)D concentrations ≥20 ng/mL. The rest 40% (racegp ≠ 2 and racegp ≠ 3) were NHW, and 75% of NHW had serum 25(OH)D concentrations ≥ 20 ng/mL (Box 5e of node 5). Thirty-two percent (32%) of the total sample were other racial/ethnic groups (racegp = 3, node 3), 16% of the total sample were other racial/ethnic females (racegp = 3 and sex = 2, node 4), and of them, 43% had serum 25(OH)D concen-

Table 3 Hazard ratios of serum 25 hydroxyvitamin D concentration and metabolic syndrome for heart disease, cerebrovascular disease, cardiovascular disease, and all-cause mortality

	Model 1			Model 2		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Ref to 25(OH)D ≥ 30 ng/dL						
25(OH)D for HD						
20-29	1.13	(0.82-1.55)	0.45	1.13	(0.83-1.52)	0.43
< 20	1.54	(1.14-2.08)	0.005	1.43	(1.07-1.91)	0.017
25(OH)D for CBVD						
20-29	0.97	(0.61-1.53)	0.88	0.98	(0.62-1.56)	0.94
< 20	1.15	(0.58-2.26)	0.69	1.14	(0.58-2.25)	0.69
25(OH)D for CVD						
20-29	1.09	(0.82-1.46)	0.54	1.10	(0.82-1.46)	0.52
< 20	1.44	(1.09-1.91)	0.011	1.36	(1.04-1.78)	0.028
25(OH)D for all-cause mortality						
20-29	1.16	(0.99-1.35)	0.06	1.16	(0.99-1.36)	0.07
< 20	1.38	(1.16-1.64)	0.001	1.32	(1.10-1.58)	0.004
Ref to Non-MetS						
MetS for HD	1.31	(1.09-1.58)	0.005	1.22	(1.00-1.49)	0.053
MetS for CBVD	1.58	(0.94-2.66)	0.083	1.60	(0.96-2.65)	0.069
MetS for CVD	1.37	(1.12-1.66)	0.002	1.29	(1.05-1.59)	0.017
MetS for all-cause mortality	1.22	(1.08-1.37)	0.002	1.20	(1.05-1.36)	0.008
Interaction of						
25(OH)D x MetS on						
HD	0.91	(0.72-1.17)	0.46	0.91	(0.72-1.15)	0.41
CBVD	0.80	(0.39-1.66)	0.54	0.79	(0.38-1.62)	0.50
CVD	0.89	(0.71-1.12)	0.31	0.88	(0.70-1.11)	0.28
All-cause	0.98	(0.84-1.14)	0.78	0.96	(0.82-1.13)	0.63

Model 1 adjusted for age, sex, race/ethnicity, education, and regions; Model 2 adjusted covariate in Model 1 plus smoking status, physical activity, alcohol consumption, and baseline CVD. HR: Hazard ratio; 25(OH)D: Serum 25 Hydroxyvitamin D concentration; HD: Heart disease; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease; MetS: Metabolic syndrome.

trations ≥ 20 ng/mL (note: the oval-shaped box is labeled as 25(OH)D < 20 ng/mL because 0.43 is less than 0.5). The rest 16% of the total sample were other racial/ethnic males (racegp = 3 and sex = 1). Of the males, 65% had serum 25(OH)D concentrations ≥ 20 ng/mL (Box 5d of node 5). Among the females (node 4), the CART algorithm further identified serum folate concentrations (FOP, a marker of folate intake) as an important factor to continue the classification. Sixteen percent (16%) of the total sample were other racial/ethnic females, 14% of them had serum folate concentrations (FOP) < 8.9 ng/mL, and 38% of them had serum 25(OH)D concentrations ≥ 20 ng/mL. Overall, node 3 it suggests that sex and serum folate level play a role in the further classification among the other racial/ethnic groups. The classified rates for those with serum 25(OH)D concentrations ≥ 20 range from 62% [*i.e.*, (1-0.38 = 0.62), Box 5b of node 5] to 75% (box 5e of node 5). Figure 3B depicts the top 10 important factors that predicted those with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL. These ranks are assigned based on the values of their MDG indexes, a larger bubbler size indicating a stronger predictor.

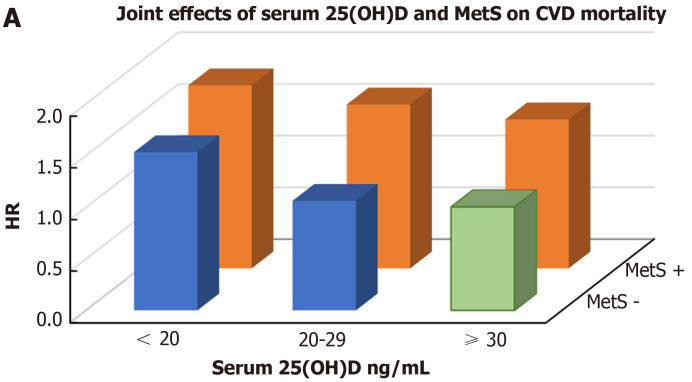
Table 4 shows the final selected top 10 predictors. Race/ethnicity was consistently selected as one of the important predictors in sample 1 (S1, the total sample) to sample 6 (in females). In S1, the top 10 important predictors for classifying those with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL were: race, serum folate level, sex, region, red blood cell folate (RBP, a marker of tissue stores of folate), poverty, educational level, glomerular filtration rate (GFR), serum uric acid (UAP), and alcohol

Table 4 Top 10 important predicators for classifying serum 25 Hydroxyvitamin D levels in the total and sex-specific samples

	S1: In both sex		S2: In males		S3: In females		S4: In both sex		S5: In males		S6: In females	
	≥ 20 *vs* < 20		≥ 20 *vs* < 20		≥ 20 *vs* < 20		≥ 30 *vs* < 30		≥ 30 *vs* < 30		≥ 30 *vs* < 30	
Rank	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG
1	Race	519.5	Race	229.7	Race	267.7	Race	200.0	Race	95.2	Race	103.9
2	Folate	90.4	RBP	19.6	Folate	101.3	Age	97.5	WC	34.0	Age	79.4
3	Sex	57.3	Age	14.8	Age	77.5	Folate	65.1	BMI	29.0	GFR	50.6
4	Region	34.3	Glucose	14.2	GFR	73.7	GFR	54.8	AGE	28.9	Folate	49.6
5	RBP	34.0	GFR	13.1	RBP	50.7	BMI	48.8	Region	24.8	RBP	34.1
6	Poverty	33.3	Poverty	12.8	Poverty	50.1	WC	42.2	GFR	22.7	WC	32.0
7	Edu	30.3	Region	11.9	WC	22.9	Poverty	41.4	Insulin	18.9	SBP	26.9
8	GFR	29.6	WC	11.1	VEP	21.1	RBP	39.8	C1P	18.8	BMI	23.2
9	UAP	27.7	Folate	10.9	SBP	16.1	Glucose	22.0	RBP	18.6	VEP	22.0
10	Alcoh	21.6	Edu	9.8	A1C	14.6	DairyHEI	20.8	Poverty	17.4	Poverty	18.8
Accuracy,%	71.1		70.8		68.0		81.5		79.3		81.8	
Precision, %	68.4		68.2		68.2		83.0		82.4		85.6	
Recall,%	63.0		47.5		68.5		97.0		93.5		94.0	
F1 score, %	65.6		56.0		68.3		89.5		87.6		89.6	

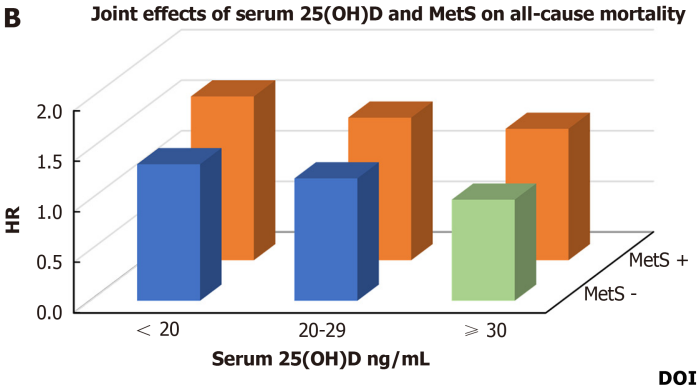
S1-S3: Samples 1 to 3. S1 to S3 for the classification of serum 25(OH)D ≥ 20 *vs* <20 ng/mL. Of them, S1: In the total sample. S2: In males. S3: In females. S4-S6: Samples 4 to 6. S4 to S6 for the classification of serum 25(OH)D ≥ 30 *vs* <30 ng/mL. Of them, S4: in the total sample. S5: In males. S6: In females. MDG: Mean decrease in Gini index. A higher MDG index indicates higher variable importance; RBP: Red blood cell folate; Edu: Educational level; GFR: Glomerular filtration rate; UAP: Serum uric acid; Alcohol: Alcohol consumption; WC: Waist circumference; BMI: Body mass index; VEP: Serum concentrations of vitamin E; SBP: Systolic blood pressure; A1C: Hemoglobin A1c; DairyHEI: Dairy healthy eating index; C1P: Serum C-peptide.

consumption. Table 4 also gives the prediction accuracy rate (the proportion of the correct predictions for both true positives and true negatives), precision rate (the proportion of the correct predictions for the true positives among the total positive predications), the recall rate (the proportion of the true positive predictions among the total true (observed) cases, and F1 score (a weighted average of the precision and recall rates, where an F1 score reaches its best value at 1 and worst at 0). For example, in S1, the average accuracy rate to classify individuals with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL was 71.1%, the precision rate was 68.4%, the recall rate was 63%, and the F1 score was 65.6%. These rates vary with sex-stratified samples and by the cutoffs of serum 25(OH)D concentrations.



Vitamin D and MetS for CVD

25(OH)D	MetS	HR	(95%CI)	*P* value
≥ 30	No	1		
20-29	No	1.06	(0.69 – 1.62)	
		0.79		
< 20	No	1.53	(1.08 – 2.17)	0.02
≥ 30	Yes	1.44	(0.96 – 2.22)	0.08
20-29	Yes	1.59	(1.12 – 2.24)	0.01
< 20	Yes	1.77	(.122 – 2.58)	< 0.01



Vitamin D and MetSyn for All-cause

25(OH)D	MetSyn	HR	(95%CI)	*P* value
≥ 30	No	1		
20-29	No	1.21	(1.01 – 1.46)	0.04
< 20	No	1.35	(1.07 – 1.72)	0.02
≥ 30	Yes	1.30	(0.95 – 1.78)	0.09
20-29	Yes	1.41	(1.08 – 1.85)	0.01
< 20	Yes	1.62	(.126 – 2.09)	< 0.01

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Figure 2 Joint effect of serum 25 hydroxyvitamin D and metabolic syndrome on the risk of cardiovascular disease (A) and all-cause mortality (B). Serum 25(OH)D: Serum 25-hydroxyvitamin D; MetS: Metabolic syndrome; CVD: Cardiovascular disease; HR: Hazard ratio.

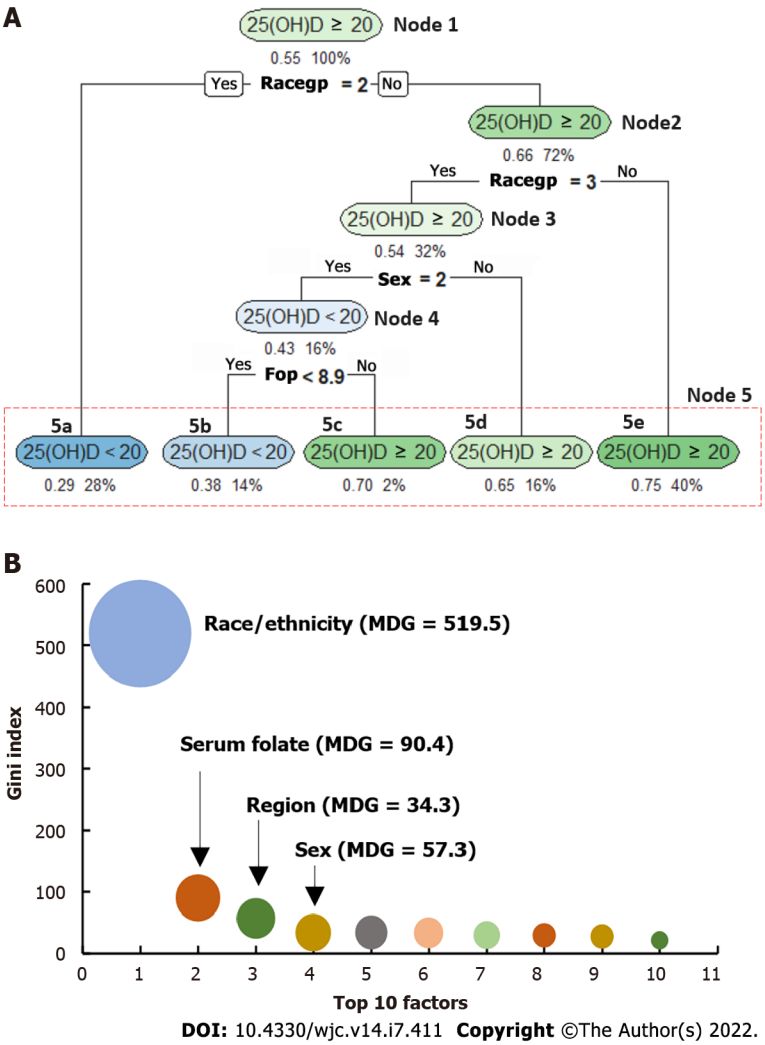
In the CART analyses, race/ethnicity, sex, age, and serum folate level were included as the important predictors in most prediction models (S1-S6). Figure 4 further depicts these associations that non-Hispanic Black (NHB) had significantly lower mean serum 25(OH)D concentrations (16 ng/mL in females, and 18.5 ng/mL in males, Figure 4A) than NHW and the other race/ethnicity groups in both males and females. Overall, a decreased trend of serum 25(OH)D concentrations by age was observed in NHW (Figure 4B). However, among female NHB and males in the other racial/ethnic groups, serum 25(OH)D concentrations decreased after age 65 years older (Figure 4B). An increasing trend of mean 25(OH)D concentration was observed among females in the other racial/ethnic groups (Figure 4B). Figure 4C indicates an overall increasing trend of serum 25(OH)D concentrations with the increase in serum folate levels in both males and females and NHW, NHB, and the other racial/ethnic groups, except for male NHB with a decreased trend of serum 25(OH)D concentrations at around 10 ng/mL of serum folate concentrations, and with a decreased trend for male NHW and males in the other racial/ethnic groups at around 15 ng/mL of serum folate concentrations.

Finally, results from the sensitivity analysis, by the exclusion of those who died within the first year of follow-up from the longitudinal analysis, do not change the overall results. Therefore, we present the results without this exclusion in the report.

DISCUSSION

The main findings from this study indicate that: (1) Individuals with serum 25(OH)D deficiency and MetS had a significantly higher risk of CVD and all-cause mortality; (2) There was a significant joint effect of serum 25(OH)D concentrations and MetS on the mortality risk; and (3) Among both males and females (sample 1 of Table 4), the top 10 predictors were race/ethnicity, serum folate concentrations, sex, region, serum retinol-binding protein, poverty, educational level, glomerular filtration rate (GFR), serum uric acid, and alcohol consumption.

The impact of vitamin D deficiency on the risk of a variety of chronic diseases, including diabetes mellitus, multiple sclerosis, cancer, and CVD, has been reported in recent decades but is still a matter of debate[21-23]. Because findings from previous studies are inconsistent[9,22,24]. For example, in meta-analyses of eight prospective cohort studies, in which 2624 participants died of CVD during follow-up, individuals in the lowest quantile of serum 25 (OH)D concentrations had an increased risk of CVD and all-cause mortality[24]. However, this finding may be confounded by the heterogeneity of data from different study designs, adjustment for different covariates in each study, several studies were possibly

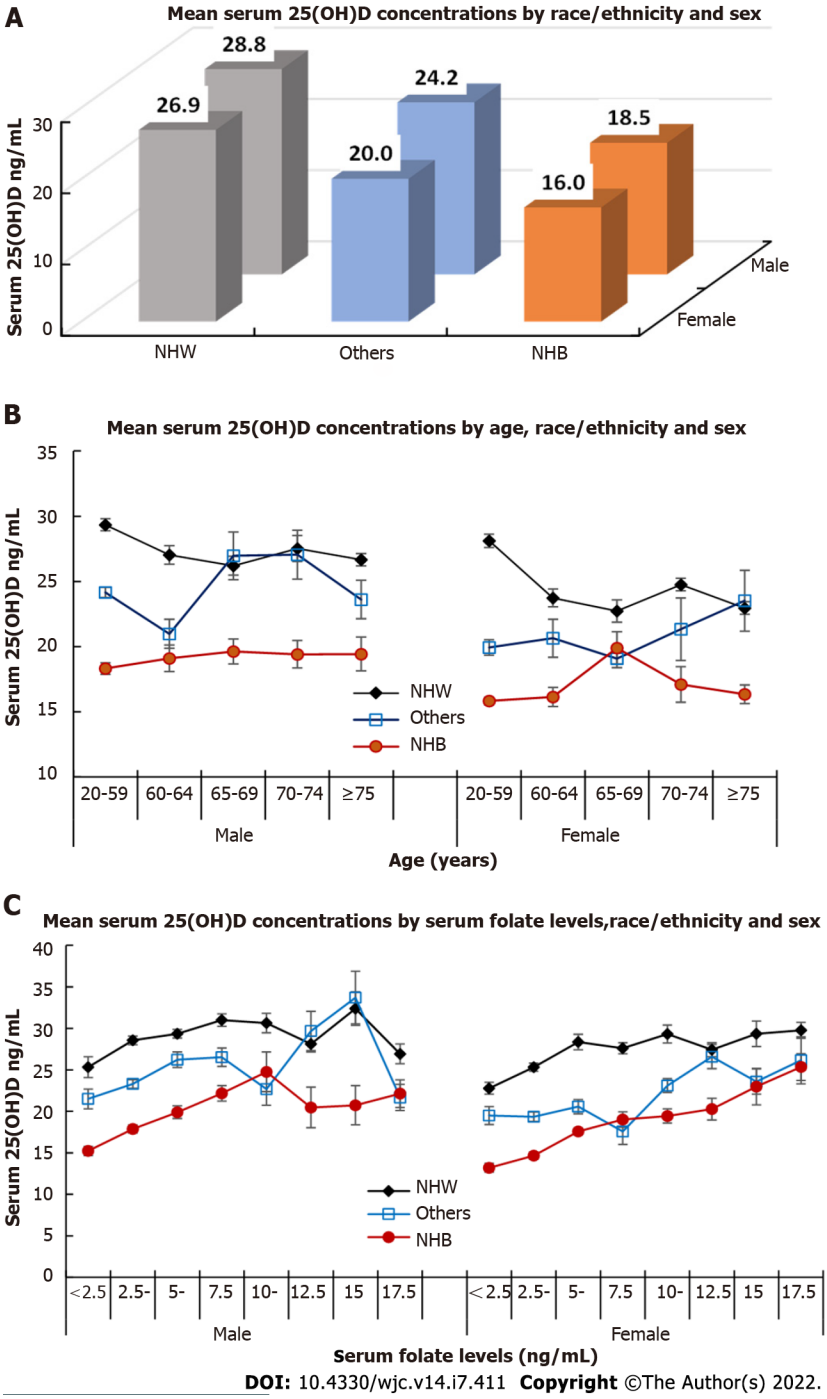


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Figure 3 Example of classification and regression trees with serum 25 hydroxyvitamin D ≥ 20 *vs* < 20 ng/dL in both sexes. A: Decision tree. Node 1: is the "root" node. Nodes 2 to 5 are the "leaves". Node 5 is also called as the terminal node, including five sub-nodes (5a – 5e). Each "leaf" is a classification labeled for the output variable {serum 25-hydroxyvitamin D [25(OH)D]}, showing in each oval-shaped box. Under each box, the values listed on right indicates the % of total sample size, and the value listed on the left indicates the % of those with serum 25(OH)D concentration ≥ 20 ng/mL. If the value on the left-listed is > 0.5 then the corresponding oval-shaped box is labeled as 25(OH) ≥ 20 ng/mL, otherwise labeled as < 20 ng/mL; B: An example of top 10 important variables presented by their mean decrease in Gini (MDG) index, a higher MDG indicates a stronger predictor for the output variable. 25(OH)D: 25-hydroxyvitamin D; RACEGP: Race group, coded as racegp = 1 for non-Hispanic White, racegp = 2 for non-Hispanic Black, and racegp = 3 for all the other race groups; Sex = 1 for male, and sex = 2 for female; FOP: Serum folate level; MDG: Mean decrease in Gini index.

confounded by other lifestyle-related factors, such as body weight and physical activity. Studies have shown that serum 25(OH)D concentrations are significantly associated with obesity and physical activity[5,25], as well as MetS is significantly associated with other CVD risks[2]. In our analysis, we adjusted key covariates and further examined the joint effect of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality, which also demonstrated that individuals with vitamin D sufficiency [serum 25(OH)D concentration ≥ 30 ng/mL] had a significant protective effect on CVD and all-cause mortality reduction even among those with positive MetS.

The mechanism by which vitamin D deficiency and MetS lead to an increased risk of CVD and all-cause mortality has not been fully elucidated. Several potential mechanisms have been hypothesized. First, the heart and the vasculature possess vitamin D receptors as well as the 1α–hydroxylase enzyme to activate serum 25(OH)D to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and thus are important target tissues for vitamin D. Second, several vitamin D effects on the electrophysiology, contractility, and structure of the heart suggest that vitamin D deficiency might be a causal factor for myocardial diseases [22,26]. Third, significant associations of vitamin D deficiency with obesity, hypertension, insulin resistance, and dyslipidemia (*i.e.*, the major components of MetS) have been reported by several researchers[5,24]. Although the complex association of vitamin D and MetS with risk of CVD requests more studies, findings of the joint effect of vitamin D deficiency and MetS, as well as a strong protective effect of vitamin D on CVD and all-cause mortality risk highlight the importance to control vitamin D deficiency and MetS for risk reduction of CVD and all-cause mortality.



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Figure 4 Mean Serum 25-hydroxyvitamin D concentrations (ng/mL) by race/ethnicity and sex (A), and by age (B), and serum folate levels (C). Serum 25(OH)D: Serum 25-hydroxyvitamin D; NHW: Non-Hispanic White; NHB: Non-Hispanic Black; Other: All other race/ethnicity.

In CART analysis, we observe that the top 10 important predictors varied by the study samples, and the cutoffs of the output variables [*i.e.*, serum 25(OH)D concentrations]. The main results indicate that race/ethnicity was one of the most important predictors. NHB had the lowest mean of serum 25(OH)D concentrations followed by the other racial/ethnic groups, and NHW. Differences in socioeconomic status and biological factors may explain the race/ethnic difference in mean serum 25(OH)D concentrations as well, including education, overweight and obesity, and prevalence of chronic conditions of hypertension, diabetes mellitus, and chronic kidney disease. Findings from the CART analysis suggest that to classify individuals with different serum 25(OH)D concentrations, sociodemographic factors (age, sex, poverty level, and regions) and biomarkers (BMI, waist circumference, glomerular filtration rate, and serum total folate, red blood folate, glucose, insulin, C-peptide, triglyceride, and serum vitamin E concentrations) were potential predictors. Of these biomarkers, serum folate and red blood cell folate concentrations had a relatively higher mean decrease in the GINI index (*i.e.*, a higher impact on the classification analysis) than several other biomarkers (Table 4). Folate is an essential micronu-

trient from diet or diet supplementation and is also synthesized locally by the intestinal microbiome [27]. A positive association between serum folate and serum 25(OH)D concentrations and a significant association between serum folate and muscle strength have been reported by other studies[28,29]. Although a detailed analysis of potential interactions of these biomarkers is beyond the scope of the present study, the role of serum folate with serum 25(OH)D in cardiovascular health and mortality warrants further study.

It should be noted that there are several limitations of the study when interpreting the main findings. First, the NHANES III does not include participants who were hospitalized at the time of the baseline survey, which may lead to an underestimation of the association between serum 25(OH)D concentrations and mortality risk. Because individuals with the severe disease might have been hospitalized or have died before the baseline survey. Second, the estimated associations of serum 25(OH)D concentrations and MetS with risk of CVD and all-cause mortality may be under-or over-estimated if the values of baseline serum 25(OH)D concentrations and MetS components changed during the follow-up. Third, the nonsignificant association of serum 25(OH)D concentrations and MetS with risk of cerebrovascular disease (CBVD) was possibly due to the small sample size of CBVD cases. Further studies are needed to focus on CBVD risk using a larger sample size. Last but not the least, although Machine Learning (ML) offers a useful tool to develop a prediction algorithm, findings from ML, including CART analysis offer an overall and useful data mining approach. For example, the results from Table 4 suggest that stratified samples are needed to improve the CART algorithms.

This study also has several strengths. First, the NHANES III, using a complex survey sampling approach, provides a nationally representative sample of residents living in the United States. Second, the survey design, process, and laboratory measures employed standard protocols that are supported and coordinated by the CDC. Third, the measures of CVD and all-cause mortality were highly reliable by using a standardized record process of the National Death Index system[13,30]. Fourth, we analyzed the association prospectively, which allowed us to test a potential causal association of baseline serum 25(OH)D concentrations and MetS with CVD and all-cause mortality risk. Last, to the best of our knowledge, the study is the first to examine the joint effect of vitamin D and MetS on the risk of CVD and all-cause mortality using a nationally representative sample and has the longest follow-up by using the NHANES III. Findings from the CART analysis add to new insights into classifying high-risk groups with lower vitamin D concentrations.

CONCLUSION

In conclusion, vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. There was a significant joint effect of vitamin D deficiency and MetS on the risk of mortality. Findings of the CART analysis may be useful to identify individuals positioned to benefit from interventions to reduce the risk of CVD and all-cause mortality.

ARTICLE HIGHLIGHTS

Research background

Studies that tested whether there is a significant joint effect of vitamin D intake and metabolic syndrome (MetS) on the risk of cardiovascular disease (CVD) and all-cause mortality are sparse.

Research motivation

The third National Health and Nutrition Examination Survey provides us an unique opportunity to test the research questions using a large-scale population sample size, with an average of 18 years follow-up. An integrated analysis approach of standard statistics methods and Machine Learning may provide new insights into the study field and add new evidence of clustering risk factors to control CVD and all-cause mortality.

Research objectives

To test the hypotheses that lower serum 25 hydroxyvitamin D [25(OH)D] concentrations (a marker of decreased vitamin D intake) and MetS have a long-term impact on the risk of CVD and all-cause mortality, and individuals with vitamin D deficiency can be detected by key covariates.

Research methods

A prospective analysis of 9094 adults who participated in the Third National Health and Nutrition Examination Survey in 1988 to 1994 and were followed for each participant's vital status by December 31, 2015, was conducted.

Research results

Findings from the study add new evidence to the body of research by highlighting the joint effects of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality among the United States adults. A comprehensive intervention for both groups of risk factors are necessary to reduce the risk of CVD and all-cause mortality.

Research conclusions

There is a significant joint effect of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality. The application of standard bio-statistics and Machine Learning techniques provides a new tool to test research hypothesis and provide new insights into health promotion for individuals who are at high risk of unhealthy exposures and risk of CVD and all-cause mortality.

Research perspectives

A high proportion of populations who have lower vitamin D levels and prevalent MetS poses a serious public health issue. Further studies are needed to examine the potential mechanisms by which that may cause vitamin D deficiency and MetS.

ACKNOWLEDGEMENTS

The study used data from the National Center for Health Statistics (NCHS). Findings and conclusions in this report are those of the authors and do not necessarily reflect the views or opinions of the NCHS.

FOOTNOTES

Author contributions: Liu L conceptualized the study and analysis designs, and performed the data analysis and drafted the manuscript; Cui S performed the machine learning analysis. Volpe SL, May NS, Sukumar D, DiMaria-Ghalili RA, Cui S, and Eisen H critically reviewed the study design and analysis methods, and carefully reviewed the results and edited the manuscript. All authors contributed to the study and approved the submission.

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Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

National trend of heart failure and other cardiovascular diseases in people living with human immunodeficiency virus

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Abstract

BACKGROUND

As people living with human immunodeficiency virus (HIV) (PLWH) enjoy longer life expectancy with highly effective antiretroviral therapy, they are encountering challenging cardiovascular health risks.

AIM

To retrospectively examine the increasing burden of cardiovascular diseases in PLWH over the past decade.

METHODS

All hospitalizations for heart failure (HF), ischemic heart disease (IHD), and cerebrovascular disease (CeVD) in PLWH were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes in the National Inpatient Sample from 2008 to 2018. Outcomes included number of hospitalizations, in-hospital mortality, length of stay, and total hospital charge. Trend of the outcomes from 2008 to 2018 were analyzed using Cochran-Armitage trend test and simple linear regression.

RESULTS

The number of hospitalizations for HF in PLWH increased from 4212 in 2008 to 6700 in 2018 (P_{trend} < 0.01). Similar increasing trend was seen with those for IHD and CeVD over the decade (P_{trend} < 0.01). A decreasing trend of in-hospital mortality was observed in all hospitalizations of PLWH (P_{trend} < 0.01) and CeVD in PLWH (P_{trend} < 0.01), but not in those for HF (P_{trend} = 0.67) and IHD (P_{trend} = 0.13). The trend of length of stay was decreasing in all hospitalizations of PLWH (P_{trend} <

0.01), but increasing in those for HF in PLWH (P_{trend} < 0.01). An increasing trend of total hospital charge was observed in hospitalizations for HF, IHD, and CeVD (P_{trend} < 0.01).

CONCLUSION

The burden of cardiovascular diseases has significantly increased in hospitalizations of PLWH from 2008 to 2018. Continued efforts are needed to address the additional cardiovascular risks in this vulnerable population.

Key Words: Cardiovascular; Heart failure; Trend; Human immunodeficiency virus; People living with human immunodeficiency virus

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Core Tip: People living with human immunodeficiency virus (HIV) are at risk of developing cardiovascular diseases, including heart failure, but recent trends in the number of hospitalizations for various cardiovascular causes have not been examined on a national level. This study sought to analyze the trend in the number of hospitalizations for different cardiovascular diseases in people living with HIV to highlight the rising importance of cardiovascular diseases in this vulnerable population. More studies are needed to address the additional cardiovascular risks in people living with HIV, and tailored approach may be beneficial when managing and treating this population.

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INTRODUCTION

As of the year 2020, human immunodeficiency virus (HIV) affected 37.7 million people worldwide with 1.5 million new diagnoses and 680000 deaths due to illnesses associated with acquired immunodeficiency syndrome (AIDS)[1]. HIV infection used to be a debilitating disease leading to fatal infectious diseases, but with the advent of highly effective antiretroviral therapy, life expectancy for people living with HIV (PLWH) has increased by up to 10 years, approaching near-normal life expectancy especially in compliant patients[2,3]. As a result, the importance of cardiovascular diseases (CVDs) in PLWH is continually increasing, especially with new studies suggesting that inflammation and immune activation associated with HIV infection are contributing to additional cardiovascular risk[4].

Many previous studies have indicated that HIV infection is an independent risk factor for CVDs and cerebrovascular diseases (CeVDs), including heart failure (HF), myocardial infarction, and stroke[5-7]. However, studies on yearly dynamic changes brought about by CVDs in PLWH are lacking. Given the increasing burden of CVDs in PLWH, this study serves to elucidate the yearly trend of CVDs in PLWH by examining associated hospitalizations and in-hospital mortality from 2008 to 2018. Heart failure, along with ischemic heart disease (IHD) and CeVD, was used to represent the burden of CVDs in PLWH changing over the years[8].

MATERIALS AND METHODS

Data source

All data used in this study are openly available in the public website of Healthcare Cost and Utilization Project (HCUP) at https://www.hcup-us.ahrq.gov/nisoverview.jsp. The National Inpatient Sample (NIS), a retrospective cohort study developed for the HCUP, is the largest publicly available inpatient database that covers more than 97% of the U.S. population stratified by hospital region and type of insurance[9]. The NIS consists of demographic and hospital characteristics at discharge, which are searchable using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes[10]. As the NIS is fully de-identified and public, ethics committee approval was not required in this study. The datasets used and analyzed during this study are available at https://www.hcup-us.ahrq.gov/databases.jsp[9].

Study population

Total number of hospitalizations of PLWH was calculated as the sum of all hospitalizations with primary or secondary diagnosis of HIV: ICD-9-CM codes 042 and V08, or ICD-10-CM codes B20-24, R75, and Z21. Primary discharge diagnoses of CVDs were defined as follows: HF (ICD-9-CM codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428; ICD-10-CM codes I11.0, I13.0, I13.2, I09.81, I50), IHD (ICD-9-CM codes 410-411; ICD-10-CM codes I20-I25), and CeVD (ICD-9-CM codes 430-438; ICD-10-CM codes I60-I70). HF was chosen as the main CVD of interest as it comprised the largest proportion among the three. Other CVDs, including IHD and CeVD, were also included. The proportion of each CVD among all hospitalizations of PLWH was then calculated for each year. Only patients above 18 years were included, and hospitalizations with missing information on age, sex, and mortality status were excluded (Figure 1).

Outcome measures

The primary outcome of this study was the in-hospital mortality of hospitalizations due to each of the selected CVDs in PLWH. Secondary outcomes included length of hospital stay and total hospital charges.

Statistical analysis

To calculate estimates that represent total nationwide numbers, survey analysis methods were used based on the weights of hospital-level discharge provided by the NIS. The baseline demographic and hospital characteristics including sex, age, race, comorbidities, Charlson comorbidity index, hospital region, hospital bed size, and location were summarized as percentages for categorical variables and as means with standardized error for continuous variables. The crude mortality rate was calculated by each year and linear trends were examined using the Cochran-Armitage trend test. The trends in continuous outcomes were tested based on simple linear regression. A *P* value of less than or equal to 0.05 was considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

From 2008 to 2018, 54987 hospitalizations of adults (> 18 years) with a primary diagnosis of heart failure and secondary diagnosis of HIV were examined. Hospitalization with a primary diagnosis of HF and secondary diagnosis of HIV steadily increased from 4212 in 2008 to 6,700 in 2018 (P_{trend} < 0.001). The yearly demographics and comorbidities are shown in Table 1. About two-thirds of the population were male (65.5% in 2008 and 69.6% in 2018). In the year 2008, age less than 50 years was the largest group, but with progression of time, age group spanning from 50 to 59 years became the largest group. Majority of the population consisted of black race, which decreased over the years from 74.6% in 2008 to 71.5% in 2018 (P_{trend} < 0.001). Comorbidities of hypertension, diabetes mellitus, chronic kidney disease, obesity, and chronic obstructive pulmonary disease all significantly increased from 2008 to 2018 (P_{trend} < 0.001). Of note, hypertension and obesity markedly increased from 65.9% and 7.3% in 2008 to 91.2% and 17.1% in 2018, respectively. Such phenomenon was redemonstrated in the significantly increasing trend of Charlson comorbidity index over the years (P_{trend} < 0.001). These findings are shown in Table 1.

A total of 2,483,868 hospitalizations of PLWH with either primary or secondary diagnosis of HIV were reported from 2008 to 2018. Hospitalizations due to HF in PLWH increased from 4212 in 2008 to 6700 in 2018 (P_{trend} < 0.001). IHD (3921 in 2008 and 4,350 in 2018) and CeVD (2927 in 2008 and 3960 in 2018) followed the same pattern (both P_{trend} < 0.001). However, the overall hospitalizations of PLWH decreased from 236,809 in 2008 to 215,410 in 2018 (P_{trend} < 0.001). At the same time, the proportion of HF, IHD, and CeVD over all hospitalizations of PLWH increased from 4.7% in 2008 to 7.0% in 2018 (all P_{trend} < 0.001). These findings are illustrated in Figure 2.

There was a statistically significant decline in the in-hospital mortality of all hospitalizations of PLWH (P_{trend} < 0.001) from 3.40% in 2008 to 2.28% in 2018. A similar decline was observed in the in-hospital mortality of CeVD in PLWH (P_{trend} < 0.001) from 7.14% in 2008 to 3.67% in 2018. On the other hand, no significant difference was found in the trend of in-hospital mortality rate in hospitalizations due to HF or IHD in PLWH. In-hospital mortality rate was 1.84% in 2008 and 1.49% in 2018 for heart failure (P_{trend} = 0.672), and 1.61% in 2008 and 2.87% in 2018 for IHD (P_{trend} = 0.13). Figure 3 illustrates these findings.

Average length of hospital stay in all hospitalizations of PLWH decreased from 6.74 days in 2008 to 6.18 days in 2018 (P_{trend} < 0.001). However, that of HF in PLWH increased from 4.85 days in 2008 to 5.32 days in 2018 (P_{trend} < 0.001). No significant trend was found with IHD (P_{trend} = 0.294) and CeVD (P_{trend} = 0.341). These trends are illustrated in Figure 4.

Statistically significant increase in average total hospital charge was observed in all hospitalizations of PLWH from 2008 to 2018. Similar trend was seen in hospitalizations for HF, IHD, and CeVD in PLWH (Figure 5). In absolute terms, IHD showed the greatest increase by $53500 from $57324 in 2008 to $110824. In relative terms, HF increased by 123% from $28503 in 2008 to $63566 in 2018. The order of

Table 1 Baseline characteristics of hospitalizations due to heart failure in people living with human immunodeficiency virus from 2008 to 2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P_{trend}
n (sample)	869	954	1021	910	825	868	928	979	1074	1248	1340	< 0.001
n (weighted)	4212	4878	5225	4362	4125	4340	4640	4895	5370	6240	6700	< 0.001
Sex (%)												
Male	65.5	67.1	68.5	64.8	69.0	68.4	65.7	67.4	68.0	67.2	69.6	< 0.001
Female	34.5	32.9	31.5	35.2	31.0	31.6	34.3	32.6	32.0	32.8	30.4	< 0.001
Age (%)												
< 50	41.8	38.8	41.2	36.7	29.7	27.2	29.1	27.4	28.1	25.0	24.9	< 0.001
50-59	35.2	38.5	36.2	41.3	41.1	42.5	42.0	39.6	37.9	37.3	35.1	< 0.001
60-69	16.7	16.7	16.5	16.5	20.8	22.8	22.2	24.8	26.9	28.8	29.0	< 0.001
≥ 70	6.3	6.0	6.1	5.5	8.4	7.5	6.7	8.2	7.1	8.9	10.0	< 0.001
Race (%)												
White	11.8	12.0	12.8	13.6	16.9	15.5	18.1	16.9	17.3	17.6	15.9	< 0.001
Black	74.6	74.5	76.2	76.4	71.7	72.1	70.2	73.8	71.5	69.2	71.5	0.002
Hispanic	10.9	8.9	8.3	6.2	6.6	7.9	8.5	5.6	7.7	8.8	9.5	0.203
Asian	0.6	0.1	0.3	0.3	0.5	0.5	0.2	0.3	0.7	1.1	0.7	< 0.001
AI/AN	0.1	0.0	0.1	0.0	0.1	0.4	0.2	0.2	0.0	0.1	0.3	< 0.001
Other	2.0	4.5	2.3	3.5	4.2	3.6	2.8	3.2	2.7	3.2	2.1	< 0.001
Comorbidities (%)												
Hypertension	65.9	67.9	64.7	67.5	81.8	80.1	68.4	69.7	86.6	73.4	91.2	< 0.001
Diabetes mellitus	33.4	33.2	31.3	32.5	34.4	35.1	37.8	37.4	38.0	37.9	36.7	< 0.001
CKD	53.1	50.4	50.4	49.2	53.9	56.9	54.5	58.1	60.6	62.6	61.0	< 0.001
Obesity	7.3	7.9	11.8	11.3	10.1	12.4	14.4	18.8	16.3	16.3	17.1	< 0.001
COPD	31.2	32.7	33.0	38.1	43.8	47.1	39.4	42.2	41.4	42.6	43.4	< 0.001
Charlson comorbidity index												
Mean (SD)	NR	NR	6.18 (0.10)	6.17 (0.11)	6.11 (0.12)	6.28 (0.11)	6.27 (0.11)	5.37 (0.11)	6.86 (0.10)	7.19 (0.09)	6.99 (0.09)	< 0.001
Hospital characteristics												

Hospital region (%)												
Northwest	25.4	35.3	35.9	30.9	32.1	31.8	28.0	274	24.8	25.8	26.3	< 0.001
Midwest	11.5	11.1	13.1	11.4	11.6	9.7	13.6	11.7	10.4	9.3	11.6	< 0.001
South	58.6	48.9	44.7	52.5	46.1	49.8	50.7	54.4	54.5	54.3	53.7	< 0.001
West	4.5	4.7	6.4	5.2	10.2	8.8	7.7	6.4	10.3	10.7	8.4	< 0.001
Hospital bed size (%)												
Small	8.1	9.5	9.6	6.0	11.5	10.3	16.8	13.3	14.4	17.0	17.8	< 0.001
Medium	21.7	25.0	24.6	23.5	30.3	28.8	26.4	30.6	29.9	27.0	27.6	< 0.001
Large	70.2	65.5	65.8	70.5	58.2	60.9	56.8	56.1	55.7	56.0	54.6	< 0.001
Urban location (%)												
Rural	5.5	3.8	2.9	3.4	2.9	3.6	2.6	3.4	3.1	3.8	4.0	< 0.001
Urban nonteaching	28.0	28.7	29.2	33.3	26.4	24.3	16.9	18.0	18.0	13.9	14.1	< 0.001
Urban teaching	66.5	67.5	68.0	63.3	70.7	72.1	80.5	78.6	78.9	82.2	81.9	< 0.001

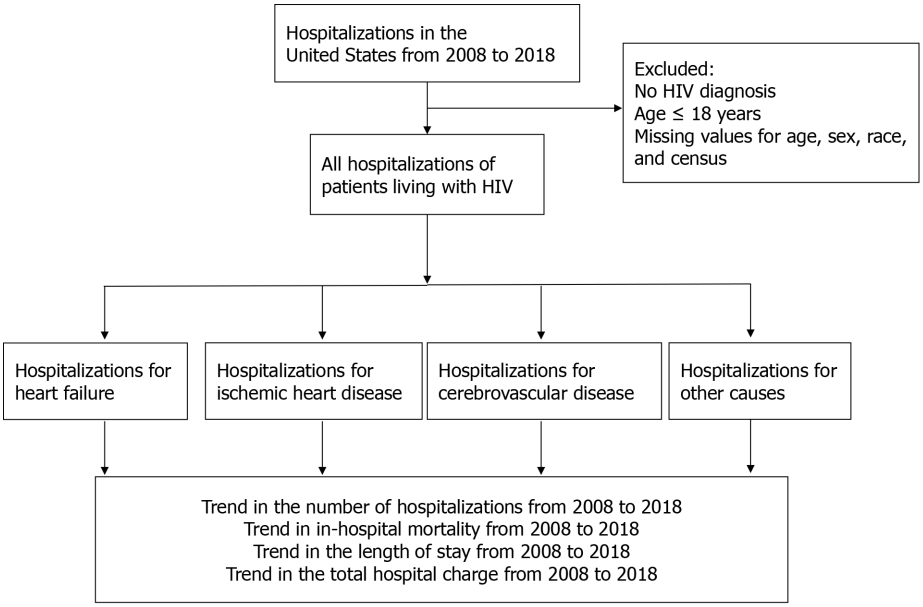
AI/AN: American Indian/Alaska Native; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus; NR: Not reported; SD: Standard deviation.

total hospital charge was IHD, CeVD, and HF from highest to lowest.

DISCUSSION

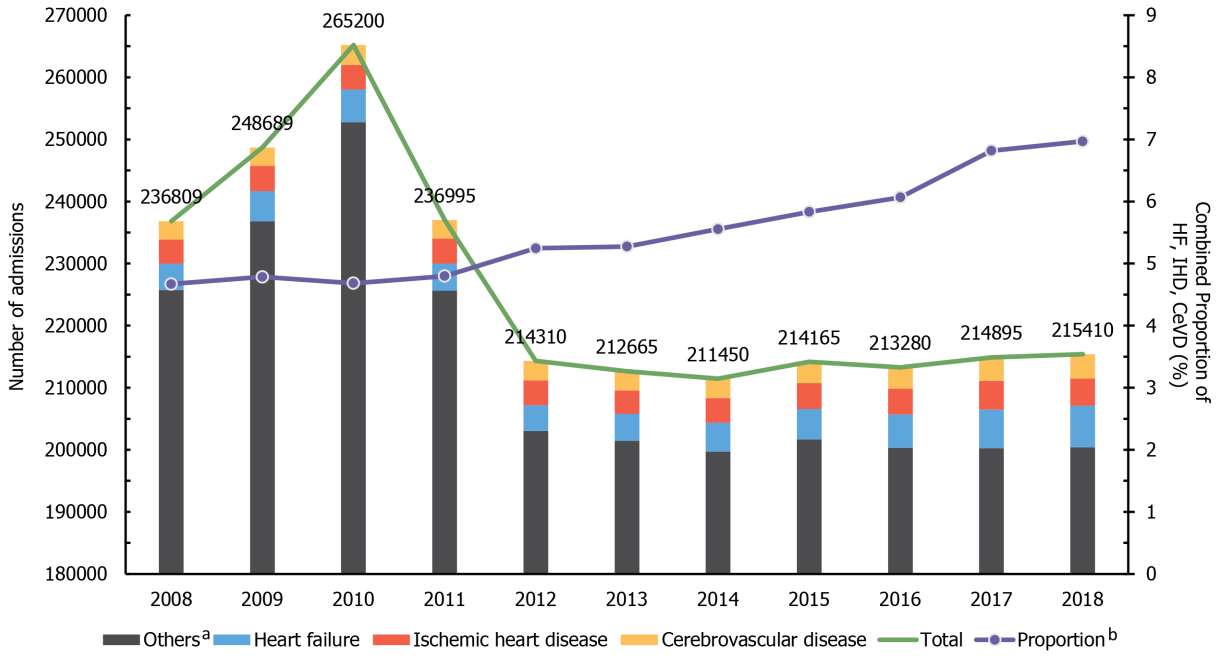
PLWH have increased risks of CVDs, including myocardial infarction, HF, sudden cardiac death, peripheral artery disease, and CeVD[11,12]. The mechanism of this increased risk has been explained by a combination of factors in HIV tropism in cardiac myocytes and effects related to the immunologic response triggered by HIV[13,14]. In addition, traditional cardiovascular risk factors, such as dyslipidemia, diabetes, smoking, and HTN are more prevalent in PLWH[15]. Genetic factors and the association of antiretroviral and metabolic abnormalities may also be playing a role in increasing cardiovascular risks in PLWH[16,17,18]. On the other hand, immune activation and chronic inflammation mediated by HIV contribute to the progression of CVD. Ongoing viral replication and release of inflammatory markers, such as hsCRP, IL-6, and D-Dimer, trigger subclinical atherosclerosis and increase CV events[4]. HIV-associated atherosclerosis is known to have its own features, such as non-calcified plaques, given this chronic inflammation[11,19]. Even with HIV suppression with antiretroviral therapy, chronic inflammation persists, putting PLWH at risk of more cardiovascular events[4].

According to the trends described in the present study, hospitalizations due to HF, IHD, and CeVD in PLWH increased while overall hospitalizations of PLWH decreased. This is likely related to the impact



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Figure 1 Flow chart of this study. The flow chart illustrates the underlying design of the present study. HIV: Human immunodeficiency virus.



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Figure 2 Yearly trend of heart failure and other cardiovascular diseases in all admissions of people living with human immunodeficiency virus. Bar graph shows the yearly trend in the admissions of heart failure (HF) (blue), ischemic heart disease (IHD) (red), and cerebrovascular disease (CeVD) (yellow) in people living with human immunodeficiency virus (HIV). Gray bars show the number of all admissions of people living with human immunodeficiency virus (PLWH) for reasons other than HF, IHD, and CeVD. Violet line represents the combined proportion of HF, IHD, and CeVD among all hospitalizations of PLWH. Green line shows the total number of hospitalizations occurring in PLWH. [a]"Others" refer to all admissions of PLWH for reasons other than HF, IHF, and CeVD. [b]"Proportion" refers to the combined proportion of HF, IHD, and CeVD among all hospitalizations of PLWH. CeVD: Cerebrovascular disease; HF: Heart failure; IHD: Ischemic heart disease; PLWH: People living with human immunodeficiency virus.

of highly effective antiretroviral therapy, which allowed PLWH to have near-normal life expectancy and resulted in a rise in morbidity and mortality associated with age-related causes[20,21]. The dramatic changes brought about by antiretroviral therapy is shown by how the annual mortality of PLWH exceeded 20% prior to 1996 but declined to less than 2% only after a decade later[22]. With improvement in life expectancy, reduction of infectious burden, and changes in lifestyle, the prevalence of CVD is also expected to increase[23]. Increase in the prevalence of comorbidities among PLWH was also noted in the

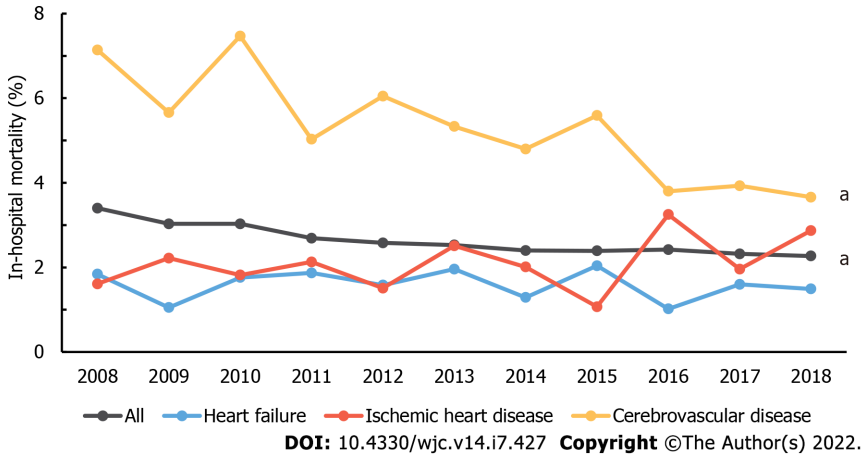


Figure 3 Yearly trend of average in-hospital mortality rate in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of in-hospital mortality in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the in-hospital mortality of all admissions occurring in people living with human immunodeficiency virus. Significant P_{trend} < 0.05 is marked with an asterisk (a) at the end of the linear graph.

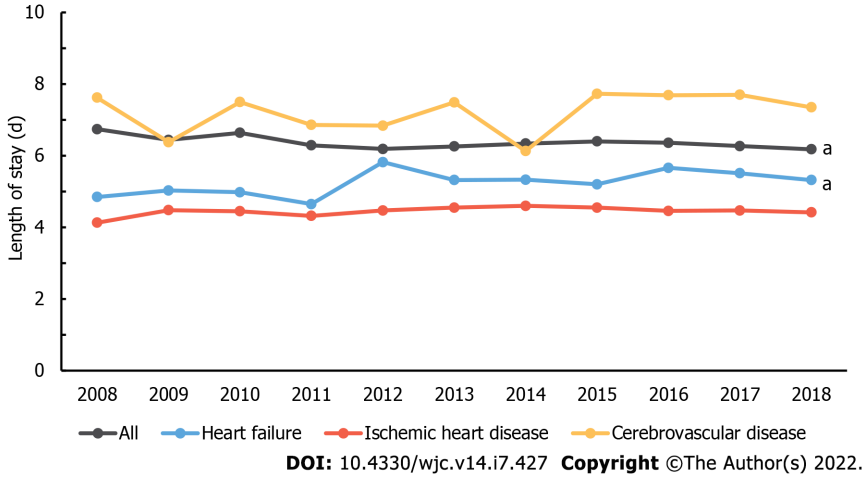
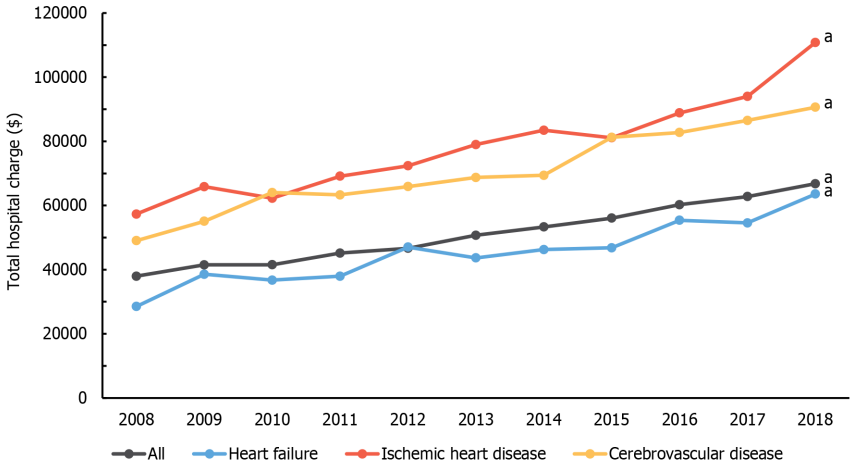


Figure 4 Yearly trend of average length of hospital stay in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of length of hospital stay in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the length of hospital stay in all admissions occurring in PLWH. Significant P_{trend} < 0.05 is marked with an asterisk (a) at the end of the linear graph.

present study (Table 1).

Interestingly, a precipitous reduction in hospitalizations of PLWH from 2010 to 2012 was observed. This may be due to the National HIV/AIDS Strategy implemented in 2010, intensifying HIV prevention efforts, facilitating access to care for PLWH, and creating a coordinated national response to the HIV epidemic[24,25]. The President's Emergency Plan for AIDS Relief in the U.S., whereby the government supported high active antiretroviral therapy (HAART) for more than 3.9 million people and provided care for nearly 13 million people, was also expanded in the year 2011[26]. With these national efforts to combat HIV, hospitalizations of PLWH have been subdued since 2012 and has been remaining relatively stable.

The trend analysis from this present study coincides with those seen in previous studies. According to a population-based cohort study from 1999 to 2018, diagnosis and mortality rate of HIV infection underwent annual decrease of 5% and 8%, respectively[27]. Earlier diagnosis, lower probability of AIDS-associated infections, and antiretroviral therapy factored into this decline[27]. The decline of in-hospital mortality of CeVD in PLWH seen in this study may be due to the reduced severity of stroke among PLHW explained by the effectiveness of HAART and better tools for stroke diagnosis and treatment[28]. This study did not show significant changes in the in-hospital mortality of HF and IHD in PLWH despite other epidemiological studies showing a decrease in the general population[29,30]. From such finding, one can hypothesize that additional cardiovascular risk factors are present in PLWH, which are not being sufficiently addressed.



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Figure 5 Yearly trend of average total hospital charge in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of total hospital charge in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the total hospital charge in all admissions occurring in PLWH. Significant P-trend < 0.05 is marked with an asterisk (a) at the end of the linear graph.

The decrease in average length of hospital stay in PLWH over time has also been reported by a retrospective study of more than 700,000 admissions in three hospitals in New York City[31]. Rowell-Cunsolo *et al*[31] reported decreases in length of stay from 2006 to 2014, but noted that the length of stay was greater in PLWH than the general population. Other studies have also produced comparable results, including Berry *et al*[32] who reported decline in hospitalizations due to AIDS-defining illnesses from 6.7 to 2.7 per 100 person-years from 2001 to 2008 and Heslin *et al*[33] who reported 10% decrease in length stay from 2006 to 2013[32,33].

To the best of authors' knowledge, the present study was the first to use the largest inpatient database in the U.S. to examine the trend in the number of hospitalizations, stratified to cardiovascular causes, in people living with HIV. In addition, trends in the in-hospital mortality, length of hospital stay, and total hospital charge were also uniquely examined. By analyzing the yearly trend of CVDs in PLWH, the objective of this study is to increase the awareness of burden of CVD in this more vulnerable population. Hospitalizations due to CVD has increased in PLWH, highlighting the importance of evaluating and managing cardiovascular risks factors imparted by HIV. Meanwhile, more research investigating the underlying mechanisms that link HIV and CVD must continue to provide potential solutions to this problem of additional risk. Mechanisms whereby antiretrovirals may contribute to this risk should also be studied. With better understanding of the association between HIV infection and CVD, tailored approaches may be warranted in managing cardiovascular risk factors in PLWH.

This study contains several limitations. Administrative data was used for clinical outcomes by using NIS in analyzing yearly trends for CVDs in PLWH. NIS data can have varying degrees of accuracy since cardiovascular events can be coded differently, leading to underestimation of event rates and misclassification[34]. As this study relied on NIS data, there was no control in either exposure or outcome. Not all cardiovascular diseases were included in the analysis. Age-standardized in-hospital mortality could not be calculated due to the skewed distribution of mortalities in different age groups. Prospective cohort studies should be implemented to better examine the burden of CVD in PLWH.

CONCLUSION

The present study used a national representative sample of U.S. hospital admissions from 2008 to 2018 to reach the following conclusions. First, hospitalizations due to HF, IHD, and CeVD in PLWH increased while total hospitalizations of PLWH decreased. Second, hospitalizations due to HF in PLWH steadily increased over 11 years along with the concomitant increase in the prevalence of comorbidities. Third, declining trends in the in-hospital mortality rate of overall hospitalizations in PLWH and those due to CeVD in PLWH were observed, whereas no change in trend was present with HF and IHD. Fourth, while the length of hospital stay in all hospitalizations of PLWH decreased, that due to HF increased. Finally, the healthcare costs increased for all admissions for all HF, IHD, and CeVD in PLWH. The results from this study demonstrate the increasing burden of CVD in PLWH as demonstrated by increasing hospitalizations, lack of improvement in in-hospital mortality, and increased length of hospital stay in those with HF.

ARTICLE HIGHLIGHTS

Research background

Recent studies have reported a strong association between human immunodeficiency virus (HIV) infection and cardiovascular diseases. However, studies examining the trend of cardiovascular diseases in people living with HIV on a national level have been lacking.

Research motivation

The trends of cardiovascular diseases in people living with HIV have not been sufficiently examined using nationally representative database.

Research objectives

To demonstrate that the burden of cardiovascular disease in people living with HIV has been increasing in the recent decade, emphasizing the need for continual efforts to address the excess cardiovascular risks in this vulnerable population.

Research methods

We retrospectively examined the National Inpatient Sample from 2008 to 2018 to analyze the trends in the hospitalizations for various cardiovascular diseases in people living with HIV. In addition, we looked at the trends of in-hospital mortality, length of hospital stay, and total hospital charge. Cochran-Armitage test and simple linear regression were used to examine the trends of categorical and continuous variables, respectively.

Research results

Hospitalizations for heart failure, ischemic heart disease, and cerebrovascular disease in people living with HIV showed an increasing trend, while the total number of hospitalizations in people with living HIV showed a decreasing trend from 2008 to 2018. The trend of in-hospital mortality and length of stay were variable in contrast to total hospital charge, which demonstrated a substantially increasing trend over the decade.

Research conclusions

Nationally representative data showed that the burden of cardiovascular diseases in people living with HIV has been significantly.

Research perspectives

Further studies and preventative measures are needed to mitigate the additional cardiovascular burden in people living with HIV.

FOOTNOTES

Author contributions: Park DY and An SK designed the research; Park DY and An SK performed the research; Park DY and An SK contributed analytic tools; Park DY and An SK analyzed the data; Park DY, An SK, Romero ME, Murthi M, and Atluri R wrote the paper, validated the results, and reviewed and edited the drafts.

Institutional review board statement: This study was exempt from institutional review board as it solely used deidentified data openly and readily available in a public database.

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

Conflict-of-interest statement: All the authors declare that they have no conflict of interest relevant to this study.

Data sharing statement: All data used in this study are openly available in the public website of Healthcare Cost and Utilization Project (HCUP) at https://www.hcup-us.ahrq.gov/nisoverview.jsp.

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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LETTER TO THE EDITOR

Heart failure with reduced, mildly reduced, or preserved left ventricular ejection fraction: Has reasoning been lost?

Andrew Xanthopoulos, Grigorios Giamouzis, John Skoularigis, Filippos Triposkiadis

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Abstract

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by end-diastolic volume, has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this LVEF-based terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions in HF, especially at the higher end of the LVEF spectrum.

Key Words: Arbitrary; Cut off; Guidelines; Limitations; Normal left ventricular ejection fraction range; Phenotypic persistence

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Core Tip: Left ventricular ejection fraction (LVEF) has been consistently used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions, especially at the higher end of the LVEF spectrum.

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TO THE EDITOR

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by LV end-diastolic volume, is the only biomarker that has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades[1]. Accordingly, HF has been classified into HF with reduced LVEF (HFrEF), HF with midrange or mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF) using various, continuously changing LVEF cutoffs. A mandatory prerequisite for the use of this LVEF-based terminology is the definition of the normal LVEF range, which is lacking. From this perspective, we discuss the limitations related to the current LVEF-based classification of HF and provide examples of erroneous conclusions that can be drawn, especially in HF patients at the higher end of the HF spectrum.

The LVEF-based classification of HF was initially applied several decades ago in the clinical trials of neurohormonal inhibitors in which LVEF cutoffs of < 35% or 40% were chosen arbitrarily to define patients with HF perceived to be at greatest risk (HFrEF). Several years later, clinical trials with similar agents and endpoints were conducted in patients with HF with an LVEF of ≥ 40%-50% (HFpEF), but they were considered unsuccessful for various reasons[2,3]. Recently, another HF phenotype (HFmrEF) was added based on the underrepresentation of patients with HF with an LVEF of 40%-50% in clinical trials. The LVEF cutoffs used for HF classification have varied continuously in the guidelines issued by scientific societies (Figure 1)[4]. The 2013 American College of Cardiology Foundation/American Heart Association guidelines defined HFrEF by an LVEF of ≤ 40%, borderline HFpEF by an LVEF of 41%-49%, and HFpEF by an LVEF of ≥ 50%[5]. By contrast, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines defined HFrEF and HFpEF by an LVEF of < 50% and ≥ 50%, respectively, and did not recognize borderline HFpEF or HFmrEF as a distinct entity[6]. Furthermore, in the recent Universal Definition and Classification of Heart Failure[7], which was adopted by the European Society of Cardiology[8], HF classification includes HFrEF with an LVEF of ≤ 40%, HFmrEF with an LVEF of 41%-49%, and HFpEF with an LVEF of ≥ 50%. Subsequently, another classification of HF was proposed, which defines HFrEF by an LVEF of < 40%, HFmrEF by 40% ≤ LVEF < normal, and HF with normal EF by an LVEF of ≥ 55% in men and ≥ 60% in women[9]. LVEF can be reduced, mildly reduced, preserved, or normal; however, what is the normal LVEF range? According to the 2015 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the normal reference range for LVEF is 52%-72% for males and 54%-74% for females[10]. The latest guidelines from the British Society of Echocardiography define LVEF ≥ 55% as normal (preserved)[11]. However, several recent studies have raised serious concerns regarding the normal LVEF range as proposed by echocardiographic societies. Wehner *et al*[12] investigated the relationship between LVEF and survival by linking physician-reported LVEF on 403977 echocardiograms obtained from 203135 patients to all-cause mortality in the United States, and validated their findings in a dataset including 45531 echocardiograms and 35976 patients from New Zealand. During follow-up, unadjusted hazard ratios for mortality showed a U-shaped relationship for LVEF with a nadir of risk at an LVEF of 60%-65% in both datasets. The results were similar after adjusting for conditions associated with an elevated LVEF, including mitral regurgitation, increased wall thickness, and anemia and when restricted to patients reported to have HF at the time of the echocardiogram (Figure 2). Slightly different but trending in the same direction were the findings of another study including approximately 500000 participants, which reported that in both women and men, mortality was lowest at an LVEF of 65.0%–69.9%[13]. However, in the same study, sex-dependent differences in the relationship between LVEF and mortality were observed. In women, an increased risk of cardiovascular-related mortality persisted to an LVEF of 60.0%–64.9%, whereas in men, the equivalent LVEF was lower (55.0%–59.9%) (Figure 3)[13]. Sex-related differences were also reported in 4632 patients from coronary computed tomography angiography evaluation for clinical outcomes, namely, an international multicenter registry in which LVEF was measured by cardiac computed tomography and participants were categorized according to LVEF (low < 55%, normal 55%–65%, and high > 65%) [14]. After 6 years of follow-up, no difference in mortality was observed in patients with high LVEF in the overall cohort. However, when data were stratified by sex, women with high LVEF died more often from any cause compared to women with normal LVEF, while an opposite trend was observed in men [14]. Thus, the LVEF-based terminology for HF classification is challenged based on recent evidence.

Therefore, it is not surprising that the LVEF-based classification might lead to erroneous conclusions when interpreting the results of various studies enrolling HF patients at the upper end of the LVEF spectrum (Table 1). A typical example is the recently published Empagliflozin outcome trial in patients with chronic HF with preserved EF (EMPEROR-preserved trial), which reported a benefit with

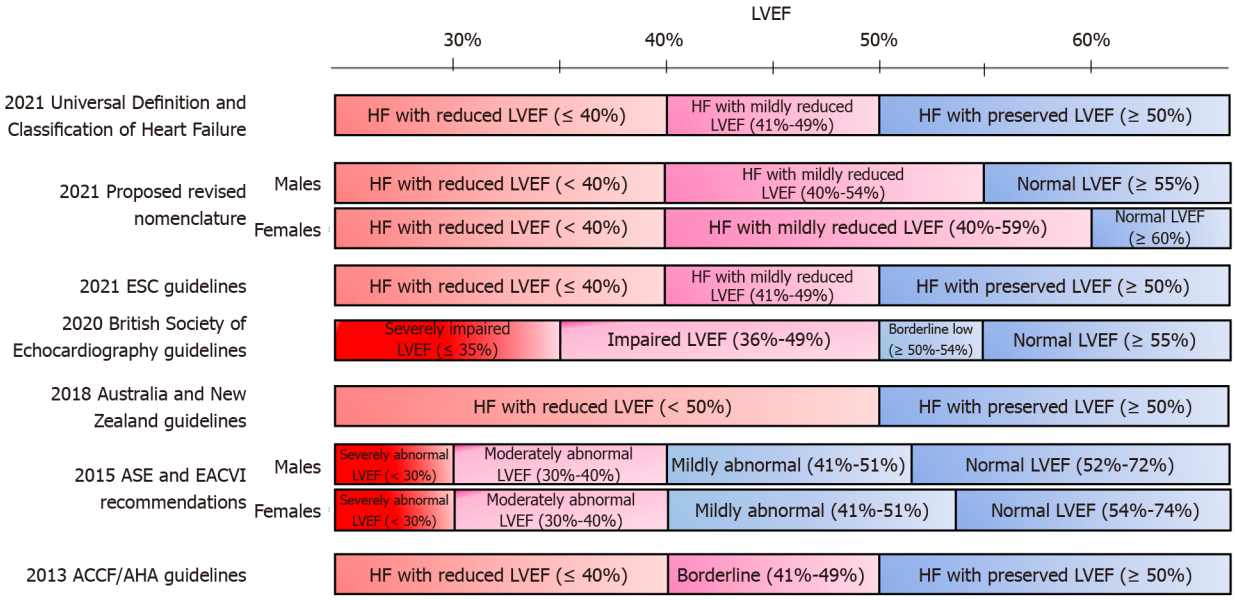
Table 1 Heart failure studies including patients with mildly reduced and preserved left ventricular ejection fraction

Ref.		Drug	LVEF cut off
Registries			
Yancy *et al*[22]	ADHERE	-	≥ 40
Fonarow *et al*[23]	OPTIMIZE-HF	-	≥ 40%; ≥ 50%
Steinberg *et al*[24]	GWTG-HF	-	≥ 50%; 40%-50%
Randomized controlled trials			
Yusuf *et al*[25]	CHARM-PRESERVED	Candesartan	> 40%
Cleland *et al*[26]	PEP-CHF	Perindopril	> 40%
Massie *et al*[27]	I-PRESERVE	Irbesartan	≥ 45%
van Veldhuisen *et al*[28]	SENIORS	Nebivolol	> 35%
Redfield *et al*[29]	RELAX Trial	Phosphodiesterase-5 inhibitors	≥ 50
Yamamoto *et al*[30]	J-DHF	Carvedilol	> 40%
Ahmed *et al*[31]	DIG-PEF	Digitalis	> 45%
Pitt *et al*[32]	TOPCAT	Spironolactone	≥ 45%
Solomon *et al*[33]	PARAMOUNT	Sacubitril/Valsartan	≥ 45%
Solomon *et al*[34]	PARAGON HF	Sacubitril/Valsartan	≥ 45%
Pieske *et al*[35]	SOCRATES-PRESERVED	Vericiguat	≥ 45%
Armstrong *et al*[36]	VITALITY-HFpEF	Vericiguat	≥ 45%
Anker *et al*[15]	EMPEROR-PRESERVED	Empagliflozin	> 40%
Solomon *et al*[37]	DELIVER trial	Dapagliflozin	> 40%
Meta-analysis			
Meta-analysis Global Group in Chronic Heart Failure[38]	MAGGIC	-	≥ 50
Zheng *et al*[39]	Systematic review and meta-analysis	Neurohormonal inhibitors	≥ 40%

LVEF: Left ventricular ejection fraction.

empagliflozin (compared with placebo) in HFpEF defined by an LVEF > 40%[15,16] which is different from the 50% cutoff recommended in the Universal Definition and Classification of Heart Failure[7]. It is noteworthy that in the EMPEROR-preserved trial, ~90% of the patients suffered from hypertension, ~49% from diabetes, and ~51% from atrial fibrillation. By contrast, in a study by Lupon *et al*[17], which was used as evidence supporting phenotypic persistence in HFpEF[18], an LVEF cutoff of 50% was used and the patient characteristics were entirely different from those in the EMPEROR-preserved trial with approximately 12% of the participants suffering from hypertrophic cardiomyopathy and 36% from valvular heart disease. Thus, when interpreting these two HFpEF studies, it would be challenging to extrapolate the findings of one to the other. Therefore, no firm conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF.

LVEF-based classification of HF phenotypes has served well over the years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as longitudinal strain[19] and cardiac power[20] outperform the LVEF. The incorporation of artificial intelligence (AI) in diagnostic modalities, outcome predictions, and management of HF (individualized precision medicine) constitutes a major development in the field of cardiovascular medicine. In this regard, developing and validating universally accepted scoring systems based on AI would be a fruitful area of research. The LVEF has been considered the holy grail for HF classification treatment guidance for years. The time for change has come, unless one wants to justify those claiming that most published research findings are false[21].



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Figure 1 There is significant discordance in the normal values of left ventricular ejection fraction reported by several major scientific societies and associations. This makes the classification of heart failure based on the left ventricular ejection fraction problematic. ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ASE: American Society of Echocardiography; EACVI: European Association of Cardiovascular Imaging; ESC: European Society of Cardiology.

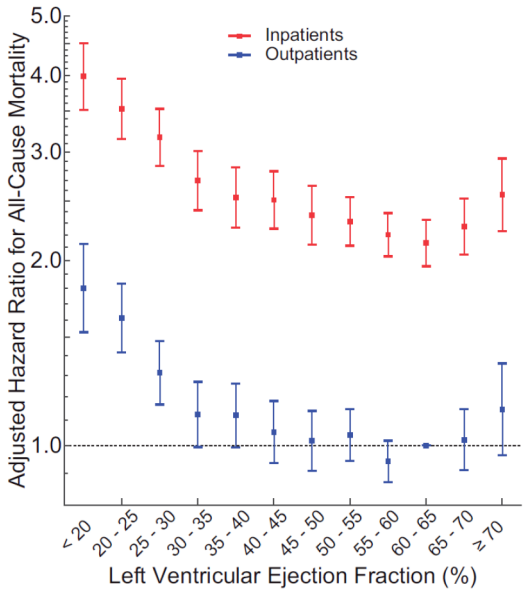


Figure 2 Left ventricular ejection fraction adjusted hazard ratios in patients with heart failure (number of echocardiograms = 40616). Left ventricular ejection fraction (LVEF) intervals are inclusive of the lower threshold. Error bars represent the 95%CI. The referent group was outpatients with an LVEF of 60%-65%. While 51192 echocardiograms were performed on patients with heart failure in the primary analysis, only 40616 echocardiograms are represented in this figure due to excluding echocardiograms missing measurements of end-diastolic volume index or wall thicknesses, for which adjustments were made in the analysis. Citation: Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020; 41(12): 1249-1257. Copyright ©The Author(s) 2019. Published by the European Society of Cardiology.

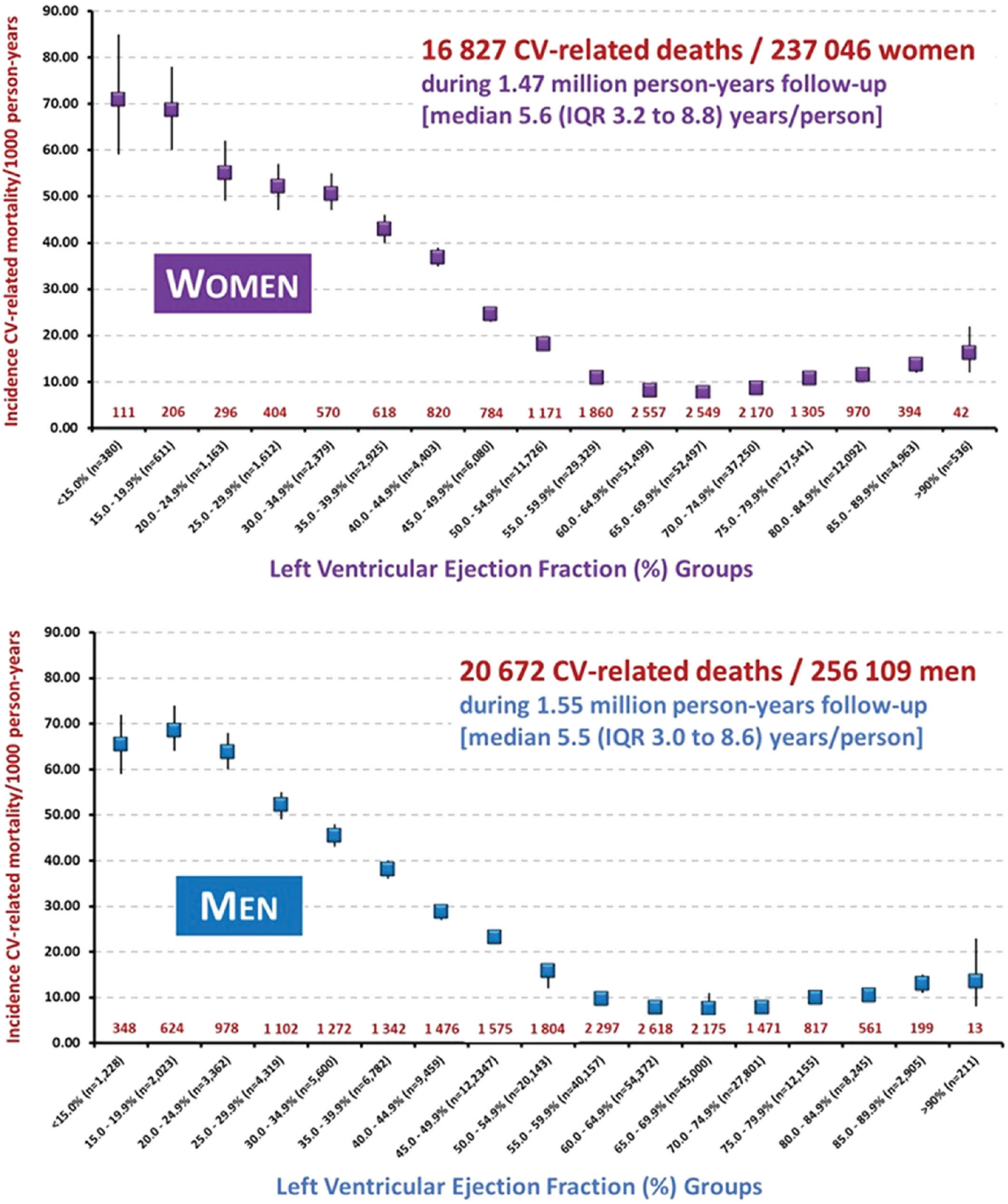


Figure 3 Incident rate of cardiovascular-related mortality. The rate of cardiovascular (CV)-related mortality per 1000 person-years is presented separately for women (top graph) and men (bottom) according to 5-unit increments in the left ventricular ejection fraction. The total number of deaths contributing to the rate of mortality in each group (red numerals) is provided above the horizontal axis. IQR: Interquartile range. Citation: Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G; NEDA Investigators. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. *Eur J Heart Fail* 2021; 23(3): 406-416. Copyright ©The Author(s) 2020. Published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

FOOTNOTES

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MINIREVIEWS

Effects of medically generated electromagnetic interference from medical devices on cardiac implantable electronic devices: A review

Walker Barmore, Himax Patel, Cassandra Voong, Caroline Tarallo, Joe B Calkins Jr

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Abstract

As cardiac implantable electronic devices (CIED) become more prevalent, it is important to acknowledge potential electromagnetic interference (EMI) from other sources, such as internal and external electronic devices and procedures and its effect on these devices. EMI from other sources can potentially inhibit pacing and trigger shocks in permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD), respectively. This review analyzes potential EMI amongst CIED and left ventricular assist device, deep brain stimulators, spinal cord stimulators, transcutaneous electrical nerve stimulators, and throughout an array of procedures, such as endoscopy, bronchoscopy, and procedures involving electrocautery. Although there is evidence to support EMI from internal and external devices and during procedures, there is a lack of large multicenter studies, and, as a result, current management guidelines are based primarily on expert opinion and anecdotal experience. We aim to provide a general overview of PPM/ICD function, review documented EMI effect on these devices, and acknowledge current management of CIED interference.

Key Words: Electromagnetic interference; Pacemaker; Implantable cardioverter defibrillator; Permanent pacemakers; Cardiac implantable electronic devices; Left ventricular assist device; Endoscopy; Bronchoscopy; Electrocautery; Capsule endoscopy; Transcutaneous electrical nerve stimulators unit; Spinal cord stimulator

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Core Tip: There are several infrequent yet significant sources of electromagnetic interference (EMI) on cardiac implantable electronic devices (CIED). These include both implantable devices and procedures. Patients with cardiac devices often may need another implanted medical device or specific medical procedures. The potential resulting EMI can be minimized in order to make these treatments safer and still provide patients with therapeutic relief. A large, prospective study is critical to provide more robust and consistent literature regarding EMI effects on CIED. This will provide a clearer assessment of risk of EMI associated with variety of sources in addition to the development of evidence based clinical guidelines regarding management of patients with CIED.

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INTRODUCTION

Cardiac implantable electronic devices (CIED) include two main broad categories of devices, implantable cardioverter defibrillators (ICD), and permanent pacemakers (PPM)[1]. Over the last decade, the indications for the use of these devices have increased. Since 2019, over three hundred thousand devices have been implanted every year alone in the United States[2]. Hence, it is important for clinicians to recognize challenges involved in the management of these devices. One of the biggest challenges with these is electromagnetic interference (EMI), which occurs as a result of exposure of a CIED to an electromagnetic signal from other devices such as a smartphone, metal detector, taser, headphones and less frequently from internal and external medical devices, and surgical procedures. EMI can lead to inappropriate CIED function and have catastrophic consequences[3]. EMI can be interpreted by PPM as an intrinsic cardiac signal and result in inhibition of pacing, leading to bradycardia, and potentially cardiac arrest[3]. Similarly, EMI in patients with ICD can lead to inappropriate shocks due to perceived ventricular tachyarrhythmia[3]. The aim of this 2-part review article is to discuss the infrequent sources of EMI: (1) From implantable devices; and (2) Surgical procedures, its interactions with CIEDs, and management options to prevent these undesirable consequences.

CIED INDICATIONS AND OVERVIEW

As PPM and ICD become more prevalent, it is important to briefly review indications and general functionality of these devices. According to the ACC/AHA/HRS guidelines, PPM are most commonly indicated for sinus node dysfunction, symptomatic bradycardia, and atrioventricular block[4]. The indications for ICD placement are divided into primary and secondary prevention[5,6]. Primary prevention focuses on those patients who are at high risk for sudden cardiac death as a result of ventricular tachyarrhythmias. This typically includes patients with cardiomyopathies who are classified in New York Heart Association functional classes II and III with a left ventricular ejection fraction of 35% or less. Secondary prevention is indicated for those patients with documented prior episodes of hemodynamically unstable ventricular arrhythmias of unknown etiology and in patients with sustained ventricular arrhythmias and heart disease[5,6].

PPM and ICD are composed of a few components: generator, lead(s), an electrode at the tip of each lead, and, if an ICD, a shocking coil(s). The generator is located in the subcutaneous tissue of the upper chest wall or under the pectoralis major and is responsible for the generating a current that is transmitted by the leads. Leads may be inserted into one or more chambers of the heart depending on the type of CIED that is indicated. Each lead tip is in direct contact with the cardiac myocytes, and these leads are either unipolar or bipolar. A unipolar lead is a single conductor lead that transmits electricity in a unidirectional fashion, meaning the generator serves as the anode and the lead tip as the cathode with electrons flowing from anode to cathode[7]. A bipolar lead has two isolated conductors on the tip with one serving as the anode and the other as the cathode.

CIED RESPONSE TO INTERNAL AND EXTERNAL DEVICES

There has been longstanding concern and scrutiny throughout the electrophysiology, chronic pain management, and physical rehabilitation communities in regard to potential electrical interference

amongst internal and external medical devices, in particular left ventricular assist devices (LVADs), CIED, deep brain stimulators, transcutaneous electrical nerve stimulation (TENS) units, and spinal cord stimulators. We have summarized some of these concerns in Table 1. In regard to LVADs, Erquo *et al*[8] presented the case of 60-year-old female patient with doxorubicin-induced dilated cardiomyopathy status post cardiac resynchronization therapy defibrillator who underwent LVAD pump exchange. The intraoperative exchange was uncomplicated; however, postoperatively it was noted that the patient was in complete heart block with her pacemaker no longer consistently pacing. The loss of consistent pacing was found to be secondary to increased RV lead sense amplification from the LVAD's pump rotation speed. To mitigate the pacemaker's oversensing, the low frequency attenuation filter was disabled, which allowed the device to function without further inhibition. Additionally, Pfeffer *et al*[9] outlined additional LVAD-ICD interference; however, this case differs from Erquo *et al*[8] as it described the interaction between subcutaneous ICD and LVAD. This case involved a 42-year-old male with nonischemic cardiomyopathy who received 31 ICD shocks one hour after LVAD placement. This adverse interaction was due to superimposed electric noise from the LVAD in the setting of diminished R waves. This mixing of electrical noise was perceived as a shockable rhythm by the S-ICD. This patient's S-ICD was removed and a transvenous ICD was placed, which resulted in regular device function and no further ICD shocks on 6-month follow-up.

In addition, deep brain stimulators (DBS) and spinal cord stimulators (SCS) are becoming more prevalent as well. However, their adverse interactions with PPM and ICD are not well-documented. There are case reports that demonstrate a safe coexistence between CIED and DBS or SCS. Obwegeser *et al*[10] demonstrates the safety of DBS in a patient being treated for essential tremor in the setting of a previously implanted ICD for sustained monomorphic ventricular tachycardia. This patient's DBS pulse generator was in close proximity of the ICD (10.5 cm away); however, after thorough testing, there was no inappropriate sensing by the ICD. The safety of DBS and ICD is further supported by Elliot *et al*[11], who analyzed 20 case reports with sub-clavicular DBS and PPM/ICD (some locations not stated) and found no effect of the DBS on a cardiac device; however, in one case a single ICD shock resulted in the deactivation of bilateral DBS devices. SCS also appear to safely coexist with PPM/ICD as demonstrated by Schimpf *et al*[12]. They noted no oversensing of the impulses from the SCS by ICD or SCS device failure after an ICD-shock. Unipolar or bipolar stimulation from the SCS in different voltages or impulse rates resulted in no oversensing or adverse interaction with ICD function. There was potentially some concern for SCS used at the cervical level to induce probable interference with ICD/PPM given their proximity; however, a report by Thomas *et al*[13] found no potential interaction between cervical SCS with ICD in five swine models. No reports of cervical SCS adverse interactions with ICD are available in human patients.

In contrast to DBS and SCS, there are more reported adverse interactions between CIED and TENS units. Both Singh *et al*[14] and Shenoy *et al*[15] reported EMI from a TENS unit that resulted in an ICD shock. Singh *et al*[14] details a S-ICD shock after a patient underwent TENS therapy in the neck, axilla, and back. This adverse interaction was likely due to the relatively superficial location of the S-ICD and its increased susceptibility to EMI, which ultimately led to an ICD shock after the device detected low-amplitude and high frequency signals[14]. Shenoy *et al*[15] further documents ICD and TENS interaction even in a patient with a transvenous ICD, who underwent TENS therapy in an unreported anatomic location. A single shock occurred during TENS therapy. Device interrogation revealed low-amplitude sinusoidal electrical activity during the patient's muscle therapy, leading to an ICD shock [15]. These two reports support the increased risk of EMI-induced shock delivery from an ICD whether subcutaneously or transvenously placed. Similarly, past reports have analyzed a potential interaction between TENS units and pacemakers, and a general consensus was contraindication of TENS units in individuals during synchronous pacing but safety while use in those with asynchronous pacing.

In summary, the above studies suggest a low risk of EMI from DBS or SCS on CIED function. However, there is a greater risk of EMI arising from LVADs on pacemakers and defibrillators, and from TENS unit on defibrillators and certain older generation pacemakers as summarized in Table 2.

In order to minimize the interaction between stimulators (DBS, TENS unit, SCS) and CIED that is implanted, the parameter for each device should be assessed under "worst case scenario" settings. The stimulator is programmed to its maximally tolerated output while the cardiac device is programmed to its maximal sensitivity to assess for the effect of EMI. Once this effect is determined, the output from the stimulator should be decreased to the minimal value that will achieve therapeutic benefit and the sensitivity of the CIED is also decreased to prevent detection of stimulator output yet recognize underlying cardiac activity. In regard to LVAD, following the optimization of the LVAD function, the sensitivity of the CIED is adjusted to minimize detection of EMI, sense R waves and allow for differentiation of R waves from T waves. Furthermore, in LVAD patients, RV pacing is preferential over biventricular pacing, as RV pacing has been associated with improved functional status, better quality of life, fewer arrhythmias, and potentially less EMI[16].

Table 1 Internal and external device interaction with permanent pacemakers / defibrillators

	Erquo *et al*[8], 2018	Pfeffer *et al*[9], 2016	Obwegeser *et al* [10], 2001	Shenoy *et al*[15], 2017	Singh *et al*[14], 2018	Schimpf *et al* [12], 2003
Internal/ External Device	St. Jude; CRT-D	Boston Scientific; S-ICD	Medtronic dual chamber ICD	Durata dual chamber ICD	Boston Scientific; S-ICD;	Medtronic dual chamber ICD
EMI Source	LVAD (pump exchange)	LVAD placement	Thalamic DBS	TENS unit (unreported location)	TENS unit on neck, back, axilla	T11 SCS
Adverse Interaction	Ventricular oversensing leading to inhibition of pacing	Oversensing leading to 31 ICD shocks	None	EMI leading to ICD shock	EMI leading to ICD shock	None
Therapeutic intervention	Turning off low-frequency attenuation filter	Transvenous ICD placement	N/A	Avoiding TENS units	Avoiding TENS units	N/A

PPM: Permanent pacemaker; LVAD: Left ventricular assist device; ICD: Implantable cardioverter-defibrillator; CRT-D: Cardiac resynchronization therapy defibrillator; S-ICD: Subcutaneous implantable cardioverter-defibrillator; DBS: Deep brain stimulator; N/A: Not applicable; TENS: Transcutaneous electrical nerve stimulation; SCS: Spinal cord stimulator.

Table 2 Device interaction on pacemaker and defibrillators

Type of device	Pacemaker	Defibrillators
LVADs	+	+
SCS	-	-
DBS	-	-
TENS	+	+

(-): No EMI noted; (+): EMI noted. LVAD: Left ventricular assist device; DBS: Deep brain stimulator; TENS: Transcutaneous electrical nerve stimulation; SCS: Spinal cord stimulator.

SURGICAL PROCEDURES ASSOCIATED EMI WITH CIED

Over the years, numerous studies have been conducted aiming to better understand the role of electromagnetic interference from surgical procedures with CIED. In this section, we will review the available literature relating to the EMI caused by various surgical procedures including endoscopy, bronchoscopy, electrosurgery and its interaction with CIEDs (Table 3).

Endoscopies have revolutionized the field of gastroenterology by allowing clinicians to effectively diagnose and manage diseases of the gastrointestinal tract. Radiofrequency energy modality is commonly utilized by gastroenterologists during endoscopies to achieve hemostasis. This therapeutic modality has been a cause of concern for clinicians as a potential source of EMI that can interfere with CIED. To elucidate this potential interaction, Samuels *at el*[17]. performed a Manufacturer and User Facility Device Experience (MAUDE) query between 2009-2019, and noted 45 reports of EMI causing CIED malfunction during endoscopy, which included 26 inappropriate shocks (65%), and less frequently, bradycardia, and asystole[17]. In contrast, there have been smaller individual retrospective and prospective studies performed to evaluate EMI during endoscopy in patients with CIED which found no adverse interaction. In a study by Guertin *et al*[18], 41 patients with ICDs underwent endoscopies with ICDs programmed to detection-only with abortive (or therapeutic) tachyarrhythmia therapies off. Post-procedural device interrogation noted no EMI or arrhythmic events triggered during the procedure[18]. Similarly, in a large cohort study of 92 patients by Cheng at al. there were no observed adverse events on patients with defibrillators. Among the patients with a pacemaker, they observed three cases of EMI that was interpreted by the pacemaker as rapid atrial activity, which resulted in mode switching from dual chamber pacing to ventricular pacing and two cases of detection of EMI as rapid ventricular activity resulting in inhibition[19]. Even though these cohort studies have shown the safety of the use of CIED during endoscopy, Samuels *et al*[17] study clearly demonstrates a small risk of CIED dysfunction and inappropriate shock that was not observed in the aforementioned studies. These three studies demonstrate the potential effects of EMI during endoscopy with electrocautery on both pacemaker and ICD function. Therefore, until large multicenter studies are performed, clinicians should be aware of the potential risk of an CIED adverse event during these procedures. To mitigate the risk, reprogramming the device or magnet therapy is recommended, which will be

Table 3 Suggested cardiac implantable electronic devices peri-procedural management

Procedure	CIED (PPM)	CIED (ICD)
Endoscopy	Asynchronous	*R* or Magnet
APC	Asynchronous	*R* or Magnet
ENB	*b*	*b*
Electrocautery	Asynchronous	*R* or Magnet

APC: Argon plasma coagulation; ENB: Electromagnetic navigational bronchoscopy; *b*: Contraindicated; *R*: Reprogramming; CIED: Cardiac implantable electronic devices; PPM: Peri-procedural management; ICD: Implantable cardioverter defibrillators.

discussed later in more detail.

The introduction of capsule endoscopy has transformed the field of gastroenterology as well; however, similar concerns of EMI during this procedure have been raised. Reassuringly, in a cohort study by Harris *et al*[20] of 118 patients undergoing capsule endoscopy, no interference with CIED was reported. To further support the safety of capsule endoscopy, Bandorski *et al*[21], performed an in-vitro investigation, in which they placed capsules used during the procedure at various distances to the lead and ICD device, and monitored device activity continuously. Interestingly, even at the closest proximity to the ICD (on top of the device), no interference was observed. However, similar to traditional endoscopy, no large studies have been performed evaluating EMI with CIED, therefore reprogramming the device may be appropriate during the procedure.

Over the last two decades, the field of interventional pulmonology has rapidly expanded. Procedures and modalities such as laser therapy, argon plasma coagulation, electrocautery, and electromagnetic navigational bronchoscopy (ENB) are being performed at higher rates than ever before. These procedures use heat and electrical energy and can produce an electromagnetic field which can generate EMI and affect devices in the vicinity, especially CIED. There are concerns of APC and electrocautery causing EMI given its configuration of current delivery. Electrocautery during bronchoscopy has two main modes of current delivery: monopolar and bipolar. In monopolar configuration, current "entry" is delivered by the cauterizing instrument and leaves through the "ground" electrode, that is typically placed somewhere on the body (often the legs). In the monopolar configuration, the current has to pass through a large body surface area and can cause significant EMI, and ICDs can spuriously interpret the EMI as a tachyarrhythmia and result in an unnecessary shock. EMI in PPM can lead to inhibition of pacing, mode-switching, or reprogramming. EMI can be avoided if bipolar current configuration is used as the "entry" and "exit" electrodes are located at the tip of the cauterizing instrument, allowing for a very narrow EMI field. Similar to the monopolar configuration of the electrocautery, APC only has monopolar circuitry, causing a high risk of EMI. Lastly, per CHEST guidelines, ENB is contraindicated in patients with CIEDs given the electromagnetic field that it creates around the subjects[22]. To better understand EMI from ENB, an in-vitro test was subsequently performed by Magnani *et al*[23]. They noted insignificant EMI, with no interaction with CIEDs. However, this test was performed using a human torso simulator, with no replicative studies performed in humans due to the theoretical risk of CIED dysfunction given the large electromagnetic field that is created during these procedures. Overall, clinicians must be aware of the potential EMI leading to CIED malfunction during bronchoscopies.

Similar to bronchoscopy, electrosurgery is commonly used during surgical procedures to cut or coagulate tissue. The current configuration of electrosurgery is either monopolar or bipolar as stated above. Therefore, individuals undergoing any surgical intervention including general surgery, cardiac surgery, abdominal surgery, etc. are at risk of EMI with CIEDs, if monopolar current configuration is used by the operator. In addition to the monopolar current configuration, another factor that increases the likelihood of EMI with CIEDs is the distance between the surgical field where electrosurgery is being performed and the location of the CIED. In a study of 171 patients with ICDs, EMI was noted with monopolar configurations in 9 of 22 procedures above umbilicus, but in none of fifty-three patients below umbilicus[3]. For procedures in close proximity to the CIED, temporary reprogramming is recommended and will be discussed in the subsequent section. Recent HRS/ASA guidelines suggest that for procedures below the umbilicus, given the low concern for EMI, reprogramming is not recommended[24]. Further detailed management of CIED interference will be discussed in the following section.

PERI-PROCEDURAL MANAGEMENT OF CIED INTERFERENCE

Due to the potential detrimental effects that EMI can cause with CIEDs, this section will discuss the interventions that can be applied to minimize and/or prevent EMI in CIEDs. The recommendations are generally based on expert opinion as there are no large multicenter studies performed to address EMI

that occurs in patients with CIED[25].

Prior to any procedure, patients with CIED should undergo CIED interrogation within 6 to 12 mo to identify the type of cardiac device implanted and if the patient is device dependent[17,25], which will ultimately dictate intraoperative and postoperative management.

The ACC/AHA guidelines recommend placing the device into an asynchronous mode for the entire duration of the procedure in device dependent patients who are undergoing EMI-generating procedures, whereas ASGE suggests it should be reserved only for prolonged (no specific length of time provided) endoscopy procedures in these patients[17]. Asynchronous modes include dual chamber asynchronous pacing, asynchronous ventricular pacing, or asynchronous atrial pacing. These modes mitigate the potential adverse EMI that can result in intermittent of loss of pacemaker function *via* delivery of a constant, fixed stimulus without sensing capability. The pulse generator will then send a constant pacing stimulus regardless of external electrical influence. In addition, reprogramming or inactivating the tachyarrhythmia detection/management of ICDs is recommended. If this is not feasible, placing a cardiac magnet over the pulse generator is an alternative method[26]. All CIED are fitted with a reed switch comprised of two magnetic metal strips that are separated. When these strips are activated *via* the application of a magnetic field, they come into contact, preventing sensing by a pacemaker resulting in asynchronous pacing and inhibition of ventricular tachyarrhythmia detection and prevention of shock delivery by an ICD[25,26]. Once the magnet is removed, the device will return to its pre-magnetic application modes/settings. Post-procedure management involves CIED interrogation and restoration of the devices to their original settings and pre-procedural therapeutic thresholds and sensing if they were reprogrammed before the procedure[25].

In addition, the expert consensus statement by HRS/ASA further recommends any procedures associated with EMI that are performed geographically above the umbilicus, such as bronchoscopy, should also undergo the post-procedure management as described above[25].

LIMITATIONS

While there is evidence to support concern for EMI on CIEDs, the literature primarily is comprised of case reports or small case series reviews. Therefore, the data regarding the risk of EMI from medical devices or procedures is often sparse and inconsistent. For instance, the MAUDE query performed by Samuels *et al*[17] demonstrates a small risk of EMI on CIEDs during endoscopic procedures. However, given the limited quality of data available in the database it is difficult to identify the exact etiology of and clinical scenario surrounding each reported CIED malfunction[27]. There are also conflicting studies reporting no adverse events during endoscopic procedures, thus it is challenging to conclude the true risk of significant EMI during endoscopy. Similar conflicting reports exist for a number of interventions suspected to interfere with CIEDs. Additionally, as a result of limited data, consensus recommendations from the HRS/ASA regarding management of CIED interference are heavily reliant on personal experience of prior patient management.

CONCLUSION

There are several infrequent yet significant sources of EMI on CIED. These include both implantable devices and procedures. Patients with cardiac devices often may need another implanted medical device or specific medical procedures. The potential resulting EMI can be minimized in order to make these treatments safer and still provide patients with therapeutic relief. A large, prospective study is critical to provide more robust and consistent literature regarding EMI effects on CIED. This will provide a clearer assessment of risk of EMI associated with variety of sources in addition to the development of evidence based clinical guidelines regarding management of patients with CIED.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

SVEAT score outperforms HEART score in patients admitted to a chest pain observation unit

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Abstract

BACKGROUND

Timely and accurate identification of subgroup at risk for major adverse cardiovascular events among patients presenting with acute chest pain remains a challenge. Currently available risk stratification scores are suboptimal. Recently, a new scoring system called the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score has been shown to outperform the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score, one of the most used risk scores in the United States.

AIM

To assess the potential usefulness of the SVEAT score as a risk stratification tool by comparing its performance to HEART score in chest pain patients with low suspicion for acute coronary syndrome and admitted for overnight observation.

METHODS

We retrospectively reviewed medical records of 330 consecutive patients admitted to our clinical decision unit for acute chest pain between January 1st to April 17th, 2019. To avoid potential biases, investigators assigned to calculate the SVEAT, and HEART scores were blinded to the results of 30-d combined endpoint of death, acute myocardial infarction or confirmed coronary artery disease requiring revascularization or medical therapy [30-d major adverse cardiovascular event (MACE)]. An area under receiving-operator characteristic curve (AUC) for each score was then calculated. C-statistic and logistic model were used to compare

predictive performance of the two scores.

RESULTS

A 30-d MACE was observed in 11 patients (3.33% of the subjects). The AUC of SVEAT score (0.8876, 95%CI: 0.82-0.96) was significantly higher than the AUC of HEART score (0.7962, 95%CI: 0.71-0.88), P = 0.03. Using logistic model, SVEAT score with cut-off of 4 or less significantly predicts 30-d MACE (odd ratio 1.52, 95%CI: 1.19-1.95, P = 0.001) but not the HEART score (odd ratio 1.29, 95%CI: 0.78-2.14, P = 0.32).

CONCLUSION

The SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

Key Words: Acute chest pain; Risk stratification tool; Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin score; History, Electrocardiography, Age, Risk factors and Troponin score

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Core Tip: Most chest pain risk stratification scores do not use several readily available data. The Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score was shown to outperform the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score in 30-d major adverse cardiovascular event. In our retrospective cohort study, we validated the performance of the SVEAT score and confirmed that the SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

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INTRODUCTION

Acute chest pain is one of the most common presenting symptoms to the emergency department[1,2]. Several non-cardiac conditions share clinical features with acute myocardial infarction and the emergency room clinician must rapidly identify those patients with chest pain who are most likely to have active coronary events from those who have chest pain due to other reasons. The key immediate task is to identify if a patient could benefit from being hospitalized for acute coronary syndrome (ACS) evaluation and those who can be safely discharged. This requires an estimation of the pretest probability of ACS. However, the accuracy of individual history, physical exam and electrocardiogram findings have been found to have limited utility for diagnosing ACS[3]. Therefore, multiple scoring systems and pathways have been proposed as risk stratification tools for these patients[4-7]. Among them, the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score is arguably the most utilized particularly in the United States. Unfortunately, it has been shown in some studies to identify less than half of low-risk patients[4-6,8]. In an unselected population of chest pain patients in the emergency department, the HEART score and clinical gestalt had the same diagnostic accuracy for ACS[9]. The HEART score assigns a maximum score of 2 for chest pain deemed "highly suspicious" for ACS and suggests further inpatient evaluation for ACS for a score of 4 or more. By not clearly defining the classification of a patient's chest pain, the score introduces subjectivity and considerable inter-rater variability[10]. The score also incorporates traditional cardiac risk factors such as diabetes, hypercholesterolemia, and hypertension, which have been shown to have limited value in diagnosis ACS especially in those older than 40 years[11]. To control health care utilization and cost, it is imperative to identify low risk patients with chest pain for discharge from the emergency department. However, it is perhaps more important to not miss real cases of ACS in otherwise low risk patients. Among patients without the traditional risk factors for ACS, the HEART score may not be sensitive in identifying those who would benefit from further evaluation. Thus, there is a need for alternative risk stratification for this patient group. Recently, a new scoring system based on five sets of clinical variables; characteristics of chest pain Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT score, Table 1) has been reported to outperform the HEART score[8]. The objective of this study is to assess the potential usefulness of SVEAT score as a risk stratification tool by comparing its performance

Table 1 Definition of the Symptoms, History of Vascular disease, Electrocardiography, Age, and Troponin score

Component	Characteristics	Points
Symptoms	Typical unstable angina pectoris	3
	Stable angina, Canadian Cardiovascular Society Class I or II	1
	Non-cardiac chest pain	-2
Vascular disease	Recent myocardial infarction or percutaneous coronary intervention < 90 days	2
	Coronary artery bypass grafting > 5 years	2
	Prior coronary event other than above	1
	Prior revascularization for peripheral disease or carotid disease	2
EKG	Dynamic or new ischemic ST or T wave changes	3
	ST depression of unknown duration without cause	2
	ST changes with left ventricular hypertrophy, intraventricular conduction delay, digitalis, or metabolic issue	1
	Old Q wave indicating prior myocardial infarction or pre-existing ST changes	1
	No ST changes	0
	Normal EKG in the presence of severe ongoing chest pain	-2
Age (years)	> 75	2
	50-75	1
	30-49	0
	< 30	-1
Troponin I (ng/mL)	0.7 or higher	5
	> 0.12 but < 0.7	2
	> 0.04 but < or = 0.12	1
	Normal (< or = 0.004) with unclear duration of chest pain	0
	Normal after > 4 h of constant chest pain	-2

Reproduced from Roongsritong *et al*[8], 2020. With permission from Elsevier, Table 1 was reprinted from: Roongsritong C, Taha ME, Pisipati S, Aung S, Latt H, Thomas J, Namballa L, Al-Hasnawi HJ, Taylor MK, Gullapalli N. SVEAT Score, a Potential New and Improved Tool for Acute Chest Pain Risk Stratification. *Am J Cardiol* 2020; 127: 36-40. Copyright © 2020 Elsevier Inc.

to HEART score in chest pain patients with low suspicion for acute coronary syndrome and admitted for overnight observation.

MATERIALS AND METHODS

The registry of patients admitted to our clinical decision units between January 1st to April 17th, 2019, were retrospectively reviewed. Our clinical decision unit allows for close observation of chest pain patients who are at low risk for true major adverse cardiovascular event (MACE). Admission to this unit allows for serial monitoring of the patient's symptoms, cardiac enzymes, and electrocardiograms. To minimize any potential biases, one group of investigators was assigned to abstract relevant information necessary to calculate SVEAT score, and another was assigned to collect information for HEART score according to the published criteria[4,8]. The occurrence of MACE defined as all-cause mortality, acute myocardial infarction, confirmed coronary artery disease requiring revascularization or medical therapy at 30 d were then validated by two independent investigators who were blinded to the SVEAT and HEART score for each patient. The abstracted data were then provided to another set of investigators who were blinded to the outcome data to calculate the SVEAT and the HEART scores. Patients with ST segment elevation myocardial infraction were excluded from the study. The fourth-generation ultra-high sensitivity troponin I assay was used in all participants at our institution during the study period like the original SVEAT score study. Acute myocardial infarction was diagnosed based on standard

criteria[12]. The predictive power of the SVEAT and HEART scores for 30-d MACE were compared using c-statistic, based on area under the receiving-operator characteristic curve (AUC). Chi-squared test for equality of area under the curve was used to compare the performance of the SVEAT score to the HEART score. Categorical variables were summarized as counts (%) and between group comparisons were performed using Fisher's exact test. Continuous variables were summarized as means ± SD and difference between means by outcome compared using Student's *t*-test. All analyses were performed at a two-tailed 5% level of significance using Stata version 16.1 (Stata Corporation, College Station, TX, United States).

RESULTS

A total of 330 subjects were included in the study. Baseline patient characteristics are shown in Table 2. There were slightly more male (52.1%) than female subjects. The mean age was 59.5 ± 13.9 years. The incidence of 30-d MACE in our population was 3.33%. The subjects who suffered 30-d MACE were significantly older than those who did not (74.3 ± 13.2 years *vs* 59.0 ± 13.6 years, $P < 0.0001$). There were however no other significant differences in baseline characteristics between the two groups (Table 2).

Figure 1 illustrates the receiver-operator-characteristic curves of the SVEAT and HEART scores in predicting 30-d MACE. The AUC of the SVEAT score (0.8876, 95%CI: 0.82-0.96) is significantly higher than AUC of the HEART score (0.7962, 95%CI: 0.71-0.88), $P = 0.03$. Using logistic model, SVEAT score ≤ 4 significantly predicted 30-d MACE (odds ratio 1.52, 95%CI: 1.19-1.95, $P = 0.001$) but the HEART score ≤ 3 did not (odds ratio 1.29, 95%CI: 0.78-2.14, $P = 0.32$) (Table 3).

DISCUSSION

Currently, despite numerous risk stratification protocols, most low-risk patients presenting with acute chest pain are not being released from emergency department. The 2020 European Society of Cardiology Guideline for ACS recommends using an ultrahigh sensitivity troponin (hs-Tn) assay with 0/1-h hs-Tn protocol for ruling out acute coronary syndrome but also emphasizes the importance of incorporating clinical information into the decision-making process[12]. It additionally proposes using Global Registry of Acute Coronary Events score for prognostic purposes but does not recommend any specific clinical risk score for initial risk stratification[12]. The American College of Cardiology/American Heart Association has not updated their guideline since 2014 when they stated that none of available risk prediction tools at the time was definitively demonstrated to be superior to clinician judgement[13].

The HEART score is perhaps the most widely used risk stratification tool in the United States due to its simplicity and large amount of supporting evidence[6,14,15]. The criteria for its History and EKG component are however somewhat subjective. Consequently, inter-observer variability and scoring inconsistency have been reported[16-18]. More importantly, it has been shown to be able to identify merely less than half of low-risk patients[5,17,18]. One of the potential contributing factors for the latter issue is that the HEART score does not incorporate some of the useful clinical information readily available on initial evaluation. To circumvent some of the pitfalls of the HEART score, the SVEAT score was developed. There are a few differences between the SVEAT and HEART scores. First, larger weight (higher points) is assigned to the findings associated with higher likelihood of subsequent acute coronary event clinically and negative point for those traditionally associated with negative likelihood of the events in a stepwise manner. This approach allows wider range of potential scores, and we believe theoretically could help better discriminating among various risk group of patients. Secondly, the criteria for EKG changes and assigned point for each change are much more clearly defined. Moreover, the presence of vascular disease is included in the SVEAT score instead of risk factor which has been shown to be only a weak predictor in acute chest pain evaluation[19]. In fact, the SVEAT score has recently been shown to outperform the HEART score[8]. Like the previous study, this analysis found SVEAT score to be superior risk stratification tool to HEART score for acute chest pain evaluation in low-risk patients.

There are certainly a few limitations in our study. Firstly, the overall 30-d MACE incidence of 3.3% in this study is rather low and substantially lower than in the previous report of 19.6%[13]. This may unfavorably increase the possibility of our finding to be due to statistical chance. An extremely low event rate in this study is likely explained by our study design to include only those retrospectively identified from a low-risk chest pain registry at our institution. The incidence of MACE in our population however is in line with the recent report of real-world data in the United States where ED visit for acute chest pain exceeds 8 million annually[20]. Among these patients, < 5% of them subsequently experienced acute coronary syndrome. Second, the sample size of our study is relatively small for a retrospective design. As indicated in the methodology section, we did try to design our study to minimize potential biases. Lastly, this is a single center study and therefore future confirmation in a multicenter study in wider range of population, and larger sample size will be needed.

Table 2 Baseline patient characteristics

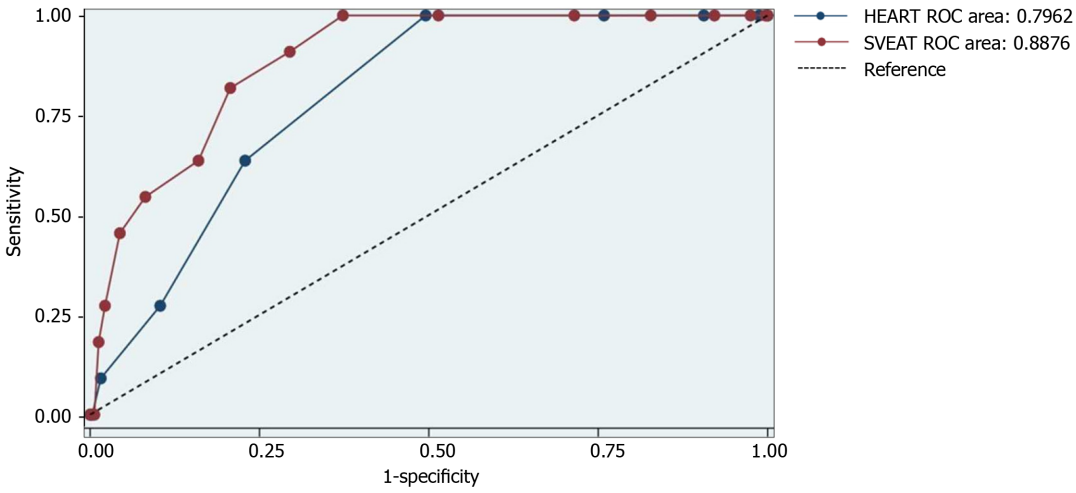
Continuous variables	Overall (*n* = 330)	30-d MACE		*P* value
		Yes, *n* = 11 (3.3%)	No, *n* = 319 (96.7%)	
Age, mean ± SD (yr)	59.5 ± 13.9	74.3 ± 13.2	59 ± 13.6	< 0.0001
BMI, mean ± SD (kg/m^2)	30.7 ± 7.8	27.8 ± 6.3	30.7 ± 7.8	0.23
Males, *n* (%)	172 (52.1)	7 (63.6)	165 (51.7)	0.55
Diabetes, *n* (%)	94 (28.5)	5 (45.5)	89 (27.9)	0.31
Dyslipidemia, *n* (%)	153 (46.4)	4 (36.4)	149 (46.7)	0.55
Hypertension, *n* (%)	206 (62.4)	10 (90.9)	196 (61.4)	0.06
Smoker, *n* (%)	177 (53.6)	9 (81.8)	168 (52.7)	0.07

Dyslipidemia: Total cholesterol > 200 mg/dL or low density lipoprotein > 130 mg/dL or non-high density lipoprotein cholesterol > 160 mg/dL. MACE: Major adverse cardiovascular events; BMI: Body mass index.

Table 3 Logistic model of major adverse cardiovascular events with HEART and SVEAT scores as covariates using cut-off of ≤ 4 points for SVEAT and ≤ 3 points for HEART for low-risk

30-d MACE	Odds ratio	*P* value	95%CI
HEART score	1.29	0.32	0.78-2.14
SVEAT score	1.52	0.001	1.19-1.95

MACE: Major adverse cardiovascular events; SVEAT: Symptoms, History of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin.



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Figure 1 Receiver operating characteristics for HEART and SVEAT scores. There area under the curve was significantly larger for SVEAT than HEART (*P* = 0.03). SVEAT: Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin; ROC: Receiver operating characteristics.

CONCLUSION

In conclusion, our study suggests potential usefulness of the newly developed SVEAT score as a risk stratification tool among low-risk patients admitted to clinical decision unit for evaluation of acute chest pain. We found that SVEAT score significantly outperforms the commonly used HEART score. Incorporating SVEAT score as part of a clinical assessment of these patients may help improve resource utilization while maintaining minimal risk of future cardiovascular events in low-risk patients presenting to emergency department with acute chest pain.

ARTICLE HIGHLIGHTS

Research background

Cardiovascular disease is the leading cause of death worldwide. Early identification of patients at risk for major cardiovascular events can expedite treatment and significantly reduce morbidity and mortality.

Research motivation

Risk stratification scoring systems used to identify patients at risk of major cardiovascular events, including the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score, are often ineffective and may exclude many patients who would benefit from urgent intervention.

Research objectives

We aimed to assess the value of a new risk stratification scoring system, the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT), by comparing its performance to that of the HEART score among chest pain patients with low suspicion for acute coronary syndrome.

Research methods

We retrospectively reviewed medical records of 330 consecutive patients admitted to our clinical decision unit for acute chest pain between January 1st to April 17th, 2019. To avoid potential biases, investigators assigned to calculate the SVEAT, and HEART scores were blinded to the results of 30-d combined endpoint of death, acute myocardial infarction or confirmed coronary artery disease required revascularization or medical therapy [30-d major adverse cardiovascular event (MACE)].

Research results

A 30-d MACE was observed in 11 patients (3.33% of the subjects). The area under receiving-operator characteristic curve (AUC) of SVEAT score (0.8876, 95%CI: 0.82-0.96) was significantly higher than the AUC of HEART score (0.7962, 95%CI: 0.71-0.88), P = 0.03. Using logistic model, SVEAT score with cut-off of 4 or less significantly predicts 30-d MACE (odd ratio 1.52, 95%CI: 1.19-1.95, P = 0.001) but not the HEART score (odd ratio 1.29, 95%CI: 0.78-2.14, P = 0.32).

Research conclusions

The SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

Research perspectives

In our study, the SVEAT score was superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients. Future research is warranted to evaluate the SVEAT score among large, heterogeneous populations and among high-risk individuals presenting with chest pain.

FOOTNOTES

Author contributions: Antwi-Amoabeng D and Roongsritong C helped design the research study and wrote the original draft of the manuscript; Taha M, Beutler BD, Awad M and Hanfy A contributed to data curation, validation, and formal analysis; Ghuman J, Manasewitsch NT, Singh S and Quang C contributed to data curation and helped review and edit the manuscript; Gullapalli N supervised the project from initiation to completion.

Institutional review board statement: The study protocol was reviewed and approved by the University of Nevada, Reno School of Medicine Institutional Review Board.

Informed consent statement: The study was conducted in accordance with the policies of the Institutional Review Board of the University of Nevada, Reno School of Medicine. The trial was conducted as a retrospective cohort study using anonymized data from existing records. Therefore, informed consent was not required.

Conflict-of-interest statement: The authors declare no actual or potential conflicts of interest or relationship with industry.

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ORIGINAL ARTICLE

Observational Study

Cardiometabolic risk factors in young Indian men and their association with parameters of insulin resistance and beta-cell function

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Abstract

BACKGROUND

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

AIM

To evaluate young North Indian men (aged 20-50 years) for burden of cardiometabolic risk factors, in relation to parameters of homeostatic model assessment for insulin resistance (HOMA-IR) and beta-cell function (oral disposition index [oDI]).

METHODS

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for HOMA-IR and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

RESULTS

We evaluated a total of 635 men at a mean (± SD) age of 33.9 ± 5.1 years and body mass index of 26.0 ± 3.9 kg/m^2. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123

(19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

CONCLUSION

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of insulin resistance and beta-cell function in phenotyping individuals for cardiometabolic risk.

Key Words: Cardiometabolic; Insulin resistance; Asian; Disposition index; Men; Young

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Core Tip: There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

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INTRODUCTION

There is a huge burden of type 2 diabetes in South Asia. According to the latest International Diabetes Federation (IDF) estimates, 90 million adults suffer from diabetes in the South-East Asia region. These numbers are projected to increase to 113 million by 2030 and 152 million by 2045[1]. Several factors contribute to the diabetes epidemic in this region, with the prominent ones being increasing urbanisation and unhealthy changes in diet and lifestyle, reduced physical activity, unfavourable changes in leisure time activities, and decreasing sleeping quality and quantity[2]. Some predisposing factors integral to a "South Asian phenotype" also contribute. For instance, it has been found that despite a lower body mass index (BMI), Asian Indians develop diabetes at least a decade earlier, and are at a higher cardiovascular risk, compared to their Caucasian counterparts[3]. Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes[4]. This dual pathophysiological defect, manifested at a lower BMI and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia[5-8]. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

MATERIALS AND METHODS

Settings and study design

This cross-sectional evaluation was performed from January 2016 to February 2020 at a tertiary care centre in North India (All India Institute of Medical Sciences, New Delhi). This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy[9-10]. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Inclusion and exclusion criteria

We included all men aged 20-50 years who participated in the aforementioned studies. For the purpose of this study, we excluded 20 participants who were diagnosed with diabetes requiring pharmacotherapy. Participants with missing blood insulin values (required to calculate IR and composite beta-cell function) were also excluded. The details of participant identification and recruitment have been provided earlier[9-10]. Briefly, participants were identified through their spouses and invited to visit the hospital, where study-related procedures (detailed below) were performed.

Procedure on the day of testing

Participants were invited to attend the hospital in a fasting state (minimum fast of 10 h) at 08:30 h. A detailed questionnaire was completed for each participant at the scheduled visit, documenting demographic details, education and employment status, and family history of diabetes mellitus.

Measurements

Weight, height, and waist circumference were recorded using standard methods (see supplementary material). A mean of three blood pressure readings was recorded. A 75 g oral glucose tolerance test with measurement of plasma glucose and serum insulin at 0, 30, and 120 min was performed using 83.3 g of glucose monohydrate (equivalent to 75 g anhydrous glucose) dissolved in 300 mL water and consumed over 5-10 min. Blood was also collected for a lipid profile and glycated hemoglobin (HbA_{1c}) measurement in the fasting state. The details of biochemical and hormonal measurements are provided in supplementary material.

Insulin index calculations

IR was measured by parameters of homeostatic model assessment for IR (HOMA-IR) using the standard formula [fasting plasma glucose (mmol/L) × fasting insulin (μIU/mL)/22.5]. Insulin secretion was measured by the insulinogenic index using the formula $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$, and composite beta-cell function was measured by the oral disposition index using the formula: $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$ X 1/fasting insulin (where $\Delta I_{0\text{-}30}$ is the change in serum insulin over 30 min [pmol/L] and $\Delta G_{0\text{-}30}$ is the change in plasma glucose over 30 min [mmol/L]). Negative insulinogenic and disposition index results because of a negative insulin or glucose response, and positive results from combined negative insulin and glucose responses were excluded[11].

Definitions of exposure variables

Participants were divided into quartiles for IR (HOMA-IR) and beta-cell function (oDI), based on which categories were defined[12]. Participants with values in the lowest (best) quartile (Q1 for HOMA-IR) and in the highest (best) (Q4 for oDI) were classified as the reference category (category 1). Participants in the worst or most affected quartile (Q4 for HOMA-IR and Q1 for oDI) were labelled as category 3. Participants with intermediate values (Q2/Q3 of HOMA-IR and oDI) were classified as category 2. Based on categories of HOMA-IR and oDI, composite IR/beta-cell function phenotypes were derived. Phenotype 1 was used as a reference category and included participants classified in category 1 (best quartile) for both HOMA-IR and oDI. Phenotype 4 was most severe, and included participants classified in category 3(worst quartile) for both HOMA-IR and oDI. Phenotype 3 included participants who had either HOMA-IR or oDI (not both) in category 3 (worst). All remaining participants were categorized as phenotype 2. These phenotypes and the categories based on HOMA-IR and oDI were used as exposure variables for the principal analysis, and cardiometabolic parameters were used as outcome variables.

Definitions of outcome variables

Individuals were classified as having normoglycaemia (fasting plasma glucose < 5.6 mmol/L, 2 h plasma glucose < 7.8 mmol/L, and HbA_{1c} < 39 mmol/mol [5.7%]), prediabetes (fasting plasma glucose 5.6-6.9 mmol/L and/or 2 h plasma glucose 7.8-11.0 mmol/L and/or HbA_{1c} 39-46 mmol/mol [5.7-6.4%]), or diabetes mellitus (fasting plasma glucose ≥ 7.0 mmol/L and/or 2 h plasma glucose ≥ 11.1 mmol/L and/or HbA_{1c} ≥ 48 mmol/mol [6.5%]) as per ADA criteria. Participants with prediabetes or diabetes were labelled as having dysglycaemia[13]. Metabolic syndrome was defined as per the IDF criteria: Waist circumference ≥ 90 cm, plus two of the following: Serum triglycerides ≥ 1.7 mmol/L, fasting plasma glucose ≥ 5.6 mmol/L, HDL-cholesterol < 1.03 mmol/L, and BP ≥ 130/85 mmHg[14]. Overweight and obesity were defined as BMI 25-29.9 and ≥ 30 kg/m^2, respectively (WHO international classification)[15]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treatment with antihypertensive medications[16].

Statistical analysis

Statistical analyses were carried out using Stata 15.0 (Stata Corp, College Station, TX, United States). Data are presented as *n* (%), the mean ± SD, or median (q25-q75), as appropriate. Qualitative variables were compared between groups using the Pearson χ^2 test or Fisher's exact test. Quantitative variables were assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution were

compared using Student's *t*-test for independent samples, and those that did not follow a normal distribution (*i.e.*, HOMA-IR, insulinogenic index, disposition index) were compared using the Wilcoxon rank-sum test. Logistic regression analysis was also used to evaluate the association of HOMA-IR, oDI, and mixed HOMA-IR/oDI categories with dysglycaemia, hypertension, and metabolic syndrome. The results are expressed as unadjusted and adjusted odds ratios (95% confidence interval [CI]). For adjusted analysis, the following covariates that are known to have a bearing on the outcome were accounted: Age and family history of diabetes (for dysglycaemia and metabolic syndrome), and age alone (for hypertension). The association of age and BMI with HOMA-IR and oDI was assessed using linear regression analysis. A P value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

We evaluated 635 men at a mean (± SD) age of 33.9 ± 5.1 years (range 21-49 years), and a mean (± SD) BMI of 26.0 ± 3.9 kg/m^2. Of the study participants, 312 (49.1%) and 76 (12.0%) were overweight and obese, respectively, and 245 (38.6%) had a family history of diabetes. Hypertension was present in 123 (19.4%) participants, and 19 (3.1%) were on pharmacotherapy. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Metabolic syndrome was present in 258 (40.6%) participants. There were only 132 (20.8%) participants who did not have any adverse cardiometabolic risk factor, *i.e.*, dysglycaemia, hypertension, metabolic syndrome, and overweight/obesity. The results of various clinical, anthropometric, and biochemical variables are summarised in Table 1.

Burden of cardiometabolic risk factors in relation to age and body mass index

The prevalence of dysglycaemia increased with age, from 39.2% (in third decade) to 52.3% (in fourth decade) and to 68.0 % (in fifth decade) (P < 0.001). The corresponding figures for hypertension and metabolic syndrome were 12.0%, 18.7%, and 32.0%, respectively (P = 0.001), and 30.4%, 41.4% and 50.5%, respectively (P = 0.009). There was no significant HOMA-IR increment [beta coefficient 0.15 (P = 0.553) for 4th decade and 0.50 (P = 0.147) for 5th decade, compared to 3rd decade] and oDI decrement [beta coefficient: -0.59 (P = 0.137) for 4th decade and -1.00 (P = 0.057) for 5th decade, compared to 3rd decade] with age.

Similarly, the prevalence of dysglycaemia (34.8%, 60.3%, and 75.0%, respectively), hypertension (12.2%, 22.5%, and 30.3%, respectively), and metabolic syndrome (15.4%, 52.6%, and 73.7% respectively) increased across the three BMI categories, namely, normal weight, overweight, and obese (P < 0.001). HOMA-IR showed a significant increment across BMI categories [beta coefficient, adjusted for age: 1.34 (P < 0.001) for overweight and 3.37 (P < 0.001) for obese, compared to normal weight participants]. On the other hand, oDI showed a significant decrement across BMI categories [beta coefficient, adjusted for age: -1.38 (P < 0.001) for overweight and -1.58 (P = 0.002) for obese, compared to normal weight participants]

Cardiometabolic risk factors in relation to different IR (HOMA-IR) categories

We found a significantly higher burden of dysglycaemia (78.5% *vs* 34.8%, P < 0.001), hypertension (32.5% *vs* 12.0%, P < 0.001) and metabolic syndrome (66.5% *vs* 13.9%, P < 0.001) in participants belonging to the worst, compared to the best HOMA-IR quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 39.5% *vs* 14.6%, P < 0.001), high LDL-cholesterol (≥ 2.6 mmol/L; 70.7% *vs* 38.0%, P < 0.001), high triacylglycerol (≥ 1.7 mmol/L; 58.0% *vs* 25.3%, P < 0.001), and low HDL-cholesterol (< 1.29 mmol/L; 61.8% *vs* 44.3%; P = 0.008), was also significantly higher in these participants (Table 2). The adjusted odds ratios (ORs) for dysglycaemia (OR = 7.04, 95%CI: 4.20-11.79; P < 0.001), hypertension (OR = 3.56, 95%CI: 1.97-6.43; P < 0.001), and metabolic syndrome (OR = 12.20, 95%CI: 6.91-21.54; P < 0.001) were significantly higher in participants belonging to quartile 4, compared to quartile 1 (Supplementary Table 1).

Cardiometabolic risk factors in relation to different composite beta-cell function (oral disposition index) categories

We found a significantly higher burden of dysglycaemia (80.4% *vs* 36.1%, P < 0.001), hypertension (30.6% *vs* 12.0%, P < 0.001), and metabolic syndrome (62.0% *vs* 26.6%, P < 0.001) in participants belonging to the worst, compared to the best oDI quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 34.8% *vs* 20.3%, P = 0.005), high LDL-cholesterol (≥ 2.6 mmol/L; 65.2% *vs* 50.0%, P = 0.023), and high triacylglycerol(≥ 1.7 mmol/L; 57.6% *vs* 32.3%, P < 0.001), was also significantly higher in these participants (Table 3). The adjusted ORs for dysglycaemia (OR = 6.54, 95%CI: 3.90-10.97; P < 0.001), hypertension (OR = 2.89, 95%CI: 1.60-5.24; P < 0.001), and metabolic syndrome (OR = 4.02, 95%CI: 2.48-6.53; P < 0.001) were significantly higher in participants belonging to the worst, compared to the best quartile (Supplementary Table 2).

Table 1 Baseline characteristics of the study cohort

Variable	Total (*n* = 635)
Age (yr)	33.9 ± 5.1
Education (graduation or beyond)	373 (58.7)
Family H/O Diabetes	245(38.6)
BMI (kg/m^2)	26.0 ± 3.9
BMI ≥ 25 kg/m^2	388 (61.1)
BMI ≥ 30 kg/m^2	76 (12.0)
Waist circumference (cm) (*n* = 633)	94.1 ± 9.6
Waist circumference ≥ 90 cm	448 (70.8)
Systolic BP (mmHg) (*n* = 634)	122.2 ± 12.4
Systolic BP ≥ 140 mmHg	46 (7.3)
Diastolic BP (mmHg) (*n* = 634)	81.5 ± 9.6
Diastolic BP ≥ 90 mmHg	111 (17.5)
Hypertension	123(19.4)
Hypertension medications (*n* = 606)	19(3.1)
Total cholesterol (mmol/L) (*n* = 634)	4.7 ± 1.0
Total cholesterol ≥ 5.2 mmol/L	193 (30.4)
LDL-C (mmol/L) (*n* = 634)	2.9 ± 0.9
LDL-C ≥ 2.6 mmol/L	378 (59.6)
HDL-C (mmol/L) (*n* = 634)	1.0 ± 0.3
HDL-C < 1.03 mmol/L	336 (53.0)
Triacylglycerol (mmol/L) (*n* = 634)	1.6 (1.2-2.2)
Triacylglycerol ≥ 1.7 mmol/L	281 (44.3)
The metabolic syndrome	258 (40.6)
HOMA-IR (mmol/L × μIU/mL)	2.7 (1.9-4.0)
Matsuda index (*n* = 633)	2.8 (1.9-4.5)
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	203.2 (109.9-348.2)
Disposition index ($l/mmol_{glu}$)	2.6 (1.5-4.3)
Dysglycaemia	331 (52.1)
Prediabetes	297(46.8)
Diabetes	34(5.4)
Glucose at 0 min [mmol/L]	5.3 ± 1.2
Glucose at 30 min [mmol/L]	8.8 ± 2.3
Glucose at 120 min [mmol/L]	6.7 ± 2.8
HbA1c%	5.6 ± 0.8
HbA1c mmol/mol	38.1 ± 8.5
Insulin at 0 min [pmol/L]	84.5 (58.3-117.0)
Insulin at 30 min [pmol/L]	719.5 (438.1-1134.8)
Insulin at 120 min (*n* = 633) [pmol/L]	495.0 (257.2-861.9)
No risk factor	132 (20.8)

Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-

cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Table 2 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of insulin resistance

Variable	Quartile 1 HOMA-IR < 25th percentile of total cohort *n* = 158	Quartile 2-3 HOMA-IR 25th to 75th percentile of total cohort *n* = 319	Quartile 4 HOMA-IR > 75th percentile of total cohort *n* = 158	*P* value[a]
Age (yr)	33.9 ± 5.0	33.8 ± 5.0	34.1 ± 5.2	0.775
Family H/O diabetes	45 (28.5)	124 (38.9)	76 (48.1)	0.002
BMI (kg/m^2)	23.3 ± 3.4	26.1 ± 3.2	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m^2	53 (33.5)	204 (64.0)	131 (82.9)	< 0.001
Waist circumference (cm)	87.2 ± 8.9	94.4 ± 7.9	100.6 ± 9.0	< 0.001
Waist circumference ≥ 90 cm	66 (41.8)	239 (74.9)	143 (91.7)	< 0.001
Systolic BP ≥ 140 mmHg	7 (4.4)	18 (5.6)	21 (13.4)	0.003
Diastolic BP ≥ 90 mmHg	17 (10.8)	49 (15.4)	45 (28.7)	< 0.001
Hypertension	19 (12.0)	53 (16.6)	51 (32.5)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	23 (14.6)	108 (33.9)	62 (39.5)	< 0.001
LDL-C ≥ 2.6 mmol/L	60 (38.0)	207 (64.9)	111 (70.7)	< 0.001
HDL-C < 1.03 mmol/L	70 (44.3)	169 (53.0)	97 (61.8)	0.008
Triacylglycerol ≥ 1.7 mmol/L	40 (25.3)	150 (47.0)	91 (58.0)	< 0.001
The metabolic syndrome	22 (13.9)	131 (41.1)	105 (66.5)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.3 (1.0-1.6)	2.7 (2.3-3.2)	5.6 (4.6-7.3)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	139.3 (85.0-218.0)	233.0 (136.4-362.0)	225.2 (99.8-425.7)	< 0.001
Disposition index ($l/mmol_{glu}$)	3.5 (2.2-5.8)	2.7 (1.6-4.1)	1.5 (0.7-2.6)	< 0.001
Dysglycaemia	55 (34.8)	152 (47.7)	124 (78.5)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Cardiometabolic risk factors in relation to phenotypes based on different combinations of HOMA-IR and oral disposition index

As mentioned in the methodology section, we evaluated the prevalence of cardiometabolic variables under four phenotypes based on different combinations of IR and beta-cell function (phenotype 4: Most affected; phenotype 1: Least affected). The burden of dysglycaemia (90.0% *vs* 28.4%; $P < 0.001$), hypertension (38.0% *vs* 9.0%; $P < 0.001$), and metabolic syndrome (70.0% *vs* 13.4%; $P < 0.001$) was significantly higher in phenotype 4 (oDI < 25th centile and HOMA-IR > 75th centile), compared to phenotype 1(oDI > 75th centile and HOMA-IR < 25th centile)). The burden of adverse lipid parameters, *i.e.* , high total cholesterol (≥ 5.2 mmol/L; 40.0% *vs* 14.9%, $P = 0.007$), high LDL-cholesterol (≥ 2.6 mmol/L; 73.8% *vs* 38.8%, $P < 0.001$), high triacylglycerol (≥ 1.7 mmol/L; 60.0% *vs* 19.4%, $P < 0.001$), and low HDL-cholesterol (< 1.03 mmol/L; 57.5% *vs* 49.3%; $P = 0.012$), was also significantly higher in these participants. These participants were also more likely to be overweight/obese (83.8% *vs* 29.9%; $P < 0.001$) and have central obesity (92.3% *vs* 35.8%; $P < 0.001$) (Table 4). The adjusted ORs for dysglycaemia (OR = 21.09, 95%CI: 8.47-52.53; $P < 0.001$), hypertension(OR = 5.60, 95%CI: 2.14-14.64; $P < 0.001$), and metabolic syndrome (OR = 13.65, 95%CI: 5.80-32.13; $P < 0.001$) were significantly higher in the participants belonging to phenotype 4, compared to phenotype 1 (Supplementary Table 3).

Table 3 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of beta-cell function (oral disposition index)

Variable	Quartile 4 oDI > 75th percentile of total cohort *n* = 158	Quartile 2-3 oDI 25th to 75th percentile of total cohort *n* = 319	Quartile 1 oDI < 25th percentile of total cohort *n* = 158	*P* value[a]
Age (yr)	33.1 ± 5.1	33.8 ± 4.9	35.0 ± 5.3	0.003
Family H/O diabetes	48 (30.4)	124 (38.9)	73 (46.2)	0.015
BMI (kg/m^2)	25.0 ± 3.9	25.9 ± 3.8	27.2 ± 3.7	< 0.001
BMI ≥ 25 kg/m^2	75 (47.5)	195 (61.1)	118 (74.7)	< 0.001
Waist circumference (cm)	91.8 ± 9.5	93.6 ± 9.5	97.6 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	93 (58.9)	224 (70.2)	131 (84.0)	< 0.001
Systolic BP ≥ 140 mmHg	9 (5.7)	20 (6.3)	17 (10.8)	0.135
Diastolic BP ≥ 90 mmHg	15 (9.5)	53 (16.6)	43 (27.4)	< 0.001
Hypertension	19 (12.0)	56 (17.6)	48 (30.6)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	32 (20.3)	106 (33.3)	55 (34.8)	0.005
LDL-C ≥ 2.6 mmol/L	79 (50.0)	196 (61.6)	103 (65.2)	0.013
HDL-C < 1.03 mmol/L	80 (50.6)	163 (51.3)	93 (58.9)	0.232
Triacylglycerol ≥ 1.7 mmol/L	51 (32.3)	139 (43.7)	91 (57.6)	< 0.001
The metabolic syndrome	42 (26.6)	118 (37.0)	98 (62.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	2.1 (1.2-3.0)	2.6 (1.9-3.7)	4.0 (2.7-6.0)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	410.5 (257.1-651.6)	215.6 (146.6-299.4)	85.6 (51.2-127.7)	< 0.001
Disposition index ($l/mmol_{glu}$)	6.1 (4.9-9.1)	2.6 (2.0-3.3)	0.8 (0.5-1.2)	< 0.001
Dysglycaemia	57 (36.1)	147 (46.1)	127 (80.4)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Odds ratio of dysglycaemia per SD change in HOMA-IR and oDI

On logistic regression analysis, the OR for dysglycaemia per SD increase in HOMA-IR was 3.22 (95%CI: 2.30-4.52; $P < 0.001$). After adjustment for age and family history of diabetes, the OR was 3.16 (95%CI: 2.24-4.47; $P < 0.001$). Similarly, the unadjusted and adjusted OR for dysglycaemia per SD decrease in oDI were 2.03 (95%CI: 1.60-2.59; $P < 0.001$) and 1.92 (95%CI: 1.51-2.44; $P < 0.001$), respectively.

DISCUSSION

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Our study cohort comprised of relatively young participants, with a mean age of ~34 years. Nearly one in two study participants had dysglycaemia, metabolic syndrome, or overweight/obesity, and every one in five participants had hypertension at such a young age. Previously, Staimez *et al*[5] reported a high dysglycaemia rate of 73% in 1264 individuals enrolled as a part of Diabetes Community Lifestyle Improvement Program in Chennai, India. The mean age and BMI were 44.2 years and 27.3 kg/m^2, respectively, compared to 33.9 years and 26.0 kg/m^2, in the current study; these differences

Table 4 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories based on beta-cell function (oral disposition index) and insulin resistance

Variable	Phenotype 1 oDI > 75th and HOMA-IR < 25th percentile of total cohort *n* = 67	Phenotype 2 oDI 25th to 75th and/or HOMA-IR 25th to 75th percentile of total cohort *n* = 332	Phenotype 3 oDI < 25th or HOMA-IR > 75th percentile of total cohort *n* = 156	Phenotype 4 oDI < 25th and HOMA-IR > 75th percentile of total cohort *n* = 80	*P* value[a]
Age (yr)	33.3 ± 4.5	33.7 ± 5.1	34.0 ± 5.2	35.1 ± 5.3	0.096
Family H/O diabetes	18 (26.9)	113 (34.0)	79 (50.6)	35 (43.8)	0.001
BMI (kg/m^2)	23.2 ± 3.3	25.4 ± 3.5	27.1 ± 3.6	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m^2	20 (29.9)	186 (56.0)	115 (73.7)	67 (83.8)	< 0.001
Waist circumference (cm)	86.9 ± 8.4	92.5 ± 8.9	97.2 ± 8.7	101.0 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	24 (35.8)	222 (66.9)	130 (83.3)	72 (92.3)	< 0.001
Systolic BP ≥ 140 mmHg	3 (4.5)	18 (5.4)	12 (7.7)	13 (16.5)	0.014
Diastolic BP ≥ 90 mmHg	4 (6.0)	45 (13.6)	36 (23.1)	26 (32.9)	< 0.001
Hypertension	6 (9.0)	48 (14.5)	39 (25.0)	30 (38.0)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	10 (14.9)	98 (29.5)	53 (34.2)	32 (40.0)	0.007
LDL-C ≥ 2.6 mmol/L	26 (38.8)	197 (59.3)	96 (61.9)	59 (73.8)	< 0.001
HDL-C < 1.29 mmol/L	33 (49.3)	159 (47.9)	98 (63.2)	46 (57.5)	0.012
Triacylglycerol ≥ 1.7 mmol/L	13 (19.4)	134 (40.4)	86 (55.5)	48 (60.0)	< 0.001
The metabolic syndrome	9 (13.4)	102 (30.7)	91 (58.3)	56 (70.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.1 (0.7-1.5)	2.4 (1.9-3.0)	4.0 (2.7-5.0)	5.9 (4.7-8.8)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	237.4 (156.4-377.1)	228.6 (147.9-348.5)	159.0 (72.8-418.7)	99.9 (57.3-166.1)	< 0.001
Disposition index ($l/mmol_{glu}$)	6.5 (5.1-9.4)	3.0 (2.3-4.1)	1.5 (1.0-2.6)	0.7 (0.3-1.1)	< 0.001
Dysglycaemia	19 (28.4)	133 (40.1)	107 (68.6)	72 (90.0)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

explain the higher burden of dysglycaemia in the former study, compared to ours. In a similar vein, we also found that the burden of various risk factors increased across age and BMI, being higher in individuals in the fourth and fifth decades of life, and in those with overweight/obesity. The mean HOMA-IR (mmol/L × μIU/mL) in the former study was 2.9, compared to 2.7 in the current study. Notably, we found that mean HOMA-IR in participants in the fifth decade of life (who also had a comparable BMI of 26.9 kg/m^2) was strikingly similar at 2.9. This highlights the convergence of phenotype in terms of obesity and IR, in two studies performed in geographically diverse regions of the country, and lends credibility to generalisation of our study findings to a wider population base.

Both IR and beta cell dysfunction contribute to the pathophysiology of diabetes, and the relative contribution of the latter is proposed to be higher in South Asians[4-6]. In fact, early beta cell dysfunction has been reported not only in Native Asian Indians, but also in migrant populations. The MASALA study found that after adjusting for visceral adiposity and other risk factors, oDI, not Matsuda index, was associated significantly with prediabetes and diabetes among migrant Asian Indians in the United States[6]. Previously, an Iranian study found that HOMA-IR is significantly associated with hypertension in subjects with and without diabetes[17]. We investigated whether and to

what extent the burden of cardiometabolic risk factors varies across severity of HOMA-IR (a parameter of IR) and oDI (a parameter of composite beta-cell function), individually and in combination. The prevalence of dysglycaemia was especially high in participants belonging to the worst HOMA-IR (78.5%) and oDI (80.4%) quartile. Further, the prevalence was 90.0% in participants who had both HOMA-IR and oDI in the worst quartile, compared to 28.4% in those with both indices in the best quartile. We also found that the adjusted ORs for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI, compared to those in the best quartile. When accounting for individuals with the worst, compared to those with the best HOMA-IR and oDI combined, the corresponding adjusted ORs further increased to 21.1, 5.6, and 13.7, respectively. Our study findings are in line with those reported in a recent cross-sectional study by Wang *et al*, where authors found that the prevalence of various cardiometabolic risk factors increased across quintiles of HOMA-IR and HOMA-B in Chinese adults (n = 93690)[18]. Compared to this study, we used oDI as a marker of composite beta-cell function, since it corresponds to biological definition of beta-cell function, in the sense that insulin secretion (Δ I0-30/ Δ G0-30) is measured in relation to existing insulin sensitivity(1/fasting insulin), and is also known to predict the development of future diabetes[19].

The strengths of our study are a comprehensive evaluation of cardiometabolic risk in a cohort of young Indian men, and reporting of data in relation to parameters of IR and beta-cell function, both relevant to the pathophysiology of diabetes. We used oDI to measure beta-cell function, compared to other more extensive studies that used HOMA-B[12]. Our study findings add to the limited and evolving understanding of diabetes pathophysiology in South Asians. We acknowledge certain limitations of this work. Our study provides a cross-sectional association between cardiometabolic risk factors and parameters of insulin action/beta-cell function; however, causality cannot be ascertained. We did not evaluate the study participants for cardiovascular complications such as coronary artery disease and peripheral vascular disease. However, it may be too early for these complications to manifest in this young cohort. In this regard, it would be of interest to follow this cohort longitudinally and evaluate incident glycemic and cardiometabolic deterioration, and development of cardiovascular complications, based on baseline quartiles of oDI and HOMA-IR.

CONCLUSION

To conclude, the burden of cardiometabolic risk factors is high among young Asian Indian men, and both IR and beta cell dysfunction contribute to the pathophysiology of dysglycaemia in this population. Future longitudinal studies should evaluate incident cardiometabolic risk among individuals profiled at baseline for these insulin parameters, and suggest strategies to mitigate the increased risk.

ARTICLE HIGHLIGHTS

Research background

Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes. This dual pathophysiological defect, manifested at a lower body mass index (BMI) and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research motivation

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research objectives

To evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

Research methods

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for homeostatic model assessment for IR (HOMA-IR) and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for

both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

Research results

We evaluated a total of 635 men at a mean (± SD) age of 33.9 ± 5.1 years and BMI of 26.0 ± 3.9 kg/m^2. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123 (19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

Research conclusions

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Research perspectives

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

FOOTNOTES

Author contributions: Gupta Y conceived the idea and wrote the manuscript; Goyal A, Kalaivani M, and Tandon N read and edited the manuscript; Kalaivani M did the statistical analysis; all authors approved the final version of this manuscript.

Institutional review board statement: This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

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Retrospective Study

Thirty-day readmission in patients with heart failure with preserved ejection fraction: Insights from the nationwide readmission database

Anil Kumar Jha, Chandra P Ojha, Anand M Krishnan, Timir K Paul

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Abstract

BACKGROUND

There are rising numbers of patients who have heart failure with preserved ejection fraction (HFpEF). Poorly understood pathophysiology of heart failure with preserved and reduced ejection fraction and due to a sparsity of studies, the management of HFpEF is challenging.

AIM

To determine the hospital readmission rate within 30 d of acute or acute on chronic heart failure with preserved ejection fraction and its effect on mortality and burden on health care in the United States.

METHODS

We performed a retrospective study using the Agency for Health-care Research and Quality Health-care Cost and Utilization Project, Nationwide Readmissions Database for the year 2017. We collected data on hospital readmissions of 60514 adults hospitalized for acute or acute on chronic HFpEF. The primary outcome was the rate of all-cause readmission within 30 d of discharge. Secondary outcomes were cause of readmission, mortality rate in readmitted and index patients, length of stay, total hospitalization costs and charges. Independent risk factors for readmission were identified using Cox regression analysis.

RESULTS

The thirty day readmission rate was 21%. Approximately 9.17% of readmissions were in the setting of acute on chronic diastolic heart failure. Hypertensive

chronic kidney disease with heart failure (1245; 9.7%) was the most common readmission diagnosis. Readmitted patients had higher in-hospital mortality (7.9% *vs* 2.9%, P = 0.000). Our study showed that Medicaid insurance, higher Charlson co-morbidity score, patient admitted to a teaching hospital and longer hospital stay were significant variables associated with higher readmission rates. Lower readmission rate was found in residents of small metropolitan or micropolitan areas, older age, female gender, and private insurance or no insurance were associated with lower risk of readmission.

CONCLUSION

We found that patients hospitalized for acute or acute on chronic HFpEF, the thirty day readmission rate was 21%. Readmission cases had a higher mortality rate and increased healthcare resource utilization. The most common cause of readmission was cardio-renal syndrome.

Key Words: Heart failure with preserved ejection fraction; Diastolic heart failure; Readmission; National readmission database; Health care resource utilization

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Core Tip: Our study highlights the current trend in heart failure with preserved ejection fraction (HFpEF) readmissions, and important causes and predictors of readmissions. It also highlights that mortality in readmission is greater compared to index admissions. The economic burden of HFpEF is also highlighted.

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INTRODUCTION

The prevalence of heart failure (HF) is constantly increasing over time. Approximately 6.2 million adults ≥ 20 years of age were diagnosed with HF between 2013 and 2016 in the United States, which was lower than that in 2009 to 2012 with an estimated 5.7 million diagnosed with HF[1]. Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome with patients having signs and symptoms of HF with normal or near normal left ventricle (LV) ejection fraction as a result of high LV filling pressure [2,3]. Among HF hospitalizations, approximately half are characterized by HFpEF[4]. The prevalence of HFpEF compared to HF with reduced ejection fraction, seems to be going up due to the increasing elderly population.

The total cost associated with HF treatment for 2012 was $30.7 billion. According to Medicare, from 2009 to 2012 the median risk-standardized 30-d readmission rate for HF was 23.0%[1,5]. Readmissions receive greater attention from researchers and policy makers as they are recognized as being related to deficient medical care and a preventable cause of higher healthcare expenditure. The Affordable Care Act introduced a financial penalty for higher readmissions for hospitals that are capped at 3% of a hospital's total Medicare payments for 2015 and beyond. Previously, Medicare's diagnosis-related group payment system lacked a financial disincentive to reduce readmissions[6]. The Centers for Medicare and Medicaid Services' (CMS) Hospital Readmission Reduction Program currently only assesses risk-adjusted 30-d readmission rates for HF, acute myocardial infarctions, pneumonia, chronic obstructive pulmonary disease, and elective total knee and hip arthroplasty[7].

The objective of our study was to use the Healthcare Cost and Utilization Project (HCUP), Nationwide Readmission Database (NRD) 2017 to assess HFpEF readmission rate, compare mortality rate between the index hospitalization and readmissions, assess etiologies, and determine predictors of HFpEF readmissions to recognize areas of improvement and implement the targeted interventions.

MATERIALS AND METHODS

We performed a retrospective analysis of the NRD database of 2017. Our study populations were derived from the HCUP NRD database. The NRD database is sponsored by the agency for healthcare research and quality. It is an administrative database which records de-identified admission data to

acute care hospitals during that specific year. The NRD includes discharges for patients with and without repeat hospital visits in a year and those who have died in the hospital.

In 2017, approximately eighteen million discharges were recorded from 2454 participating hospitals. Variable "NRD_visitlink" was used to identify the patients and the time between the two admissions was obtained by subtracting the variable "NRD_DaysToEvent." Subtracting length of stay of index admissions from time between two admissions provided the interval time to readmission. Index hospitalizations were studied between January to November to facilitate identification of 30-d readmission rates for all discharged patients for the 2017 calendar year. During this specified period, index hospitalizations were defined as non-elective admission with a primary International Classification of Diseases and Related Health Problems (ICD)-10 diagnosis code of acute diastolic heart failure/HFpEF, (I5031) or acute on chronic HFpEF (I5033). Index hospitalizations were excluded if: (1) The patients were younger than 18 years; (2) the patient died during the index hospitalization; and (3) there was no information on the length of stay (LOS).

We extracted baseline patient characteristics such as age, discharge destination, sex, primary expected payer, and median household income from the NRD database. The Charlson comorbidity index was used to determine the effect of chronic comorbidities in patients on primary and secondary outcomes [8]. Hospital-level variables included bed size, rural/urban location, and teaching status. Discharge to a rehabilitation facility was also obtained.

The primary outcome was defined as any non-elective, non-traumatic readmission that occurred within the first 30 d of discharge from the index hospitalization. For index hospitalizations with more than one readmission within 30 d, only the first readmission was included.

Secondary outcomes were: (1) In-hospital mortality rate for index admissions; (2) 30-day mortality rate for index admissions; (3) ten most common principal diagnoses for readmission; (4) in-hospital mortality rate during readmissions; (5) resource utilization due to readmission: LOS, total hospitalizations cost and charges; and (6) independent risk factors for admissions.

For the in-patient mortality rate, we used the patient's recorded vitals at discharge which are directly coded in the NRD database. The thirty-day mortality was calculated by following the patient's vital status at discharge after any readmission within 30-d of index admission.

Total hospitalization charge is the amount that hospitals billed for the entire hospital stay but not equal to the actual cost of care. The HCUP provides hospital-specific cost to charge ratios based on all-payer inpatient cost. We used this information to calculate total cost of hospitalization by multiplying total hospitalization charges by the cost to charge ratio.

We obtained the ten most common reasons for readmission by tallying the principal diagnosis for each readmission. Independent risk factors for readmission were identified using Cox regression analysis. The statistical analyses were performed using STATA statistical software (StataCorp LLC, College Station, TX 77845, United States). P values < 0.005 was considered statistically significant.

RESULTS

The study included 60514 adult patients with acute and acute on chronic HFpEF admitted between January to November in 2017, of which 61.1% of patients were female. The mean age was 74.8 years. About 59.4% patients had a Charlson comorbidity index greater than three. The majority of patients came from large metropolitan areas [46%] and had Medicare insurance (82.4%). The number of patients discharged to rehabilitation facilities was minimal [0.098%]. Teaching hospitals had a comparatively higher admission rate of 58.9% compared to non-teaching hospitals. Table 1 summarizes details of patient and hospital level characteristics of index admission.

The 30-d rate of readmission was 21%. Only 1175 (9.17%) of readmissions were associated with an admitting diagnosis of acute on chronic HFpEF. Figure 1 shows the Kaplan-Meier survival curve, which showed the total time at risk was 850749 d, with the initial readmission occurring at day one and the last readmission at day twenty-eight. Hypertensive chronic kidney disease with HF (1245; 9.7%) was the most common diagnosis at readmission. Figure 2 shows the ten most common etiologies of readmission. Readmissions showed higher in-hospital mortality compared to index admissions (7.9% *vs* 2.9%, P = 0.000).

Readmission was associated with a total of 81997 hospital days. Total inpatient healthcare-related financial burden was $206 million in costs and $779 million in charges. Statistically significant predictors of higher rate of 30-d readmission were, higher Charlson comorbidity index (CCI) (1.08, 1.06–1.09, P = 0.000), Medicaid insurance (1.15, 1.05-1.27, P = 0.004), longer LOS in the hospital (1.01, 1.01-1.02, P = 0.000) and teaching hospital admissions (1.09, 1.04-1.15, P = 0.001). Lower readmission risk was associated with female gender (0.91, 0.86-0.95, P = 0.000), elderly patients (0.99, 0.993–0.997, P = 0.000), patients from a micropolitan area (0.83, 0.77-0.90, P = 0.000) or small metropolitan area (0.91, 0.86-0.97, P = 0.003), private insurance (0.85, 0.77-0.93, P = 0.000) or self-paying patients (0.70, 0.53-0.93, P = 0.015). Interestingly, discharges to rehabilitation did not have a significant effect on re-admission rate (0.67, 0.28-1.6, P = 0.381). Table 2 displays the independent predictors of 30-d readmission.

Table 1 Baseline characteristics of patients admitted with heart failure with preserved ejection fraction

Variable	*n* (%)
Total number of index admissions	60514
Female	37156 (61.4)
Mean age in year (Confidence interval)	74.8 (74.52-75.1)
Charlson comorbidity index score	
0	0
1	8956 (14.8)
2	15613 (25.8)
≥ 3	35945 (59.4)
Median income in patient zip code, US dollars	
1-43999	16823 (27.8)
44000-55999	18275 (30.2)
56000-73999	15007 (24.8)
74000+	10408 (17.2)
Patient residence	
Large metropolitan areas with at least 1 million residents	27836 (46.0)
Small metropolitan areas with less than 1 million residents	22753 (37.6)
Micropolitan areas 18493 (9.1)	7201 (11.9)
Not metropolitan or micropolitan (non-urban residents)	2723 (4.5)
Insurance type	
Medicare	49864 (82.4)
Medicaid	4054 (6.7)
Private	5809 (9.6)
Self-pay	726 (1.2)
Rehab transfer	59 (0.098)
Hospital teaching status	
Non-teaching	24871 (41.1)
Teaching	35643 (58.9)

Mean LOS during index admissions was 5.2 d and 6.4 d during readmission. Readmitted patients had higher LOS (Coefficient 1.15, 95%CI 0.99-1.31, P = 0.000). Total cost of hospitalization was higher for readmitted patients (USD 4831, 95%CI 4251-5410, P = 0.000). Table 3 shows the primary and secondary outcome details.

DISCUSSION

Heart failure readmission is one of the major outcomes measured by CMS. Several studies have analyzed the burden of HF to identify the predictors related to readmission[4,9,10]; however, most of these combined HF as a single entity, with only a few studies focusing on HFpEF specific readmission [10]. This study specifically evaluates HFpEF readmission rates and outcomes using the latest NRD database available at the time of study.

The patient population involved was primarily elderly, with a mean age of 74.8 years and predominantly female (61.4%) in line with previous studies[11-13]. Approximately 59.4% of patients had a CCI greater than three. A prior study had shown a mean CCI of 2.9[12]. Another study revealed a higher percentage of patients with CCI>3[14].

The 30-d rate of readmission was 21%, which is comparable to other studies[11,14,15]. A study by Arora *et al*[11] using the NRD database of 2013 and 2014 showed a readmission rate of 18.5% and this is

Table 2 Independent predictors of 30 d readmission

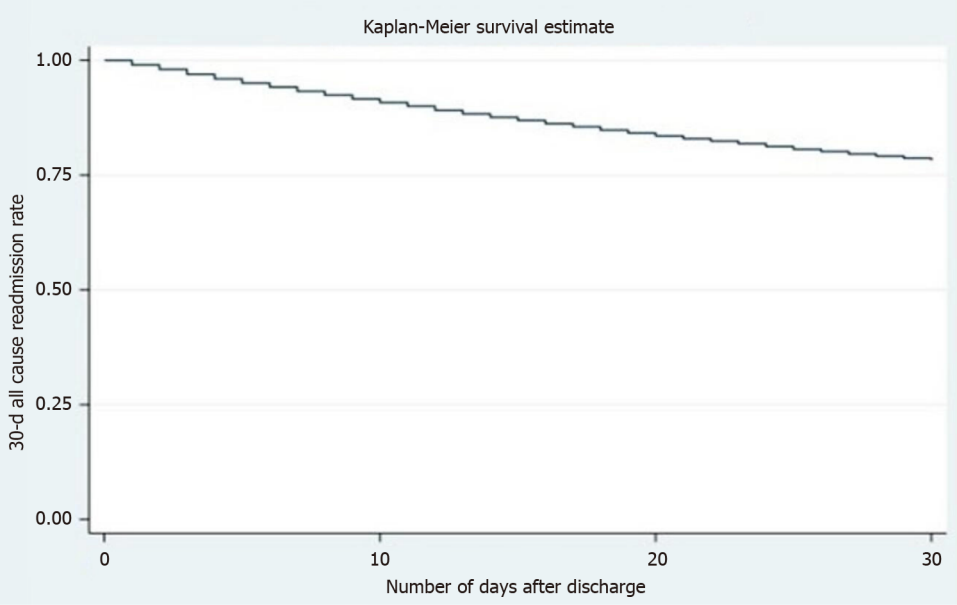
Variable	Adjusted OR (95%CI)	*P* value
Age	0.99 (0.99-0.99)	< 0.001
Female gender	0.91 (0.86-0.95)	< 0.001
Insurance provider (compared to medicare)		
Medicaid	1.15 (1.05-1.27)	0.004
Private	0.85 (0.77-0.93)	< 0.001
Self-pay	0.70 (0.53-0.93)	0.015
Charlson comorbidity index score	1.08 (1.06-1.09)	< 0.001
Patients admitted to teaching hospital	1.09 (1.04-1.15)	0.001
Length of stay	1.01 (1.01-1.01)	< 0.001
Geographic area (compared to large metropolitan area with at least 1 million residents)		
Small (area with < 1 million residents)	0.91 (0.86-0.97)	0.003
Micropolitan area	0.83 (0.77-0.90)	< 0.001
Patients admitted to teaching hospital	1.09 (1.04-1.15)	0.001
Length of stay	1.01 (1.01-1.01)	< 0.001
Geographic area (compared to large metropolitan area with at least 1 million residents)		
Small (area with < 1 million residents)	0.91 (0.86-0.97)	0.003
Micropolitan area	0.83 (0.77-0.90)	< 0.001

Table 3 Primary and secondary outcomes

Outcome measures	N (%), linearized standard error, 95%CI
Readmission rate	12812 (21%), 357.43, [12111-13513]
Mortality	
Index cases	1727 (2.9%), 76.98, [1576-1878]
Readmission	1012 (7.9%), 56.61, [901-1123]
Mean length of stay	
Index cases	5.2, 0.05, [5.15-5.32]
Readmission	6.4, 0.9, [6.21-6.56]
Total charges (in USD)	
Index cases	40570, 796.7, [39008-42132]
Readmission	60822, 1662.9, [57561-64083]
Total cost (in USD)	
Index cases	11234.2, 154.1, [10932-11536]
Readmission	16065, 349.7, [15379-16751]

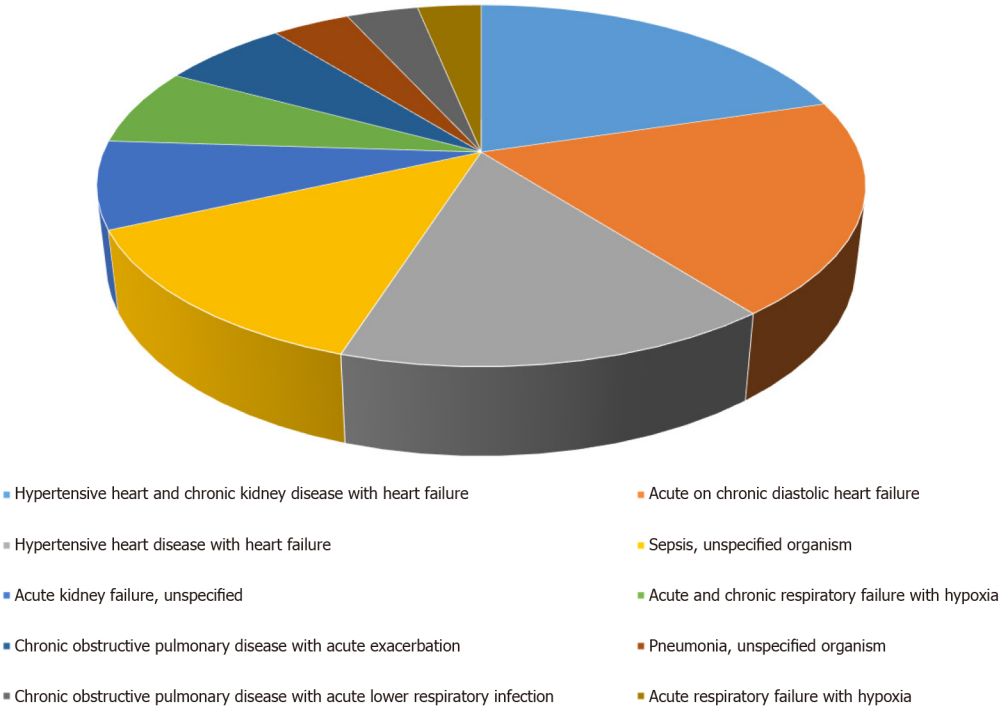
likely due to the increasing prevalence of HFpEF among the elderly accounting for increased readmission rates.

About 1175 (9.17%) of readmissions were admitted with acute on chronic HFpEF. The most common readmission diagnosis was HF associated with hypertensive chronic kidney disease (1245; 9.7%). Combining all cardiac readmission reasons, our study found approximately 26.3% readmissions were due to cardiac etiologies. A previous study reported higher numbers (approximately 41%-50%) in this category[11]. A study carried out by Goyal *et al*[14] in 2018 showed a higher percentage of non-cardiac causes of readmission. This significant reduction in cardiac cause as the reason for readmission is encouraging, as it could be due to improvement in treatment modalities for HFpEF. This is despite the fact that there is no established goal directed medical therapy for this condition or use of monitoring



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Figure 1 Kaplan-Meier curve of 30-d all-cause readmission among patients with heart failure with preserved ejection fraction.



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Figure 2 Ten most common etiologies of heart failure with preserved ejection fraction readmission.

modalities such as Cardiomems, which have been proven to reduce readmission rate.

Significant predictors of increased 30-d readmission rate were Medicaid insurance, higher CCI, patient admitted to a teaching hospital and longer LOS in the hospital. Higher CCI is an obvious indicator of high readmission rate as multiple comorbidities are associated with frequent hospitalizations. Previous studies demonstrated that patients with HFpEF are also diagnosed with multiple comorbidities[16,17]. We did not further analyze individual medical conditions associated with HF readmission, although it would be interesting to see how these conditions affect frequent readmission. Teaching hospital patient populations are generally complex and that could explain higher readmissions. Similarly, longer LOS is explained during readmissions as this occurs with sicker patients, consistent with the study by Bergethon *et al*[18].

Residence in a small metropolitan (or micropolitan area), older age, female sex, and private or no insurance were associated with lower odds of readmission. López-Vilella *et al*[19] has shown that female gender is associated with a higher number of readmissions when compared to males, independent of the left ventricular ejection fraction (females = 33.5% *vs* males = 26.8%; P = 0.009). Our study showed lower odds of readmissions in females. The study by Manemann *et al*[20] revealed that the rural population with HF has an increased risk of death but reduced risk of emergency department visits as well as hospitalizations. Our study has shown residence in a small metropolitan or micropolitan area is a predictor of decreased risk of readmission. This might be due to the decreased or delayed access to health care facilities. Further study in this direction will help identify the gaps in healthcare access in these areas.

Private insurance and no insurance are two extreme ends of the spectrum, and our study showed a lower rate of readmissions with both. The lower rate of readmission could be explained by the fact that the patients with private insurance have good preventive and acute care along with good access to healthcare compared to patients with no insurance. Patients with no insurance may have delayed care and died before hospital readmission.

Interestingly, discharges to rehabilitation facilities had no effect on readmission. There are some contradicting results as per recent studies. Arora *et al*[4] showed an increased risk of readmission in patients discharged to rehabilitation facilities. The study by Gupta *et al*[21] showed no effect on readmission rate based on discharge to a hospital-based skilled nursing facility on chronic conditions like congestive heart failure, although this study showed lower readmission rate for acute conditions such as acute myocardial infarction and pneumonia. This study's results aligned to our study even though currently we do not see many hospital-based skilled nursing facilities compared to free standing skilled nursing facilities. This result could be due to a different patient population which requires discharge to a skilled nursing facility due to their complex medical history. Further research in this regard will certainly help to identify the associated factors.

Our study showed increased in-hospital mortality in readmitted patients when compared to index admission (7.9% *vs* 2.9%, P = 0.000). Multiple studies have shown readmission cases are associated with increased mortality[22-24]. This seems to be aligned to the predictors of readmissions, as these patients are generally sicker with multiple comorbidities. It would be helpful to analyze the basic characteristics of these patients, which could further highlight mortality related to cardiac *vs* non cardiac causes.

Mean LOS during index admissions was 5.2 d while it was 6.4 d for readmission. Several studies have shown that increased LOS has a negative effect on readmission rate, with longer index LOS correlating with a higher risk for readmission[24-26]. This finding is similar to our study result, which we hypothesize could be due to sicker patients and those with multiple comorbidities requiring a longer LOS, portending to higher readmission rates.

Total cost of hospitalization was higher for readmitted patients. 81997 hospital d were associated with readmissions. The total economic burden associated with readmissions was $206 million in costs and $779 million in charges. A study by Fingar *et al*[27] using NRD HCUP databases showed the total economic burden of readmissions for congestive HF patients was approximately $2728 million in 2013. This study did not further differentiate between the cost associated with heart failure with reduced ejection fraction and HFpEF. However, given the increasing prevalence of HFpEF, it is likely that HFpEF will soon, if not already, account for the majority of the economic burden of heart failure and targeted interventions are required to reduce the economic burden while improving patient care by identifying key variables involved.

CONCLUSION

For patients hospitalized for acute or acute on chronic HFpEF, 30-d readmission rate is comparable to recent studies, although readmissions were associated with higher mortality and resource utilization compared to index admission. Multiple comorbidities were associated with increased risk of readmission. Most readmissions were due to hypertensive chronic kidney disease with heart failure.

ARTICLE HIGHLIGHTS

Research background

Heart failure with preserved ejection fraction is a growing problem with a high risk for readmissions. Highlighting the cause and effect of this condition will further help in preparing guidelines to treat and prevent readmissions.

Research motivation

This study will help to understand important variables associated with readmission risks and burden on the American health care resource utilization.

Research objectives

The main research objective is to identify common hospital and patient related variables of increased or decreased risk of readmission in patients with heart failure with preserved ejection fraction. Identifying these variables can help clinicians as well as researchers to further modify these variables to improve the morbidity as well as financial burden.

Research methods

This study used the National Readmissions Dataset for 2017 to obtain patients with heart failure with preserved ejection fraction using International Classification of Diseases (ICD) codes-10. This was a retrospective study. Cox regression analysis was used to identify the significant variables on readmission rate.

Research results

This study clearly showed different hospital-related and patient-related variables which increased the risk of readmissions. Also, we found some interesting results showing the variables with decreased risk of readmissions. Some of these results align with recent study results but some others show different results which needs further research to identify new changes in the dynamics of this condition.

Research conclusions

Our results show that the rates of readmissions are similar to recent studies which indicate that we have to work harder to reduce this rate. We were able to provide different variables which are easy to modify which can reduce the risk of readmissions. Our study showed discharge to rehabilitation facility has no effect on the rate of readmissions.

Research perspectives

Further study on this important topic will be helpful to determine the ongoing change in managing this condition and decreasing its effect both on patients as well as the health care sector.

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FOOTNOTES

Author contributions: All the authors have equally contributed in developing this manuscript.

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Informed consent statement: This study did not require informed consent from patients as de-identified patient records were used.

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Data sharing statement: Technical appendix, statistical code, and data-set available from the corresponding author at dranil3jha@gmail.com. Participants gave informed consent for data sharing.

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SYSTEMATIC REVIEWS

Association of electrocardiographic markers with myocardial fibrosis as assessed by cardiac magnetic resonance in different clinical settings

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Abstract

BACKGROUND

Cardiac magnetic resonance (CMR) is a unique tool for non-invasive tissue characterization, especially for identifying fibrosis.

AIM

To present the existing data regarding the association of electrocardiographic (ECG) markers with myocardial fibrosis identified by CMR - late gadolinium enhancement (LGE).

METHODS

A systematic search was performed for identifying the relevant studies in Medline and Cochrane databases through February 2021. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com).

RESULTS

A total of 32 studies were included. In hypertrophic cardiomyopathy (HCM), fragmented QRS (fQRS) is related to the presence and extent of myocardial fibrosis. fQRS and abnormal Q waves are associated with LGE in ischemic cardiomyopathy patients, while fQRS has also been related to fibrosis in myocarditis. Selvester score, abnormal Q waves, and notched QRS have also been associated with LGE. Repolarization abnormalities as reflected by increased Tp-Te, negative T-waves, and higher QT dispersion are related to myocardial fibrosis in HCM patients. In patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed. In atrial fibrillation patients, advanced inter-atrial block is defined as P-wave duration ≥ 120 ms, and biphasic morphology in inferior leads is related to left atrial fibrosis.

CONCLUSION

Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by CMR.

Key Words: Myocardial fibrosis; Late gadolinium enhancement; Electrocardiogram; Cardiac magnetic resonance

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Core Tip: Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable electrocardiogram (ECG). However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by cardiac magnetic resonance.

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INTRODUCTION

Cardiac magnetic resonance (CMR) is a useful non-invasive and radiation-free imaging modality that is the gold standard for estimating left ventricular volumes and ejection function[1]. Furthermore, CMR is a unique tool for non-invasive tissue characterization, especially for identifying edema, infarction, scar, and fibrosis. Tissue characterization can provide useful data not only for diagnostic purposes but also for the risk stratification of patients in different clinical settings[2-6]. In this setting, late gadolinium enhancement (LGE) is a commonly used CMR technique to identify myocardial fibrosis. However, CMR is not a widely available imaging modality, and also the high cost limits its widespread use in clinical practice.

On the other hand, electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from CMR evaluation. This systematic review aimed to present the existing data regarding the association of ECG markers with myocardial fibrosis identified by CMR-LGE.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement; PROSPERO ID: CRD42021225119)[7].

Search strategy

This study aimed to identify all relevant studies that provided data about the association of ECG markers with myocardial fibrosis as depicted by CMR. Two independent investigators searched Medline and Cochrane databases systematically through February 2021. The reference lists of all included studies, relevant review studies, systematic reviews, and meta-analyses were manually searched. The following keywords were used in the search strategy: "(CMR OR cardiac magnetic resonance) AND (LGE OR late gadolinium enhancement) AND (ECG OR electroc*)" without any limitations. We first screened the titles and abstracts of each retrieved study, and in case of considering a study relevant, we studied the full text. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com).

Inclusion/exclusion criteria

We included studies that provided data regarding the association of any ECG markers with myocardial fibrosis as depicted by CMR in different clinical settings. We excluded studies that did not provide data about the studied outcome, studies that provided data about the association of endocardial electrograms with fibrosis, or data about the association of atrial LGE with atrial fibrillation, as well as review studies, case reports/series, and experimental studies.

Data extraction

The data extraction was performed independently by two authors. The following data were extracted: First author, year of publication, journal, type of study (single or multicenter), number of patients, gender, age, clinical setting, ECG markers that were studied, as well as the major outcomes reported in each study. The Newcastle-Ottawa Quality Assessment Scale was used for the quality assessment of the observational studies[8].

RESULTS

Study search

Of the 616 studies initially retrieved, 534 were excluded at the title/abstract level, and 50 were excluded at the full-text level. Finally, 32 studies were included in the systematic review[9-40]. The search strategy is shown in Figure 1.

Study characteristics

The baseline characteristics and the main findings of the included studies are presented in Tables 1 and 2. Our search strategy identified 15 studies in hypertrophic cardiomyopathy patients[9-23], two with ventricular arrhythmias patients[24,25], two with non-ischemic cardiomyopathy patients[26,27], one with drug refractory AF patients[32], two with myotonic dystrophy patients[28,29], two with myocardial infarction patients[30,31], two about myocarditis[33,34], two including general population [35,36], one with arrhythmogenic cardiomyopathy patients[37], one with patients with preserved ejection fraction[38], one in cardiac sarcoidosis patients[39], and one in patients with left bundle branch block (LBBB)[40]. The quality assessment of the included studies is summarized in Supplementary Tables 1 and 2 (Supplementary material). Overall, the included studies were classified as high-quality studies.

Association of ECG markers with LGE in different clinical settings

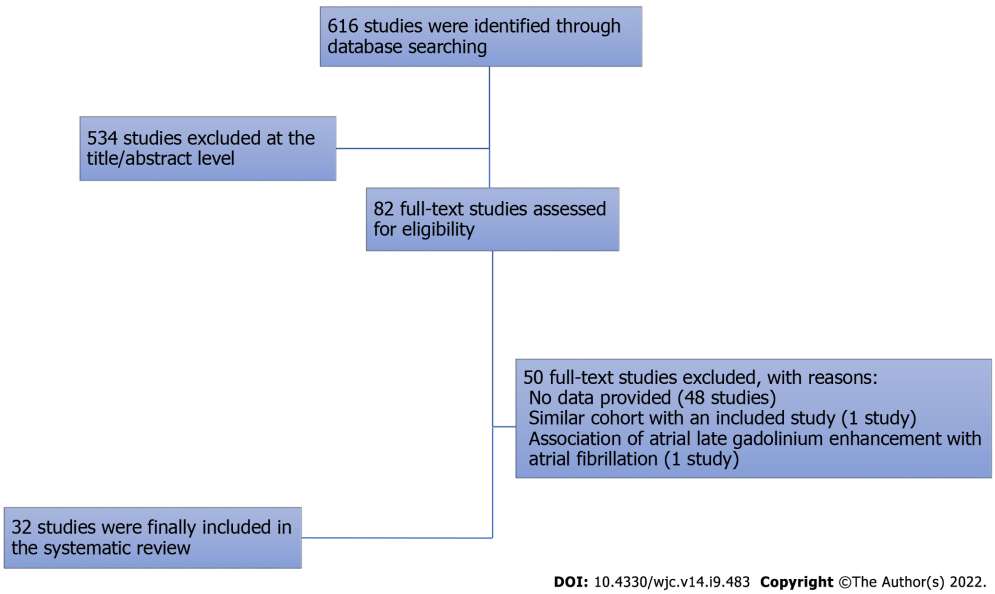
Hypertrophic cardiomyopathy: Fragmented QRS (fQRS) is defined as additional notches in the QRS complex. FQRS has been found to be related to more extensive myocardial fibrosis in HCM patients (Figure 2A)[9]. A recent study showed that quantitative fQRS, defined as the total amount of deflections in the QRS complex in all 12 routine ECG leads together, was an independent predictor of myocardial fibrosis and showed a good performance in identifying patients with a higher fibrotic burden[9]. Dohy

Table 1 Baseline characteristics of the included studies

Ref.	Setting	Country of origin	Multicenter	*n*	Enrolment period	Mean age	Male (%)	LVEF (%)
Oebel *et al*[25], 2017	PVCs ablation	Germany	No	101	2015-2016	57	59	46
Sakamoto *et al*[24], 2015	VT/VF	Japan	No	34	-	60	71	45
Piers *et al*[26], 2016	NICM	Netherlands	No	40	2011-	57	83	30
Becker *et al*[27], 2020	DCM	Netherlands	No	165	2016-2018	59	62	36
Cho *et al*[29], 2017	Duchenne muscular dystrophy	Korea	No	37	-	16	-	55
Cardona *et al*[28], 2019	Myotonic dystrophy 1	United States	No	52	2012-2017	41	38	60
Nadour *et al*[30], 2014	MI	United States	No	235	2006-2009	62	82	33
Chew *et al*[31], 2018	MI	Canada	No	705	2011-2014	64	84	40
Ciuffo *et al*[32], 2020	AF	United States	No	152	2010-2015	60	76	57
Ferrero *et al*[33], 2020	Myocarditis	Italy	Yes	80	2008-2019	34	82	55
Fischer *et al*[34], 2020	Myocarditis	Switzerland	No	587	2002-2015	48	59	48
Inoue *et al*[35], 2017	General population	United States	Yes	1669	2000 - 2002	67	50	62
De Lazzari *et al*[37], 2018	AC	Italy	No	79	2006-2016	33	60	58
Mewton *et al*[38], 2016	HFpEF	United States	No	77	2009-2010	60	68	60
Sobue *et al*[39], 2015	Sarcoidosis	Japan	No	59	2006-2010		29	51
Wieslander *et al*[36], 2015	General population	United States	No	193	2011-2013	63	66	49
Wieslander *et al*[40], 2018	LBBB	United States	Yes	325	-	63	52	36
Bi *et al*[9], 2020	HCM	China	No	69	2015-2020	46	62	65
Chen *et al*[10], 2014	HCM	China	No	118	2005-2012	46	72	72
Chen *et al*[11], 2020	HCM	China	No	135	2012-2016	51	51	62
Riza-Demir *et al*[12], 2019	HCM	Turkey	No	74	2016-2018	51	65	66
Dohy *et al*[13], 2020	HCM	Hungary	No	181	-	49	57	63
Fronza *et al*[14], 2016	HCM	Italy	No	88	2004-2014	42	74	62
Grall *et al*[15], 2014	HCM	France	No	42	2008-2012	47	72	62
Guerrier *et al*[16], 2016	Pediatric HCM	United States	No	37	2006-2014	16	89	69
Kawasaki *et al*[17], 2015	HCM	Japan	No	60	2010-2013	66	76	64
Konno *et al*[18], 2015	HCM	Japan	No	108	2008 - 2014	62	65	-
Matsuki *et al*[19], 2020	HCM	Japan	No	41	-	62	76	65

Park *et al*[20], 2018	HCM	Korea	No	88	-	57	74	6
Sakamoto *et al*[21], 2015	HCM	Japan	No	42	2004-2014	59	79	58
Suwa *et al*[22], 2014	HCM	Japan	Yes	50	2004 - 2012	-	-	-
Tangwiwat *et al*[23], 2019	HCM	Thailand	No	144	2005 - 2015	66	60	73

LVEF: Left ventricular ejection fraction; PVC: Premature ventricular complex; VT/VF: Ventricular tachycardia/ fibrillation; NICM: Non-ischemic cardiomyopathy; DCM: Dilated cardiomyopathy; MI: Myocardial infarction; AF: Atrial fibrillation; AC: Arrhythmogenic cardiomyopathy; HFpEF: Heart failure with preserved ejection fraction; LBBB: Left bundle branch block; HCM: Hypertrophic cardiomyopathy.



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Figure 1 Flow diagram of the search strategy.

et al[13] showed that fQRS and the strain pattern predicted more fibrosis, while the Cornell index was a negative predictor of myocardial fibrosis. The number of fQRS leads has been significantly correlated to %LGE, average ECV, and T2, while more than one lead with fQRS could predict > 5% of LGE mass with a 58% sensitivity and 63% specificity[20]. Suwa *et al*[22] showed that the presence of fQRS was associated with apical LGE. On the other hand, Tangwiwat *et al*[23] showed that fQRS was not associated with LGE. Chen *et al*[11] studied the role of Selvester QRS scoring criteria in diagnosing myocardial scar in HCM patients. The authors found that the Selvester score 1 showed a better performance in predicting LGE presence. Also, the same study showed a positive association between the Selvester score and the extent of LGE[11]. Abnormal Q waves are more prevalent in patients with LGE, but no correlation between the location of Q waves on ECG and territory of LGE on CMR was revealed (Figure 2B)[15]. Interestingly, quantitative analysis of LGE was not related to the presence of abnormal Q waves[15]. However, findings of another study showed that abnormal Q waves were associated with more ventricular segments with extensive LGE[10]. In a cohort study, LGE was associated with notched QRS, leftward QRS axis, and prolonged QRS duration, but not with abnormal Q waves, R-wave amplitude, or ST-T changes[17]. fQRS has been found to have higher diagnostic accuracy for detecting myocardial fibrosis compared to abnormal Q waves in HCM patients[18]. A cut-off of the number of leads with notched QRS ≥ 2 was found to predict the presence or absence of myocardial fibrosis, with a sensitivity of 70% and specificity of 81%[17]. Interestingly, the same study showed that the number of notched QRS leads was positively correlated with LGE volume, while a correlation between the lead distribution of notched QRS and the location of LGE was revealed[17]. Although giant negative T waves have been associated with apical HCM, no significant association was demonstrated with apical LGE[10]. On the other hand, in another observational study, repolarization disturbances, including negative T waves in lateral and anterior leads, have been correlated with "parietal" LGE scores, while QT dispersion has been associated with "global" LGE score[14]. Tp-Te has also been found to be an independent predictor of LGE, while a cut-off value of 99.4 ms can detect the LGE with a sensitivity of 64.3% and specificity of 84.2%[12]. In a small cohort of the pediatric population, the presence of LGE was associated with significantly decreased voltages in SV1, RV6, and

Table 2 Summary of the main findings of all included studies in the systematic review

Ref.	ECG markers studied	Main findings
Bi *et al*[9], 2020	fQRS, AF, bundle branch block	Quantitative fQRS was an independent predictor for myocardial fibrosis in HCOM
Chen *et al*[10], 2014	ST and T waves, LVH, Q waves, 1° AV block, 2° and 3° AV block, QRS duration	Abnormal Q waves were related to basal anteroseptal hypertrophy and extensive segmental LGE in HCM
Chen *et al*[11], 2020	QRS duration, QTc, LVH, RBBB, LAFB, LBBB, Selvester score	Selvester score showed a significant positive correlation with the extent of LGE enhancement in HCM
Riza Demir *et al*[12], 2019	QRS duration, QTc, TP-e interval, TP-e/QTc	Tp-e interval was an independent predictor of LGE in HCM
Dohy *et al*[13], 2020	fQRS, Q wave, ST deviation, Sokolow, Cornell, and Romhilt-Estes score	fQRS and ST deviation (strain pattern) predicts myocardial fibrosis in HCM
Fronza *et al*[14], 2016	Q waves, LBBB, signs of LV hypertrophy, negative T waves, ST depression	Negative T waves were correlated with LGE, whereas Q waves were associated with asymmetric hypertrophy in HCM
Grall *et al*[15], 2014	AF, QRS duration, ST deviation, negative T wave, Q wave, Sokolow, Cornell, Romhilt-Estes score	Q waves were more prevalent in the presence of LGE but didn´t correlate with LGE location and extent in HCM
Guerrier *et al*[16], 2016	QRS axis, QTc, PR interval, T wave inversion, ST depression, Q waves, LVH	Low left ventricle precordial voltages in ECG were associated with LGE in pediatric HCM patients
Kawasaki *et al*[17], 2016	QRS duration and axis, QTc, AF, LVH, Q wave, ST deviation, T wave inversion, notched QRS	Notched QRS was correlated with LGE in HCM without LBBB
Konno *et al*[18], 2015	Pathological Q waves and fQRS	fQRS was correlated with LGE in HCM, whereas Q waves were not correlated with LGE
Matsuki *et al*[19], 2020	QT interval, QRS duration, Sum of R-wave amplitude, ventricular late potentials	Ventricular late potentials were not correlated with LGE in HCM
Park *et al*[20], 2018	QRS, QTc, biphasic T wave, Q waves, sum S V1-3, Sokolow, Cornell, fQRS, AF, giant T wave inversion	The number of fQRS leads was significantly correlated to LGE in HCM
Sakamoto *et al*[21], 2015	24-hour ECG recordings and Time-domain T-wave alternans and QT dispersion	T-wave alternans and QT dispersion were associated with LGE in HCM
Suwa *et al*[22], 2014	QRS, QTc, Sokolov, max ST, max T waves, fQRS	fQRS was associated with impaired apical contraction and apical LGE in HCM
Tangwiwat *et al*[23], 2019	QRS duration, QTc, QRS axis, T-wave inversion, Sokolov, Cornell	fQRS in HCM was found to be associated with myocardial fibrosis in univariate analysis but not in the multivariate analysis
Sakamoto *et al*[24], 2015	HR, QT, QTc, QTe/RR slope, QTa/RR slope, day/night slope, VT/FV	QTe day/night and QTa day/night ratios were significantly greater in patients with Ventricular Arrhythmias and LGE
Oebel *et al*[25], 2017	PVC morphologies	RBBB, LBBB morphology and multiple PVC morphologies were associated with LGE in patients undergoing PVC ablation
Piers *et al*[26], 2016	Prolongation of the paced QRS duration after premature stimulation	QRS duration was associated with ventricular tachycardia but not with LGE in non-ischemic cardiomyopathy
Becker *et al*[27], 2020	HR, AV delay, 1° AV block, QRS duration, LBBB	QRS-prolongation was not correlated with LGE in non-ischemic dilated cardiomyopathy
Cardona *et al*[28], 2017	PR, QRS, QT, QTc, Frontal QRS-T angle, LVH Cornell	Surface conduction abnormality was not associated with LGE in myotonic muscular dystrophy type 1
Cho *et al*[29], 2019	fQRS	f-QRS was correlated with LGE in Duchenne muscular dystrophy with low statistical significance levels
Nadour *et al*[30], 2014	Q waves	Q waves in ECG have low value to detect a past myocardial infarction in the general population
Chew *et al*[31], 2018	QRS 120 ms, QRS fragmentation, Axis, AF	fQRS was associated with increased peri-infarct zone LGE and unfavorable left ventricle remodeling
Ferrero *et al*[33], 2020	fQRS	fQRS was correlated with LGE in patients with myocarditis
Fischer *et al*[34], 2020	QTc, QRS-T angle, fQRS, BBB, ST deviation, PR depression, low voltage, Q and T wave	fQRS, low voltage and QRS-T angle > 90° were independently correlated with LGE in myocarditis

Inoue *et al*[35], 2020	QRS duration, QTc, Sokolov and Cornell	QRS Cornell voltage, QRS duration, and QTc were significantly associated with LGE presence, while QRS Sokolow-Lyon voltage was not shown a significant correlation with LGE-CMR
Wieslander *et al*[36], 2015	LBBB, RBBB, LAFB, RBBB + LAFB and Selvester score	Selvester score was not accurate to detect myocardial scar and LGE in patients with conduction abnormalities and BBB
De Lazzari *et al*[37], 2018	Depolarization and repolarization abnormalities	Low QRS voltages in limb leads predicted LGE in Arrhythmogenic Cardiomyopathy
Mewton *et al*[38], 2016	QRS d, QTc, QRS-T angle, QRS score, T wave alternans	A significant association between T-wave alternans value and total scar. Patients with a myocardial ischemic scar had greater QRS duration. QRS-T angle was not associated with total myocardial scar size, core of scar, and gray zone size in grams by LGE-CMR
Sobue *et al*[39], 2015	QRS duration, atrioventricular block, LAFB, RBBB, Selvester QRS score	Selvester score was correlated with LGE in cardiac sarcoidosis
Wieslander *et al*[40], 2018	LBBB	Selvester score was not accurate to detect myocardial scar and LGE in patients with LBBB
Ciuffo *et al*[32], 2020	Inter-atrial block	Advanced IAB is associated with more fibrosis, while longer P-wave duration is also associated with more LA fibrosis.

fQRS: Fragmented QRS; AF: Atrial fibrillation; HCOM: Hypertrophic obstructive cardiomyopathy; HCM: Hypertrophic cardiomyopathy; AV: Atrioventricular; LGE: Late gadolinium enhancement; LVH: Left ventricular hypertrophy; RBBB: Right bundle branch block; LBBB: Left bundle branch block; LAFB: Left anterior fascicular block; PVC: Premature ventricular complexes; IAB: Inter-atrial block.

SV1 + RV6 despite increased septal dimensions[16]. Furthermore, the slopes of the QTe/RR and QTa/RR have been found to be significantly steeper in the LGE positive patients, while both slopes have been significantly correlated with the total LGE scores[24]. The association of late potentials with myocardial fibrosis has also been studied in HCM patients. However, ventricular late potentials were not found to be a reliable marker for the detection of myocardial fibrosis as assessed by LGE on CMR [19].

Ischemic and non-ischemic cardiomyopathy: Two studies were identified through the search strategy regarding the association of ECG markers with fibrosis as identified by CMR. Nadour W *et al*[30] studied the comparative efficacy of Q waves and CMR-LGE to predict prior myocardial infarction. Interestingly, the authors found that ECG-defined scars had a lower sensitivity compared to CMR-LGE-defined scars. Specifically, it was found that a significant number of pathological Q waves had absent infarct etiology, indicating high false positivity[30]. Chew *et al*[31] showed that in myocardial infarction patients, fQRS has been found to be significantly associated with the peri-infarct zone but not with core infarct volume. In the setting of non-ischemic cardiomyopathy, two studies were identified. Specifically, Piers *et al*[26] found that prolongation of the paced QRS duration after premature stimulation was related to long, thick strands of fibrosis but not to focal LGE-CMR. CMR has been reported to have a complementary role to ECG findings in dilated cardiomyopathy patients[27]. Specifically, it has been found that while QRS prolongation and septal mid-wall LGE are often co-existed, no significant correlation between these markers was revealed[27].

Myocarditis: Two studies that provided data about ECG markers with CMR fibrosis were identified. In myocarditis patients, fQRS has been correlated with the distribution of LGE (Figure 2C and D)[33]. Interestingly, fQRS was also associated with ongoing inflammation and poor prognosis in terms of ventricular function and fatal arrhythmias[33]. Fischer *et al*[34] studied the association of ECG parameters with LGE-CMR in patients with clinical suspicion of acute or subacute myocarditis. In this population, a wide QRS-T angle, low voltage, and fQRS were found to be significantly associated with LGE-CMR[34].

Myotonic dystrophy: Two studies were found to provide data about ECG markers and myocardial fibrosis in patients with muscular dystrophy. Specifically, in patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed[29]. On the other hand, in patients with myotonic muscular dystrophy type 1, PR, QRS, and QTc duration, frontal QRS-T angle, absolute Cornell voltage, LVH-Cornell, LBBB, right bundle branch block (RBBB), fascicular block, bifascicular block, AH interval, and HV interval were not significantly different between LGE positive and LGE negative patients[28].

Other clinical settings: Ciuffo *et al*[32] studied the association between the interatrial block and atrial fibrosis using CMR imaging in patients with drug-refractory AF. It was found that advanced inter-atrial block, defined as P-wave duration ≥ 120 ms and biphasic morphology in inferior leads, was significantly associated with left atrial fibrosis[32]. Furthermore, P-wave duration was also independently associated with left atrial fibrosis in this clinical scenario[32]. Mewton *et al*[38] studied the association of ECG markers in patients with preserved ejection fraction. A significant independent and positive association

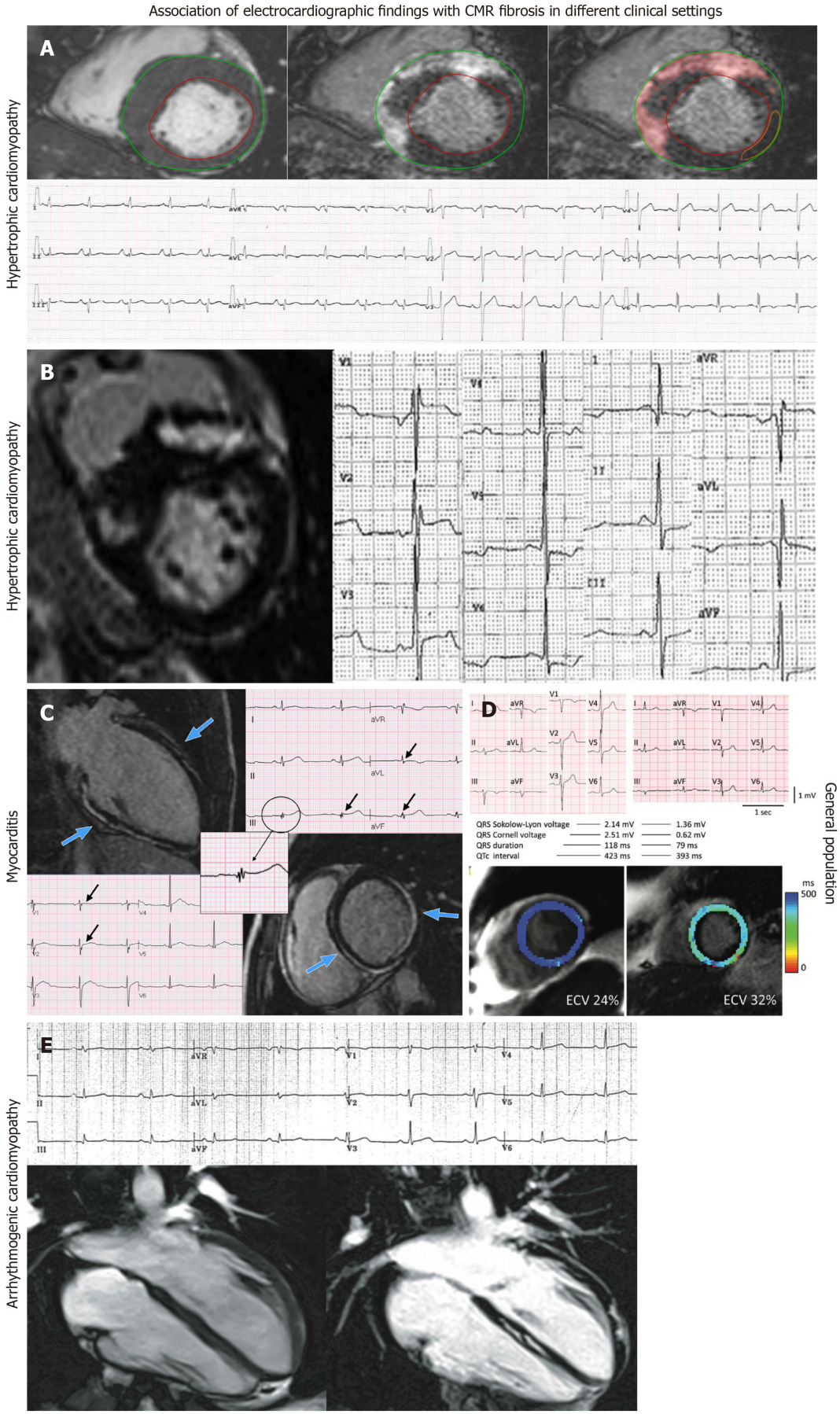


Figure 2 Association of electrocardiographic indices with cardiac magnetic resonance fibrosis in different clinical settings. A: Association of Fragmented QRS (fQRS) with myocardial fibrosis in hypertrophic cardiomyopathy patients (Adapted from Dohy Z *et al*[13], 2020-permission is not required for this

type of reuse); B: Association of Q wave with fibrosis in hypertrophic cardiomyopathy patients (adapted from Grall S *et al*[15], 2014-permission is not required for this type of reuse); C: Association of fQRS with fibrosis in myocarditis patients (adapted from Ferrero P *et al*[33], 2020-permission is not required for this type of reuse); D: Association of QRS voltage, QRS duration and QTc with fibrosis in the general population (adapted from Inoue YY *et al*[35], 2017-with permission from the Radiological Society of North America); E: Association of low QRS voltages with fibrosis in arrhythmogenic cardiomyopathy patients (adapted from De Lazzari M *et al*[37], 2018- permission is not required for this type of reuse).

between T-wave alternans value and total scar was revealed[38]. Furthermore, patients with a myocardial ischemic scar had significantly greater QRS duration as compared with patients with nonischemic scar and patients without a myocardial scar. On the other hand, QRS-T angle was not associated with total myocardial scar size, core of scar, and gray zone size in grams by LGE-CMR[38]. In the clinical setting of PVC, the presence of an RBBB pattern as the clinically dominant PVC morphology or the presence of multiple PVC morphologies were significantly correlated with the presence of LGE-defined fibrosis[25]. On the other hand, in patients with VT or VF, the slopes of the QTe/RR (QT measured at the apex of the T waves) and QTa/RR (QT measured at the end of T waves) were significantly steeper in the LGE positive patients while both slopes were significantly correlated with the total LGE scores[24]. Interestingly, the QTe day/night and QTa day/night ratios were significantly greater in LGE positive patients than in LGE negative patients, clearly demonstrating the correlation between fibrosis and QT dynamicity[24]. In the setting of cardiac sarcoidosis, QRS estimated scar using Selvester QRS score was significantly correlated with CMR-LGE scar while it was related with life-threatening arrhythmic events[39]. However, the Selvester QRS score intended for use in the presence of conduction abnormalities was not found to predict CMR-defined LV scar in a general population with suspected cardiovascular disease[36]. Similarly, the LBBB Selvester QRS score showed poor accuracy in the detection and quantification of myocardial scar in LBBB patients[40]. In ARVC patients, ε wave and terminal activation duration > 55 ms were not associated with either right or left ventricular LGE[37]. On the other hand, the presence of low QRS voltages in limb leads was associated with the presence of left ventricular LGE but not with right ventricular LGE (Figure 2E)[37]. In addition, the presence and extent of right precordial T-wave inversions were associated with the presence of right ventricular but not with left ventricular LGE[37]. Finally, in a prospective cross-sectional study that included individuals free of prior coronary heart disease, QRS Cornell voltage, QRS duration, and QTc were significantly associated with LGE presence, while QRS Sokolow-Lyon voltage was not shown to have a significant correlation with LGE-CMR (Figure 2D)[35].

DISCUSSION

In our systematic review, we examined in detail studies that have reported associations between ECG markers and CMR-reported myocardial fibrosis. In the literature, studies have reported controversial results regarding the association between pathological Q wave presence in ECG and LGE-CMR at first glance[10,17]. Moreover, another controversy on the association between fQRS and LGE in apical hypertrophic cardiomyopathy was reported[22,23]. These findings should be evaluated with caution because the study population, study design, ECG parameters used, and statistical approach have been heterogeneous among the included studies. Considering all included data, fQRS, QRS duration, Selvester QRS score, and ventricular repolarization variables have been detected to have great predictive value for myocardial fibrosis, which is validated by LGE-CMR in various cardiovascular diseases. The studies examining the association between ECG markers and CMR have been first evaluated in patients with HCM and ischemic cardiomyopathy. HCM has always been attracted attention due to its heterogenous electrocardiographic presentations, and it is rational to assess the fibrosis markers of ECG in HCM with the validation of CMR[41]. Since myocardial fibrosis has been associated with the arrhythmia burden in patients with HCM, early detection of myocardial fibrosis using 12-lead ECG has the potential to rapidly change management strategy in these patients[42,43]. LGE-CMR has been proposed as one of the predictors of clinical prognosis in patients with HCM[44]. Thus in the next step, ECG parameters correlated with LGE-CMR may be investigated in the risk scoring of HCM in addition to other well-known risk factors to provide more precise prediction in the follow-up of these patients. As the use of CMR is limited due to its high cost, ECG parameters found to represent myocardial fibrosis according to LGE-CMR may easily be used for the risk assessment.

In the evaluation of myocardial scar in patients with ischemic and non-ischemic cardiomyopathy, there appears to be a clear performance difference between CMR and ECG. The highly promising ECG parameters such as fQRS and pathological Q waves have not satisfied the expected performance compared to LGE-CMR[30]. The pathophysiological occurrence of myocardial scar in infarction may play an important role while explaining the poor performance of pathological Q waves in predicting myocardial fibrosis of LGE-CMR. Since Q waves symbolize a loss of electrical activity, not purely myocardial fibrosis, pathological Q waves without evident LGE-CMR may be explained for this reason

[45]. However, fQRS, which has not been correlated with core infarct volume, has been associated with peri-infarct volume[31]. In myocarditis, fQRS has been demonstrated to have a good LGE-CMR prediction performance, similar to its significance in patients with HCM[33,34]. Since ECG variables, including fQRS, change dynamically during the disease course of myocarditis, more investigations are warranted to determine the time of obtained ECG, which should be examined to correlate LGE-CMR. On the other hand, ECG parameters regarding atrial tissue fibrosis have been closely related to LGE-CMR because there have been several investigations defending the association between P-wave duration and morphology and left atrial fibrosis. Therefore, P-wave duration and inter-atrial block have a great potential to present left atrial fibrosis, which has been validated by CMR[32].

CONCLUSION

Myocardial fibrosis, which is a reliable marker of prognosis in a wide spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. More investigations are needed on a specific disease basis to fill the gap of evidence regarding the association of ECG markers and CMR, which may practically change our daily clinical practice.

ARTICLE HIGHLIGHTS

Research background

Electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from cardiac magnetic resonance (CMR) evaluation.

Research motivation

ECG can be a valuable tool for the risk stratification of sudden cardiac death in different clinical settings.

Research objectives

To elucidate the association of ECG markers with CMR-late gadolinium enhancement in different clinical settings.

Research methods

Methodology of Systematic reviews in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).

Research results

Our results summarize the existing evidence about the association of ECG markers with fibrosis as identified by CMR. Existing data show that fragmented QRS, Q waves and repolarization abnormalities are some of the ECG indices that are associated with myocardial fibrosis.

Research conclusions

Myocardial fibrosis, a marker of prognosis in a wide spectrum of clinical settings, can be easily identified by ECG indices.

Research perspectives

Future research should be focused on the identification of ECG markers that are reliably associated with myocardial fibrosis in different clinical settings. Furthermore, the association of ECG markers with all-cause mortality and arrhythmic events is of great importance.

FOOTNOTES

Author contributions: Bazoukis G had the inception of the idea and wrote the first draft; Bazoukis G and Garcia-Zamora S performed the systematic search; Bazoukis G, Garcia-Zamora S, Cinier G, Lee S, Gul EE, García JA, Miana G, Hayıroğlu MI, Tse G, Liu T, and Baranchuk A performed major revisions and approved the final manuscript; Baranchuk A supervised the study.

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CASE REPORT

Intravascular lithotripsy for coronary calcium: A case report and review of the literature

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Abstract

BACKGROUND

Coronary calcium poses a challenge for the interventional cardiologist often leading to stent under-expansion and subsequent ischemic events. Aggressive balloon post-dilatation though helpful is usually inadequate. Multiple plaque ablation techniques are in vogue, but they are technically demanding and are not without complications. Shockwave intravascular lithotripsy (S-IVL) has emerged as a user-friendly and effective mechanism for calcium management with a high safety margin. A series of trials (DISRUPT CAD I-IV) have demonstrated both short-term and long-term safety and efficacy of the technique. As experience with the technique grows more and more, therapy areas like stent restenosis are being covered by the S-IVL.

CASE SUMMARY

We report a series of 2 cases successfully managed with S-IVL therapy at our center. The first case is of a 57-year-old smoker who presented with acute coronary syndrome. His left anterior descending coronary artery revealed calcified 90% stenosis on angiogram and a combination of superficial-deep calcium on intracoronary imaging. The calcium was treated with 20 pulses of S-IVL to create discontinuity and a sirolimus eluting drug-eluting stent was successfully implanted. The second case is that of an elderly lady who presented with stable angina and demonstrated diffuse calcified lesions in the left anterior descending artery on angiogram. She also demonstrated a mixture of superficial and deep seated calcium zones on imaging. S-IVL therapy was applied to generate fractures in calcium, and two overlapping drug-eluting stents were implanted successfully without any complications.

CONCLUSION

S-IVL is an emerging, efficient, user-friendly and safe therapy for managing intracoronary calcium in routine interventional practice.

Key Words: Coronary artery calcification; Acute coronary syndromes; DISRUPT-CAD; Shock wave; Premature ventricular contraction; Case report

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Core Tip: The presence of severe calcification in coronary arteries poses a challenge for the interventional cardiologist. If inadequately addressed, it leads to inadequate stent expansion, difficulty in delivery of stent/balloon, balloon rupture, stent dislodgement, stent thrombosis and even perforation. Intravascular lithotripsy is a novel technique utilizing ultrasonic waves to disrupt the calcium in the vessel wall while retaining them in situ. With the accumulation of data and growing expertise of operators with intravascular lithotripsy, it is turning out to be an indispensable tool in catheterization laboratory. We present 2 cases in which intravascular lithotripsy was successfully utilized.

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INTRODUCTION

Calcified coronary artery lesions continue to be one of the pivotal challenges faced by interventional cardiologists. Stent under-expansion due to calcified lesions is a strong predictor of procedural failure and may lead to various acute complications, such as stent thrombosis and long-term stent restenosis [1]. Although aggressive balloon dilatation can sometimes achieve adequate room for stent deployment, the degree of final luminal gain is often limited. Furthermore, in eccentric lesions, high-pressure balloon dilatation can lead to overstretching of the noncalcified wall with minimal impact on the calcified lesion, which exacerbates the risk for coronary dissection and perforation[2].

Shockwave intravascular lithotripsy (S-IVL) or intravascular lithotripsy (IVL; Shockwave Medical Inc., Santa Clara, CA, United States) has recently been approved by the United States Food and Drug Administration for plaque modification in calcified coronary lesions. Contrary to rotational atherectomy, S-IVL uses ultrasonic waves to interrupt the calcium arc while retaining the residual chunks inside the vessel wall. Optical coherence tomography (OCT) sub-study of the DISRUPT-CAD trial revealed that circumferential lithotripsy fractures the superficial as well as deep layers of calcium, thereby enhancing the plaque compliance[3]. S-IVL is quite safe and easy to perform. Moreover, the traditional complications associated with rotational atherectomy, viz. distal microembolization, slow or no-flow, coronary perforation and bradycardia, necessitating temporary pacing lead insertion are not seen in lithotripsy. Herein, we share our experience with shockwave lithotripsy in two separate scenarios and a brief review of literature.

CASE PRESENTATION

Chief complaints

Case 1: Our patient was a 57-year-old man who smoked and was admitted with a diagnosis of acute coronary syndrome.

Case 2: A 58-year-old woman with chronic stable angina (CCS Class III) presented to a peripheral hospital where her coronary angiogram revealed triple vessel disease.

History of present illness

Case 1: He presented with intermittent retrosternal chest pain at rest with radiation to arm for the past 7 d.

Case 2: She had effort angina despite medical therapy for past 4 mo.

History of past illness

Cases 1 and 2: There was no past history of any specific illness.

Personal and family history

Case 1: He was a chronic smoker, and there was no family history of coronary artery disease (CAD).

Case 2: She was a nonsmoker, non-diabetic and had no family history of CAD.

Physical examination

Case 1: He was hemodynamically stable at admission with blood pressure of 134/70 mmHg and pulse rate of 80/min.

Case 2: She was hemodynamically stable at admission with blood pressure of 124/78 mmHg and pulse rate of 68/min.

Laboratory examinations

Case 1: A 12 lead electrocardiogram was normal except for a q wave and t wave inversion in lead III. His routine biochemistry and hemogram were within normal limits. His cardiac troponin value was 0.016 ng/mL (Normal < 0.014 ng/mL).

Case 2: A 12 lead electrocardiogram was unremarkable as was her routine biochemical and hematological profile.

Imaging examinations

Case 1: He exhibited normal left ventricular functions without any regional wall motion abnormality on echocardiography. Coronary angiography was performed with an intention to revascularize, which revealed calcific 90% stenosis in the proximal left anterior descending (LAD) coronary artery, 70%-80% stenosis in the major obtuse marginal artery and 80% stenosis in the distal left circumflex coronary artery (Figure 1A and B).

Case 2: The LAD showed severe calcified 90% stenosis in the proximal-mid part, whereas the left circumflex coronary artery exhibited 30%-50% disease in the distal part. There was mild disease in the left main coronary artery, whereas the non-dominant right coronary artery had severe stenosis. The patient was referred to our center for revascularization (Figure 2A-C). Her left ventricular ejection fraction was 62%.

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 2: After the meeting of the cardiac team, she was given the options of coronary artery bypass graft surgery and percutaneous coronary intervention (PCI) to the LAD, and she opted for the latter.

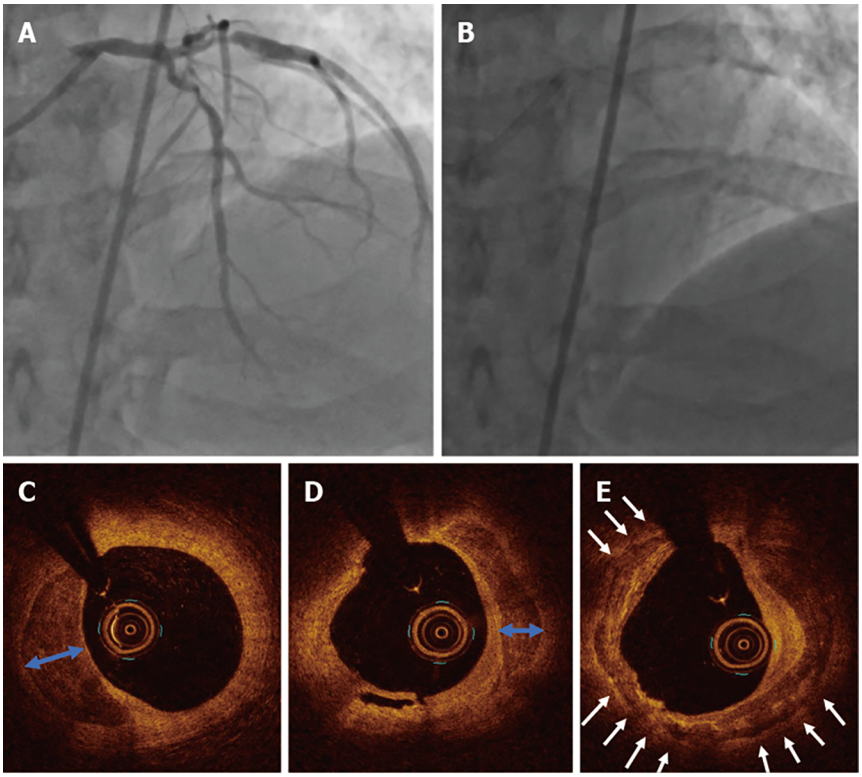
FINAL DIAGNOSIS

Based on clinical, biochemical and angiographic features, a diagnosis of acute coronary syndrome-unstable angina with calcified double vessel disease was made in the first case. In the second case, chronic stable angina with calcified triple vessel disease was made.

TREATMENT

Case 1: The lesion in the proximal LAD was predilated using a 2.5 mm × 10 mm semicompliant balloon. Subsequently, OCT was performed to evaluate the degree of calcium, which revealed both superficial and deep circumferential calcium (Figure 1C-E). An IVL balloon catheter (C2IVL from Shockwave Medical Inc., Santa Clara, CA) measuring 3 mm × 12 mm was then placed across the lesion and dilated at 4 atmospheric pressure (atm). Ten pulses of shock wave were then delivered followed by IVL balloon dilatation at 6 atm. The cycle was repeated twice, which resulted in calcium fractures as seen in OCT performed after IVL (Figure 3). Next, a 3.0 mm × 40 mm sirolimus-eluting stent was deployed at 10 atm. The lesion was then post dilated with 3.5 mm × 12 mm noncompliant balloon. The final angiographic run revealed thrombolysis in myocardial infarction (TIMI) 3 flow and well expanded without any residual dissection (Figure 4A). A corresponding OCT run revealed a well-expanded and opposed stent, with a minimum stent area of 6.2 cm^2.

Case 2: Because of severe calcification of the LAD, imaging-assisted PCI was planned. The lesion in the proximal LAD was predilated using a 2.5 mm × 12 mm noncompliant balloon to allow the passage of the OCT catheter, which revealed both superficial and deep circumferential calcium (Figure 2D-F). In view of the deep calcium, we selected S-IVL as the plaque modification strategy. An IVL balloon (C2IVL



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Figure 1 Coronary angiogram of case 1. A and B: A severe calcific lesion in the left anterior descending coronary artery and proximal major obtuse marginal artery; C-E: An optical coherence tomography showed circumferential (white arrows) and deep calcium arc (blue arrow) prior to percutaneous coronary intervention.

from Shockwave Medical Inc., Santa Clara, CA) measuring 2.5 mm × 12 mm was then placed across the distal lesion and dilated at 4 atm. Subsequently, 10 pulses of shock waves were delivered, followed by dilatation at 6 atm. The cycle was repeated twice in the proximal lesions too. Subsequently, two overlapping sirolimus drug-eluting stents, 2.5 mm × 30 mm (distal) followed by 3 mm × 21 mm (proximal), were deployed at 10-12 atm. The lesions were then post dilated with a noncompliant balloon (sequentially 2.5 mm and 2.75 mm and subsequently 3.0 mm). Unfortunately, the OCT catheter could not be maneuvered into the LAD for final imaging as the patient became transiently unstable after post dilatation because of the slow-flow/no-reflow phenomenon. However, following intracoronary pharmacotherapy, the final angiography revealed TIMI 3 flow without residual dissection or stenosis (Figure 4B).

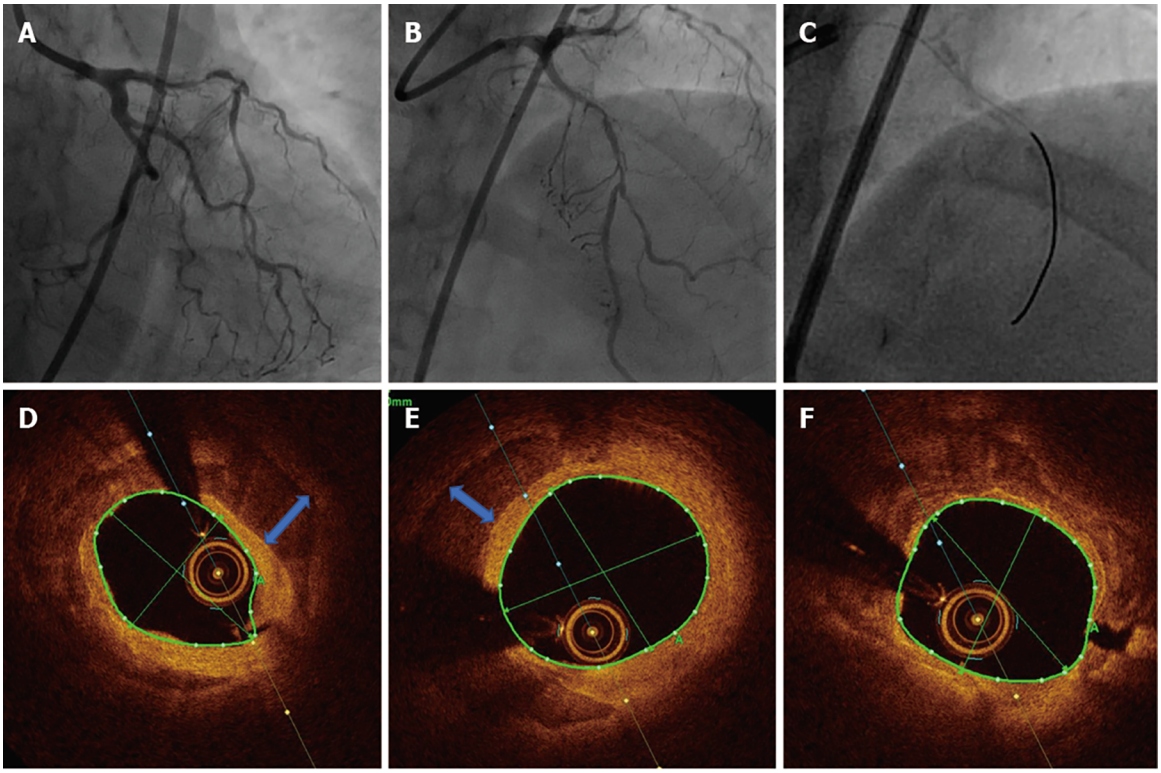
OUTCOME AND FOLLOW-UP

Both patients were doing well at the 30-d and 3-mo follow-up without any symptoms.

DISCUSSION

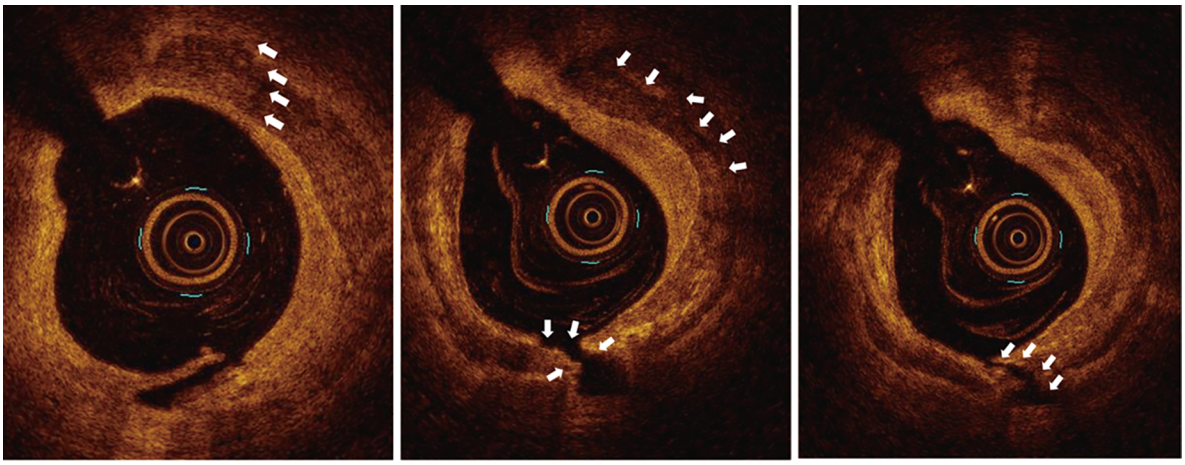
Coronary calcification is a part of the aging process and is exacerbated by concomitant cardiovascular risk factors and comorbidities[4,5]. Approximately 20% of the coronary interventions are complicated by severe calcific lesions, which are independent predictors of procedural failure and adverse cardiac events in the future[6,7]. Moreover, calcific lesions heighten the risk for procedural complications and increase the procedural time. Characteristics of calcific lesions, viz. location inside the coronary arteries (superficial *vs* deep) and calcium burden (thickness of the calcified plaque, arc angle subtended, and longitudinal extension), are the factors that determine plaque compliance, stent delivery, adequate stent expansion and finally procedural success and long-term outcomes[8].

Several techniques are available for plaque modification in severely calcified coronary lesions, including high pressure noncompliant balloons, scoring balloons, cutting balloons, rotational/orbital atherectomy and excimer laser. These devices cause plaque compression or plaque debulking and are not without complications, such as distal embolization, slow flow, coronary dissection and perforation. Moreover, they are less successful if the calcification is deep, thick or eccentric, and the tissue injury



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Figure 2 Coronary angiogram of case 2. A-C: A severe calcific lesion in the left anterior descending coronary artery; D-F: Optical coherence tomography showed circumferential calcium and deep calcium (blue arrow) prior to percutaneous coronary intervention.



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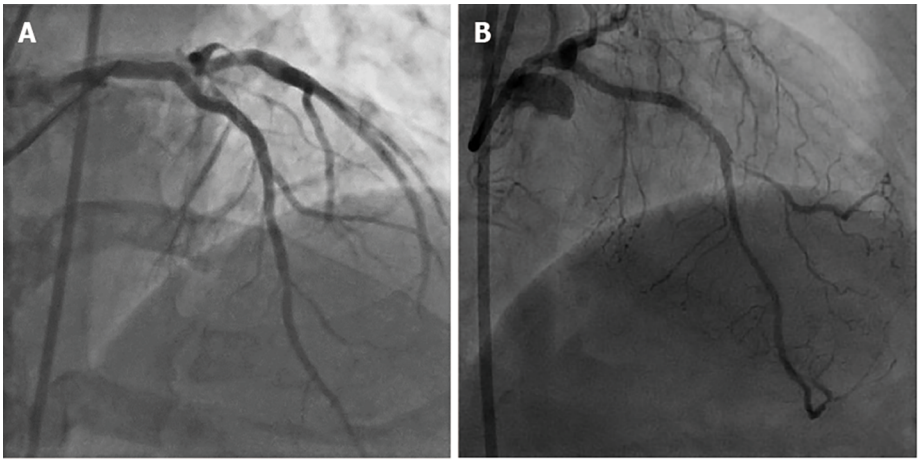
Figure 3 Post intravascular lithotripsy optical coherence tomography images of left anterior descending coronary artery of case 1 depicting calcium fracture (white arrow).

occurring in the process may induce uncontrolled neointimal proliferation and restenosis[9].

IVL is a novel technique for bed preparation in severely calcified lesions in coronary as well as peripheral arteries. Calcium fractures are achieved with pulsatile mechanical energy delivered *via* lithotripsy emitters mounted inside a low-pressure balloon catheter (max 4-6 atm). The electrohydraulic-generated high-speed sonic pressure waves pass through the soft vessel wall tissue and selectively modify the subendothelial calcium, which disrupts the calcified plaque. IVL has been approved by the United States Food and Drug Administration for the treatment of calcified peripheral lesions and has obtained the CE mark for coronary lesions.

Mechanism of IVL

The mechanism of IVL is similar to the commonly utilized electrohydraulic lithotripsy or commonly



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Figure 4 Post percutaneous coronary intervention coronary angiogram. A: Post percutaneous coronary intervention coronary angiogram showed a well expanded left anterior descending coronary artery in case 1; B: Post percutaneous coronary intervention coronary angiogram showed fully expanded stent and thrombolysis in myocardial infarction 3 flow in case 2.

referred to as extracorporeal shockwave lithotripsy for fragmentation of urogenital tract stones[10]. IVL therapy uses the same technology with some modifications to address vascular calcium. The adaptations include the incorporation of lithotripsy emitters on the shaft of a balloon angioplasty catheter, which delivers localized pulsatile acoustic pressure waves circumferentially to modify vascular calcium.

In electrohydraulic lithotripsy, a spark gap discharge between two electrodes causes the formation of an acoustic pressure wave within the transmitting fluid medium. This pressure wave expands spherically outwards from the emitter. The energy discharged from the spark gap results in the formation of a plasma vapor bubble, and this immediately follows the initial acoustic shockwave. The rapid expansion and collapse of the vapor bubble, which is known as a cavitation bubble, and secondary shockwaves causes stone fracture on encountering differing acoustic impedances, such as the transition from soft tissue to calcified tissue.

Electrohydraulic lithotripsy spark gap technology was leveraged for use in IVL, but several modifications were done to ensure effective and safe intravascular treatment. Three key modifications were done for IVL: (1) IVL pressure waves deliver tissue-safe positive and minimal peak negative pressure pulses allowing sufficient compressive force to modify vascular calcium. This helps in mitigating soft tissue injury due to excessive cavitation or tensile stress; (2) Pressure wave emitters are enclosed within an inflated, fluid-filled balloon to prevent thermal injury; and (3) Multiple emitters are present in series along the shaft of the catheter for longitudinal treatment of the calcified vessel.

The IVL shockwaves are unfocused, which produces much lower energy flux density (the amount of acoustic energy per unit area) as compared to extracorporeal shockwave lithotripsy. Much less energy is required here as the IVL shockwaves are initiated in close proximity to the target vascular calcium. In addition, IVL integration of a semicompliant balloon with emitters on the shaft has several advantages. First, the mixture of contrast and saline in balloon dissipate heat generated during the formation of vapor bubbles and shields the emitters from direct contact with the vessel wall. Since the balloon is deflated in between two cycles, it helps in dissipating heat and residual gas bubbles allowing tissue perfusion and preventing ischemia. Second, it provides mechanical support, which minimizes any tissue deformation during IVL therapy. Last as the integrated balloon is thin and acoustically transparent, it provides efficient fluid to tissue transmission and effective coupling of IVL pressure pulse propagation from emitter to vascular wall. The appropriately sized IVL balloon catheter inflated at subnominal pressure (4 atm) produces efficient ring calcium fracture avoiding barotraumas.

Components of the IVL system

The IVL system comprises the following components: (1) *The IVL generator*: The IVL generator is a portable and rechargeable orthogonal "box" weighing 6.8 kg and measuring 28.0 cm × 15.2 cm × 29.2 cm, which delivers small electrical pulses of up to 3000 V of electrical energy. The discharge frequency is one pulse per second (1 Hz), and the maximum number of continuous pulses per cycle is fixed and depends on the type of the IVL catheter used. The machine is user friendly and comprises two buttons, one for power and the other one for delivering energy. There are no external connections, except from the IVL connector cable. There is a color-coding that depicts the number of pulses remaining after each cycle and the size of the IVL catheter being used[9,11-13]; (2) *The IVL connector cable:* The IVL connector cable is 1.53 m in length and contains two magnetic poles. One pole is connected to the IVL generator, and the other one is specially designed with a push button that triggers energy emission and is

connected directly to the proximal end of the IVL catheter. It forms the route and the gate for electrical energy transfer from the IVL generator to the IVL catheter[9,11-13]; and (3) *The IVL catheters:* The IVL catheters are balloon angioplasty catheters that possess a series of unfocused electrohydraulic lithotripsy emitters, which convert electrical energy into sonic pressure pulses. The sonic pressure waves travel circumferentially and create a spherical field at an effective pressure of approximately 50 atm. The waves selectively disrupt and fracture the calcium in situ and alter the vessel compliance while minimizing the injury and maintaining the integrity of the fibroelastic components of the vessel wall. The catheters are available in different sizes, internal design and maximum cycles and total pulses based on their use in coronary or peripheral vessels[9,11-13].

Technical aspects of IVL

In general, the coronary IVL balloon is sized 1:1 to the reference artery diameter and is inflated to low pressure (4 atm). One cycle of ultrasound energy, *i.e.* 10 pulses over 10 s, is delivered. This process is followed by IVL balloon dilatation to the size of the reference vessel according to the balloon compliance chart. The procedure should be repeated to provide a minimum of 20 pulses in the target lesion, with a period of deflation in between the pulses to allow for distal perfusion. The required number of cycles depends upon the lesion resistance; however, a maximum of 80 pulses (8 cycles) can be emitted by a single catheter. If the lesion length exceeds the balloon length (12 mm), then the balloon can be repositioned and the lithotripsy repeated. Although the currently available IVL balloon is relatively bulky, contemporary rapid exchange guide extension catheters can accommodate it easily and aid in its smooth delivery.

Clinical studies on IVL

Clinical studies on IVL are shown in Table 1.

Randomized trial data: (1) DISRUPT CAD I Trial. This trial was a prospective multicenter study designed to evaluate the safety of IVL in 60 patients with heavily calcified coronary lesions. The incidence of major adverse cardiac events (MACE), defined by cardiac death, myocardial infarction and target vessel revascularization, was low (5.0% at 30 d and 8.6% at 6 mo). Clinical success rate (defined by a residual stenosis of < 50% and no in-hospital MACE) and device success rate (defined by successful device delivery and IVL treatment at target lesion) were high (95.0% and 98.3%, respectively). The major mechanism for calcium modification was fracture, as evidenced on OCT, and it was independent of the depth[14].

(2) DISRUPT CAD II Trial. This trial was also a prospective multicenter study involving 120 patients with severe coronary artery calcium and an indication for revascularization. The primary endpoint was in-hospital MACE (cardiac death, myocardial infarction and target vessel revascularization). Furthermore, an OCT substudy was performed to elucidate the mechanism of calcium modification. The incidence of primary endpoint was 5.8%, and there was no evidence of abrupt closure, slow flow-no reflow or perforation. Post PCI OCT showed calcium fracture in 78.7% of the lesions[15].

(3) DISRUPT CAD III Trial. This trial was a larger multicenter international study that enrolled 431 patients with severely calcified de novo lesions undergoing PCI. The primary safety endpoint was freedom from MACE at 30 d, and the primary efficacy endpoint was procedural success. The overall primary safety endpoint achieved was 92.2%, whereas the procedural success rate was 92.4%. The study also noted that the procedure was well tolerated, with a low rate of periprocedural complications. An OCT substudy showed calcium fracture in 67.4% of the lesions[16].

(4) DISRUPT CAD IV Trial. This trial was a prospective multicenter study designed for Japanese regulatory approval for coronary interventions. Again, the primary safety endpoint was freedom from MACE at 30 d, and the primary efficacy endpoint was procedural success (residual stenosis < 50%). A propensity-matched historical control group was used for the comparison. The primary endpoints were noninferiority for freedom from MACE at 30 d (CAD IV 93.8% *vs* control 91.2%, P = 0.008) and procedural success (CAD IV 93.8% *vs* control 91.6%, P = 0.007). There were no complications in the form of perforations, abrupt closure or slow-flow/no-reflow during the procedure[17].

(5) Pooled Analysis of the DISRUPT Trials. A pooled analysis of the four above mentioned studies comprising 628 patients enrolled at 72 sites spread across 12 countries was performed[18]. Severe calcium was seen in almost all patients, with an average calcium segment size of 41.5 mm. The efficacy and safety outcomes were achieved in approximately 92% of the patients, whereas the 30-d cardiac death and stent thrombosis rates were < 1% each. Perforation, abrupt closure and slow flow were characteristically absent.

(6) Long-term follow-up. Long-term (1 year) follow-up data were published recently[19]. The MACE rate at 1 year was low at 13.8% (*vs* 7.8% at day 30 *vide supra*). The cardiac death and stent thrombosis rates were low at 1.1% each. Repeat revascularization (ischemia-driven) rates were also low at 4.3% for the target lesion and 6% for the target vessel.

Registry experience: A total of 71 patients from three centers who were eligible for IVL were taken into a prospective registry. Three patient groups participated, namely primary IVL therapy (Group A) with calcified de novo lesions (n = 39 lesions), secondary IVL therapy (Group B) for patients with failed

Table 1 Major clinical studies with intracoronary intravascular lithotripsy

Trial	Year	No. of patients	Severe calcification at baseline	Calcified segment length in mm	Primary endpoints	Outcome	Luminal gain post IVL	Luminal gain post stenting	Residual stenoses	Calcium fracture on OCT
DISRUPT CAD I	2019	60	100%	22.3 ± 12.3	30 d MACE	5% MACE observed		1.7 mm	< 50% in 100 lesions; < 30% in 92% lesions; < 20% in 73% lesions	78%
DISRUPT CAD II	2019	120	94.3%	25.7 ± 12.4	In-hospital MACE	MACE occurred 5.8% patients	0.83 ± 0.47 mm		7.8 ± 7.1%	78.7%
DISRUPT CAD III	2020	431	100%	47.9 ± 18.8	Freedom from in-hospital MACE, procedural success	Freedom from in-hospital MACE occurred in 92.2%; Procedural success in 92.4%		1.7 mm	11.9%	67.4%
DISRUPT CAD IV	2021	64	100%	49.8 ± 15.5	Freedom from in-hospital MACE, procedural success	Freedom from in-hospital MACE occurred in 93.8%, Procedural success in 93.8%	1.42 ± 0.42 mm	1.67 ± 0.37 mm	Residual diameter stenosis < 50% and < 30% in all	53.5%

MACE: Major adverse cardiovascular events; IVL: Intravascular lithotripsy; OCT: Optical coherence tomography.

dilatation of lesion with noncompliant balloon (n = 22 lesions) and tertiary IVL therapy (Group C) for patients with stent under-expansion after previous stenting (n = 17 lesions). The primary endpoints were procedural success (< 20% residual stenosis) and safety outcomes. The mean diameter of the pre-IVL stenosis was 71.8% ± 13.1%, which reduced to 45.1% ± 17.4% after IVL and 17.5% ± 15.2% after the stenting. Similarly, the mean minimal lumen diameter increased from 1.01 ± 0.49 mm at baseline to 1.90 ± 0.61mm after IVL and 2.88 ± 0.56 mm after the stenting. The procedural success rates were 84.6% (Group A), 77.3% (Group B) and 64.7% (Group C). There was no in-hospital MACE[20].

In another registry, patients treated with IVL were studied retrospectively to assess the clinical and angiographic outcomes of coronary IVL use in all-comers with moderate to severe calcified coronary lesions. The primary endpoint was in-hospital MACE (cardiac death, myocardial infarction and target vessel revascularization), and the secondary endpoints were clinical success [stent expansion with < 30% in-stent restenosis (ISR) and no in-hospital MACE] and angiographic success. A total of 50 calcified lesions were treated with IVL in 45 patients divided into three subgroups, similar to the above registry: primary IVL therapy (n = 23 lesions), secondary IVL (n = 15 lesions) and tertiary IVL (n = 12 lesions). The mean diameter of the stenosis decreased from 63.2% ± 10.2% at baseline to 33.5% ± 10.9% post IVL (P < 0.001) and 15.0% ± 7.1% post stenting (P < 0.001). The mean minimal lumen diameter increased from 1.1 ± 0.3 mm at baseline to 1.90 ± 0.5 mm post IVL and 2.80 ± 0.50 mm post stenting. The overall clinical success and angiographic success rates were 90% and 94%, respectively[21].

Systemic reviews and meta-analyses: In a meta-analysis performed by Sattar *et al*[22] involving 282 patients from four studies, IVL significantly improved the size of the vessel lumen to facilitate coronary stent delivery and deployment in severely calcified plaques. The mean pre-IVL diameter was 1.01 mm,

whereas the post-IVL mean diameter was 2.70 mm. The post-IVL lumen diameter was significantly higher than the pre-IVL mean diameter, with a mean difference of -4.16 (95% confidence interval: from -5.08 to -3.24, $P = 0.000001$).

In another meta-analysis performed by Sattar *et al*[23] involving 24 patients from case reports and series, a success rate of 100% was achieved for stent implantation, with minimal complications. No significant differences were observed in the mortality rates of patients undergoing IVL for LAD, left circumflex coronary and left main coronary artery. The mortality rate was higher in patients who had prior comorbidities or required more than three cycles of IVL. Kaul *et al*[24] compared IVL with traditional rotational atherectomy in severely calcified coronary stenosis. Trials on rotablation and IVL revealed that the latter was safer than the former primarily because it reduced the risk for atheromatous embolization. The studies also revealed that IVL yielded better results for parameters such as acute lumen gain and residual stenosis; however, in-hospital MACE was better with rotablation.

Limitations

One of the limitations of IVL is that it is contraindicated in angulated and tortuous coronary lesions because of its bulky design. The presence of uncrossable lesions may preclude its application; however, the use of hybrid techniques, such as "RotaTripsy," can overcome this shortcoming.

RotaTripsy: When the balloon cannot cross

RotaTripsy refers to the hybrid and tandem utilization of rotablation followed by IVL for lesions with extremely severe calcification in which a balloon cannot cross the lesion or fails to expand. The initial use of rotablation allows the passage of the IVL balloon while debulking the superficial calcium. The subsequent use of IVL fractures the deep calcium, thus leading to extraluminal gain. The technique aims to achieve the best of both contemporary avenues for managing calcium, *i.e.* combining the advantages of the balloon-based procedure and the ablation-based procedure. In an observational study of 34 patients in a real-world setting, the technique attained 100% procedural success without any in-hospital MACE[25]. Another case series also demonstrated the safety and feasibility of the "RotaTripsy" technique underscoring the frequent coexistence of superficial and deep calcium on intracoronary imaging[26].

IVL in ISR

Although not approved for use in ISR, there are many emerging reports on the successful use of IVL in calcific ISR with drug-eluting stents where the use of noncompliant balloons and rotablation failed to produce satisfactory luminal gain[27,28]. Recently, a report has been published on the use of IVL for treating neointimal hyperplasia after bare metal stent implantation where cutting balloon and nonslip element balloon had failed[29]. A single center retrospective study found that angiographic success was achieved in all but 1 patient with an IVL-guided management strategy for moderate to severe ISR (65%-88% stenosis)[30]. In the multicenter SMILE registry for ISR, IVL was utilized after the failure of noncompliant balloons. The use of IVL led to significant improvements in minimal stent area and minimal stent diameter in 87% of the patients[31]. There were no cases of death or stent thrombosis at 30 d.

The recently published IVL-DRAGON registry ($n = 62$) has also explored the role of S-IVL in stent under-expansion[32]. The primary end point (stent expansion > 80% as seen by qualitative coronary angiography) was seen in 72.5% cases. Significant increase in stent expansion following application of IVL was confirmed by contemporary imaging techniques: OCT (37.5 % to 86%) and intravascular ultrasound (57% to 89%). Device oriented composite end point was seen in only 1.6%. Furthermore, there is a report on the combined use of IVL and brachytherapy in such cases[33]. Hence, the use of IVL in cases of ISR appears promising.

Complications

Serious angiographic complications were witnessed in up to 2.1% of the patients in the pooled analysis of DISRUPT trials[18]. These complications were dominated by dissections and slow flow. Perforations, no reflow and abrupt closure were not reported. The data in the registries mirrored similar findings, with minimal complications and a predominance of dissections[20-21]. Premature ventricular ectopic beats or "shocktopics" and asynchronous ventricular pacing were observed in some subjects on electrocardiogram but were not associated with clinical consequences[34]. Bradycardia at baseline (heartrate < 65 bpm) was the most powerful predictor of ventricular capture although it also tended to occur in younger patients, those with higher creatinine levels and those with previous infarction. A few case reports on transient atrial arrhythmias have emerged, but the course was benign[35,36]. The use of S-IVL in proximal coronary arteries has been associated with supraventricular tachyarrhythmias because of the anatomical proximity. Synchronization of the shock waves with R waves on the electrocardiogram has been suggested as a precautionary measure to ameliorate these arrhythmic effects.

Indications for S-IVL

Currently, S-IVL is approved for severely calcified coronary lesions with clinical indications for revascularization. Intravascular imaging (especially OCT) can help identify severe lesions that will benefit from this novel technology thereby allowing judicious usage of this costly therapy. Calcium arc more than 180 degrees, calcium length more than 5 mm and thickness more than 0.5 mm indicate increased calcium burden that will necessitate specialized lesion modifying therapies[37]. Being a balloon based technology, this eliminated any specialized training and hence almost no learning curve. However, this makes balloon uncrossable lesions a contraindication for S-IVL. As previously described a combined approach with rotablation first followed by IVL - "Rotatripsy" can be applied for such cases. In addition, rotational or orbital atherectomy can be followed by S-IVL to address deeper and stubborn calcific lesions. A simplified algorithm by De Maria *et al*[1] for heavily calcified coronary lesions places S-IVL into context.

S-IVL vis-a vis contemporary calcium therapies

Current techniques for calcium modification can be broadly divided into "atherectomy" type and "balloon" based. S-IVL offers many advantages over many of these techniques[1,9,24]. It obviates the need for any proprietary wire like Rota wire (rotablation) or Viper Wire (orbital atherectomy), and the procedure is carried on a routine workhorse wire. This makes it cost and time effective. Again being a balloon-based technology, it does not require any additional equipment like an advancer, foot pedal and saline infusion as needed for atherectomy devices. The technique is also similar to the "run of the mill" monorail balloons used in daily interventional practice making it easy to master even for the beginners recusing the need for special training. It also offers uniform and circumferential calcium modification as the balloon emits acoustic waves all round compared to other local atherectomy techniques that might be subject to wire bias. There is also amelioration of any distal embolization as with atherectomy techniques like rotablation and orbital atherectomy making it a safe procedure.

The balloon inflation is done at low pressures compared to other balloon based methods (with some utilizing ultrahigh pressures), which has the potential to minimize vascular trauma and increase safety. There is no data of any reported case of perforation with S-IVL so far. There also is no need to remove additional wires in the vessel lumen like side branch wire or buddy wire as with other atherectomy techniques. Temporary pacemaker insertion again is not needed as with rotablation. Both superficial and deep calcium are taken care of by S-IVL, whereas all the contemporary calcium modification techniques target only superficial calcium due to their localization at the luminal surface of the vessel. Very severe lesions where a balloon cannot cross remains the Achilles' heel for S-IVL therapy.

CONCLUSION

Calcific coronary stenosis is one of the biggest challenges for interventional cardiologists. If not treated properly, then the condition can lead to inadequate stent expansion and result in stent thrombosis and restenosis. Techniques such as rotablation, orbital atherectomy and excimer laser are commonly used to modify the coronary calcium; however, they are associated with high procedural complications and are less successful in cases of deep and eccentric calcium. S-IVL is a novel technique that selectively modifies the subendothelial calcium and is easy to perform. Based on the short-term and long-term success demonstrated in the DISRUPT-CAD trial series, S-IVL is being employed in hitherto unexplored areas, such as ISR, vein graft and balloon uncrossable lesions (coupled with rotablation). S-IVL is gradually becoming an indispensable tool for managing calcified lesions in the cardiac catheterization laboratory.

FOOTNOTES

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CASE REPORT

Rare case of chronic Q fever myocarditis in end stage heart failure patient: A case report

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Abstract

BACKGROUND

Q fever myocarditis is a rare disease manifestation of Q fever infection caused by *Coxiella burnetii*. It is associated with significant morbidity and mortality if left untreated. Prior studies have reported myocarditis in patients with acute Q fever. We present the first case of chronic myocarditis in an end-stage heart failure patient with chronic Q fever infection.

CASE SUMMARY

A 69-year-old male was admitted with dyspnea on exertion, hypotension and bilateral lower extremity edema for a few months. He has a past medical history of ischemic cardiomyopathy with left ventricular ejection fraction of 25%, implantable cardioverter defibrillator in place, bioprosthetic aortic valve and mitral valve replacement. He continued to have shortness of breath despite diuresis along with low grade fevers. Initial infectious work up came back negative. On further questioning, the patient was found to have close contact with farm animals and the recurrent fevers prompted the work-up for Q fever. Q fever serologies and cardiac positron emission tomography confirmed the diagnosis of chronic Q fever myocarditis. He was then successfully treated with doxycycline and hydroxychloroquine for 18 mo.

CONCLUSION

Chronic Q fever myocarditis, if left untreated, carries a poor prognosis. It should be kept in differentials, especially in patients with recurrent fevers and contact with farm animals.

Key Words: Chronic Q fever; Myocarditis; *Coxiella burnetii*; Heart failure; Farm animals; Case report

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Core Tip: Q fever myocarditis is a rare disease (< 1% of cases) caused by infection with *Coxiella burnetii* (gram-negative proteobacteria). Q fever normally has a pleomorphic and non-specific clinical presentation which leads to delayed diagnosis and treatment, which can lead to worse outcomes. Q fever myocarditis should be kept in differentials not only in patients with acute Q fever but also with chronic Q fever infection, like in our case. Q fever serologies help in making a diagnosis of acute and chronic Q fever. Cardiac positron emission tomography and magnetic resonance imaging can be utilized to diagnose myocarditis in the setting of Q fever. Hydroxychloroquine and doxycycline, in combination, are used for treatment of Q fever myocarditis.

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INTRODUCTION

Q fever is caused by infection with gram-negative proteobacteria, *Coxiella burnetii*[1]. *Coxiella burnetii* is found in many domestic animals like deer, rabbits, rodents, birds, horses and even in arthropods like ticks[2]. Q fever is a zoonosis and is transmitted to humans *via* inhalation of contaminated aerosols[1]. *C. burnetii* can survive for extended periods of time and can be carried long distances *via* wind, hence direct animal contact may not be required for transmission[3]. Disease presentation is variable, ranging from asymptomatic, flu like symptoms to intensive care admission. The variability is mostly due to host factors, bacterial virulence factors and extent of exposure[1]. Myocarditis is a rare disease manifestation of acute Q fever (< 1% of cases)[1]. To the best of our knowledge, less than 30-35 isolated cases of myocarditis with Coxiella have been reported in the literature. However, no case of chronic myocarditis in Chronic Q fever infection has been reported. We present an interesting and rare case of chronic Q fever leading to chronic myocarditis in a patient with a prior history of ischemic cardiomyopathy and valvular heart disease.

CASE PRESENTATION

Chief complaints

A 69-year-old male presented with chief complaints of shortness of breath, fatigue, and intermittent fevers for the last 6 mo which were treated with antibiotics twice.

History of present illness

The patient's symptoms of dyspnea and fatigue had been ongoing for the last few months with severe hypotension, bilateral lower extremity edema and dyspnea on exertion. He denied any chest pain or pressure.

History of past illness

The patient had several comorbidities including ischemic cardiomyopathy with left ventricular ejection fraction (LVEF) of 25%, prior ST-elevation myocardial infarction status post (s/p) stent to proximal left anterior descending artery, s/p implantable cardioverter defibrillator (ICD) in 2018 for primary prevention, bicuspid aortic valve s/p aortic valve replacement with 25 mm Carpentier-Edwards bioprosthetic prosthesis in October 2012 followed by transcatheter aortic bioprosthetic valve in valve (26 mm Sapien S3) in April 2019, mitral valve repair with 32 mm seguin ring repair in October 2012 and subsequent transcatheter bioprosthetic mitral valve replacement with 29 mm Sapien 3 bioprosthetic valve for mitral regurgitation in June 2019, hyperlipidemia, chronic kidney disease stage III and atrial fibrillation.

Personal and family history

The patient denied pertinent family history.

Physical examination

On physical examination, the vital signs were as follows: T max of 100.04 degrees Fahrenheit, blood pressure of 91/61 mmHg, heart rate of 80/minute and oxygen saturation of 96% on room air. The patient's jugular venous pressure was elevated, and a diastolic murmur was heard at the aortic area, bilateral bibasilar crackles at the lung bases, and minimal bilateral lower extremity edema was present.

Laboratory examinations

Troponin-I level was 0.01 ng/mL (normal) and BNP was 1562 pg/mL. WBC count was normal and multiple blood cultures were negative.

Imaging examinations

ECG on admission showed atrial paced rhythm with left bundle branch block. Transthoracic echocardiogram (TTE) on admission showed LVEF of 20%-25% with global hypokinesis, mild to moderate aortic regurgitation, mitral valve mean gradient of 10 mmHg (@ HR of 72 bpm) with normal right ventricle size and function and no vegetation. His most recent TTE prior to admission was done at an outside facility on July 2019 and showed LVEF of 30%, no aortic valve or mitral prosthetic valve regurgitation, mean mitral valve gradient of 7 mmHg (@ HR of 67 bpm), and normal RV function. The chest X-ray on admission showed moderate cardiomegaly with central venous congestion and interstitial edema.

Further diagnostic work-up

To determine his cardiac hemodynamics, shock profile, and whether escalation to temporary mechanical support device is needed, an urgent right heart catheterization was done on admission that showed right atrial pressure 12 mmHg, right ventricular oressure 54/6 mmHg, pulmonary artery pressure 54/25 mmHg, mean pulmonary artery pressure 35 mmHg, pulmonary capillary wedge pressure 24 mmHg and cardiac index by Fick of 2 L/min/m^2 with pulmonary artery saturation of 57%. An infectious disease specialist was consulted. He underwent trans-esophageal echocardiogram to look for endocarditis. It showed a moderate paravalvular aortic valve regurgitation, the replaced mitral valve was functioning normally with no stenosis or regurgitation, and no definitive vegetation was noted on defibrillator leads and prosthetic material.

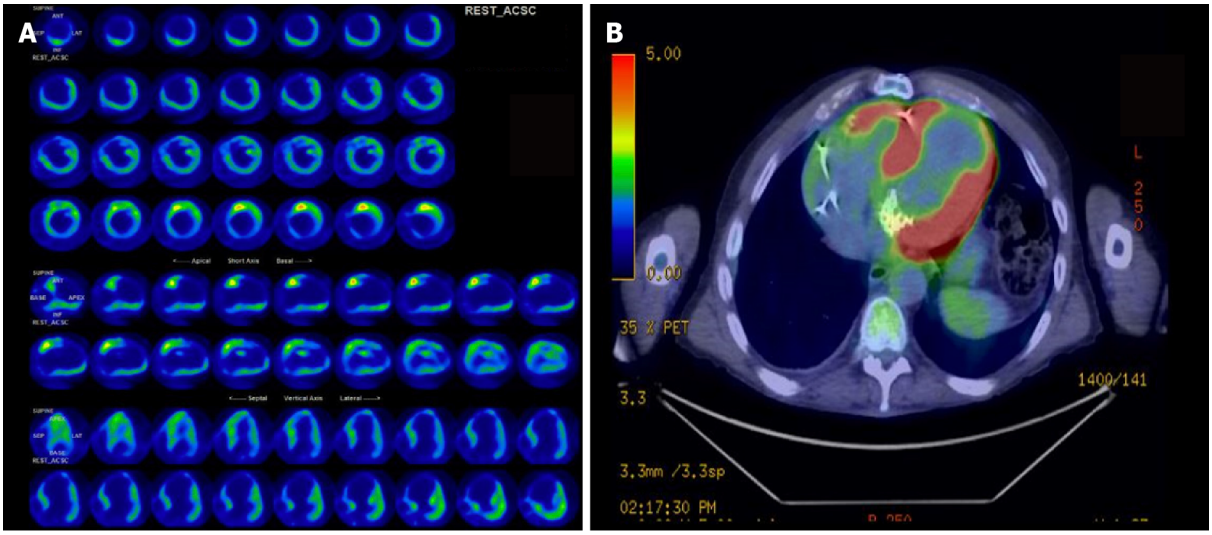
On further discussion with the patient's wife, his functional status decline was associated with intermittent fevers for the last 6 mo that were treated with antibiotics twice, but no source was identified. On further questioning, the patient reported that he raised horses for the last 30 years and has been in close contact with dogs and cats his whole life. Due to close animal contact, Q fever was suspected. Q fever titers were significantly high: Phase I IgG (1:16384), Phase II IgG (>1:32768), Phase I IgM (1:>2048), and Phase II IgM (>1:2048). 18-Flourine fluorodeoxyglucose (FDG) cardiac positron emission tomography (PET) was preferred over magnetic resonance imaging (MRI) due to the presence of ICD. It revealed heterogenous areas of increased 18-F FDG uptake in the left ventricle raising the concern for myocarditis. The heterogenous uptake was identified in septal, lateral, and anterior walls of the left ventricle (Figure 1A). The basal anterolateral wall demonstrated maximum SUV of 6.9 and basal anteroseptal demonstrated maximum SUV of 5.3. No increased uptake around the valvular structures was noted.

FINAL DIAGNOSIS

Based on the history above, physical examination, laboratory findings, and discussions with our infectious disease colleagues, the most likely etiology of the patient's presentation was chronic myocarditis secondary to chronic Q fever infection. Patient met criteria of both chronic Q fever and chronic myocarditis[4,5].

TREATMENT

The patient was started on milrinone 0.125 mcg/kg/min and intravenous diuresis for his acute presentation of acute on chronic heart failure; however, it was stopped after a few days due to ventricular ectopies. Moreover, he did not feel any improvement in symptoms with milrinone. For the Q fever myocarditis, treatment with doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily was initiated for an 18-mo course. Prolonged treatment course was utilized due to his history of prosthetic valves. Due to the patient's significant underlying comorbidities, our advanced heart failure therapy committee meeting deemed him an unsuitable candidate for advanced heart failure therapies at the time of admission. Due to his hypotension, he could not be discharged on guideline directed medical management.



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Figure 1 18-Flourine fluorodeoxyglucose positron emission tomography scan. A: Heterogenous areas of increased uptake involving septal, lateral as well as basal and anterior wall of left ventricle suggestive of myocarditis; B: Whole body positron emission tomography obtained after 1 mo with focus on cardiac structure showing no evidence of residual myocarditis.

OUTCOME AND FOLLOW-UP

On subsequent follow up clinic visits, the patient was noted to have significant improvement in his heart failure symptoms and his fevers resolved. Repeat Cardiac PET after 1 mo showed complete resolution (Figure 1B). The patient was doing better at 1 wk post discharge follow-up and his blood pressure improved. He was started on dapagliflozin 10 mg daily, losartan 25 mg daily and metoprolol XL 100 mg daily. At the patient's 6-month routine follow up, he was doing well and repeat phase I and phase II titers were significantly down: Phase I IgG (1:16384), Phase II IgG (1:16384), Phase I IgM (1:256), and Phase II IgM (1:16) (Table 1). Repeat echocardiogram at 6 mo showed no change in the LVEF, no aortic regurgitation and no stenosis or regurgitation of the mitral valve. He will continue doxycycline and hydroxychloroquine for 18 mo.

DISCUSSION

To the best of our knowledge, this is the first case of chronic myocarditis in a patient with chronic Q fever. Our patient suffered from chronic Q fever infection which ultimately led to chronic myocarditis. Certain conditions like immunosuppression, pregnancy, vascular abnormalities and heart valve conditions predispose individuals to chronic Q fever infection[1]. Our patient had significant valvular heart disease which may have been a predisposing factor for this chronic infection. Myocarditis secondary to *Coxiella burnetii* is a rare manifestation (< 1%)[6,7]. Chronic Q fever diagnosis can often be delayed for months due to nonspecific symptoms and pleomorphic presentation. Endocarditis is the most commonly reported cardiac pathology in chronic Q fever cases[5]. Myocarditis has been almost always reported in the setting of acute Q fever[8,9].

Myocarditis is most likely underestimated in this population due to non-specific signs and symptoms, and a high index of suspicion is required for diagnosis. The diagnosis of Q fever myocarditis is challenging as *C. burnetii* does not grow in routine cultures. Thus, serology is used in most cases for diagnosis[3,10]. *C. burnetii* displays a two-phase antigenic variation due to changes in lipopolysaccharide C antigens: Phase I (often seen in chronic Q fever) and phase II (often seen in acute Q fever). Indirect immunofluorescent assay is used for serological detection. Cut-off for serological titers varies between countries, but the screening test is generally considered positive for acute disease when anti-phase II IgG anti-immunoglobulins return active at a dilution of ≥1:200 or IgM ≥1:50[8]. These positive tests are then diluted and tested for presence of anti-phase I IgG and IgM. Chronic Q fever is found when phase I IgG ≥1:800, usually in the presence of anti-phase II antibodies[3,11]. Cardiac MRI and ^{18}FDG-PET scan have been used before to diagnose Q fever myocarditis[12]. Another point worth mentioning is the negative troponin-I in our patient. Prior studies have shown negative troponin-I with biopsy proven myocarditis. The lack of troponin-I release does not rule out myocarditis[13]. There have been a few cases in the past showing Q fever infection leading to valvulitis[14], and this may explain the aortic regurgitation in our patient which got better with treatment of Q fever.

Table 1 Q fever serology

Variables	Reference range	Admission	3 months	6 months
Phase I IgG	<1:16	1:16384	1:32768	1:16384
Phase II IgG	<1:16	>1:32768	1:131072	1:16384
Phase I IgM	<1:16	>1:2048	1:1024	1:256
Phase II IgM	<1:16	>1:2048	1:2048	1:16

IgG: Immunoglobulin G; IgM: Immunoglobulin M.

The prognosis of Q fever myocarditis is uncertain, but it has worse prognosis compared to other forms of Q fever diseases. In some studies, mortality with Q fever myocarditis has been reported to be up to 30%[8,15]. Patients with chronic *C. burnetii* are usually unable to eradicate the infection without utilizing antibiotics[1]. Center for Disease Control and Prevention recommends doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times a day for ≥ 18-24 mo as the treatment of choice for Q fever myocarditis, endocarditis or vascular infection[16,17]. Hydroxychloroquine is used mainly to increase the efficacy of doxycycline and prevents the development of chronic Q fever endocarditis. Although this regimen seems long, the addition of hydroxychloroquine has reduced the treatment time from 5 years to 18-24 mo[17]. Our patient was started on the long course of antibiotics to prevent endocarditis due to significant valvular abnormalities. Both doxycycline and hydroxychloroquine can cause photosensitivity, and patients should be warned to avoid excessive sun exposure. Regular heart and eye examinations are needed due to the risk of hydroxychloroquine induced retinopathy[16].

CONCLUSION

Q fever myocarditis is a rare disease, and a high index of suspicion is required for diagnosis. Given the poor prognosis of Q fever myocarditis and the presence of reliable therapy, it should be kept in differentials for patients with fevers and cardiomyopathy, especially in patients with a history of animal exposure. Multimodality imaging like echocardiogram, cardiac MRI and cardiac PET can be utilized in diagnosing myocarditis in patients with Q fever.

FOOTNOTES

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CASE REPORT

Intra-atrial course of right coronary artery: A case report

Giulio Barbiero, Giuseppe Maiolino, Anna Argiolas, Luca Testolin, Giorgio De Conti

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Abstract

BACKGROUND

Intra-atrial right coronary artery (RCA) is a rare and generally asymptomatic anomaly of development of the coronary arteries. This malformation could potentially expose the patient to a catastrophic outcome in the case of injury during interventional or surgical procedures. Currently, only a few case reports and no systematic reviews are available in the literature.

CASE SUMMARY

We report the case of a 54-year-old man with atypical chest pain who underwent multi-detector computed tomography angiography (MDCTA). The exam revealed no significant coronary artery stenoses; however, an intra-atrial course of mid RCA was evident. Medical therapy was administered, and the patient was discharged to home without undergoing a conventional angiography. Previously reported autoptic and clinical cases were retrieved from the PubMed literature database to compare the clinicopathological features of this case.

CONCLUSION

MDCTA depicted the abnormal course of the coronary artery in this patient as an intra-atrial course of the mid RCA. Finding this abnormality was crucial to avoid an inadvertent injury during interventional or surgical procedures.

Key Words: Coronary artery anomaly; Anomalous course of right coronary artery; Intra-atrial right coronary artery; Intracavitary right coronary artery; Multi-detector computed tomography angiography; Case report

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Core Tip: We present a rare case of an intra-atrial course of the mid right coronary artery (commonly referred to as right coronary artery) detected by multi-detector computed tomography angiography (MDCTA). We performed a systematic review of the few cases in the literature. Since this anomaly could potentially expose the patient to catastrophic outcome in case of injury during interventional or surgical procedures, its recognition *via* MDCTA is crucial before such interventions.

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INTRODUCTION

Intra-atrial or intra-cavitary course of the right coronary artery (RCA) is defined as a segment of the RCA that courses through the right atrial (RA) chamber[1,2]. It is a relatively rare vascular anomaly, with a reported incidence of 0.09%-0.1%[1,2].

Historically, this anomaly of development was most often identified by accident, during coronary surgery or autopsy, due to its benign outcome; however, in the era of multi-detector computed tomography angiography (MDCTA), it is now detected more frequently, and its incidence rate has risen to 1.8%[1]. From a radiological point of view, it was defined as a segment of RCA entirely surrounded by intra-atrial contrast in all phases of the cardiac cycle, unlike the myocardial bridge, in which a segment of the coronary artery appears as entirely surrounded by myocardial muscle[1,2]. Its recognition is very important before cardiac surgery or endocavitary procedures (*i.e.* ablation for arrhythmias, catheterization of the RA, and pacemaker implantation) since it carries a concerning potential for injury to the intra-atrial RCA, which could have a catastrophic outcome[1].

Herein, we report the case of a patient with an anomalous course of the RCA through the RA which was identified using MDCTA. Furthermore, to the best of our knowledge, we provide, for the first time, a discussion based on a review of all cases of intra-atrial course of RCA in the literature. The review was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Padua.

CASE PRESENTATION

Chief complaints

A 54-year-old Caucasian male with moderate cardiovascular risk factors (*i.e.*, obesity, hyperlipidemia, and hypertension) presented to the cardiologic clinic with atypical angina presenting without dyspnea.

History of present illness

The patient reported that the symptoms had started 2 h before presentation, describing atypical chest pain without dyspnea.

History of past illness

The past history of the patient was unremarkable.

Personal and family history

The patient denied any personal history relevant to atypical angina, dyspnea, or other cardiovascular symptoms and any family history of cardiovascular disease.

Physical examination

On physical examination, the significant vital signs were as follows: body mass index of 28.7 kg/m^2; heart rate at regular pulse of 80 beats per min; and blood pressure of 163/92 mmHg. Dyspnea, heart murmurs, and other signs of heart failure were absent.

Laboratory examination

Levels of myocardial injury enzymes (*i.e.*, troponin T and creatine kinase) were normal. Electrocardiography demonstrated a sinus rhythm of 77 beats per min and absence of ST depression with minimal alterations in lateral repolarization.

Imaging examination

The patient underwent MDCTA (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan) using the following scan parameters: prospective protocol; gantry rotation time of 350 ms; 512 × 512 matrix; slice thickness of 0.5 mm with 0.25 mm increments using kernel FC03; automatic exposure control (SURE bExposure 3D; Toshiba Medical Systems) (SD 110 for contrast-enhanced images); and iterative reconstruction.

An intravenous contrast (60 mL Iomeron® 400 mg iodine/mL; Bracco Imaging Italy s.r.l., Milan, Italy) was administrated at 5 mL/s flow. Heart rate was set between 50 and 60 beats per min with intravenous administration of metoprolol. The data were transferred to an external workstation (Vitrea2 FX version 6.3; Vital Images, Plymouth, MN, United States) providing multiplanar reformation (commonly referred to as MPR) and volume rendering technique (commonly referred to as VRT).

From the scans, mild coronary calcification (Agatston calcium score of 34) of the left anterior descending (LAD) coronary artery, without significant stenoses (> 70%) of all segments, was detected. Additionally, an abnormal course of the mid RCA was identified. As demonstrated by axial images and CT multiplanar reconstruction, the origin and the proximal tract of the RCA were normal, with an epicardial course in the right atrio-ventricular groove; however, the artery penetrated the anterior RA wall and then exhibited an intracavitary course of 25 mm (Figure 1). After the exit from RA, the RCA passed normally in the atrio-ventricular groove and then continued normally at the level of the diaphragmatic crux.

FINAL DIAGNOSIS

Considering the patient's medical history along with the MDCTA imaging findings, the final diagnosis was an intra-atrial course of the mid RCA without significant coronary atherosclerosis.

TREATMENT

The patient responded well to standard medical therapy (*i.e.*, rosuvastatin, administered at 5 mg per day) and was discharged home on postoperative day 2 without having to undergo a conventional angiography study.

OUTCOME AND FOLLOW-UP

At the last follow-up (5 mo postoperatively), the patient was still alive.

DISCUSSION

RCA anomalies are rare and abnormal courses of the RCA are even more rare, with an incidence of 0.1% [2]. In the literature, an intra-atrial course of the RCA was reported only in 9 autoptic cases[3,4] and in about 80 clinical cases[1,2,5-26] (Table 1). Most clinical cases were case reports, but a few case series were reported[1,2,5,9,10,16,21].

An intra-atrial course of RCA was first described in 1975 by McAlpine[27]. The prevalence of this variant was initially reported to be between 0.09% and 0.1%[5-7], but these rates probably represented underestimations because the conventional angiographic luminographic 2D assessment may not be able to recognize this abnormal variant. The most recent studies – involving cases that are being diagnosed by the new advanced imaging techniques – have reported a prevalence of 1.3%[2] and 1.8%[4]; certainly, the increasing use of MDCTA of the coronary arteries will lead to an even greater increase in identification of this anomaly[8].

Reportedly, the segments of the RCA most frequently involving an intra-atrial course were segments 3 (47%) and 2 (40%)[9], with mean length ranging from 14 mm to 53 mm[9]. In our perusal of the literature, the most frequent intra-atrial segment of the RCA reported was the mid segment (Table 1), with a length of intra-atrial RCA ranging from 13.2 mm[10] to 55 mm[5]. Rarely, the intra-atrial course of the RCA involved segments 1 and 4 (13%)[9] or has lengths shorter (as low as 13 mm) or longer (up to 55 mm)[10-12].

In our review of the literature, most cases were female, and the patient's ages ranged from 45 years [20] to 78 years[13]. In none of the cases was there presence of significant coronary artery stenoses nor were mild atherosclerotic plaques indicated[9]. A possible explanation could be the absence of mechanical stress on the segment of the coronary artery when it coursed intra-atrially or intra-myocardially rather than in the epicardial fat, although this conclusion is not definitive[9].

Table 1 Literature summary of intra-atrial course of the right coronary artery

Ref.	Patients, *n*	Type	Sex	Age in yr	Risk factors	Symptoms	Imaging	Segment of RCA	Intra-atrial course length in mm	Stenosis, %	Outcome
Kolodziej *et al*[3], 1994	3	Autoptic series	UNK	UNK	UNK	UNK	Postmortem examination	Mid	15; 20; 30	No	Mortem
Rosamond *et al* [14], 2007	1	Case report	M	54	NR	Palpitation, atrial fibrillation	MDCTA 64	Distal	35	No	No atrial fibrillation
Scheffel *et al*[11], 2007	1	Case report	F	77	Hypertension, hyperlipidemia, family history	Atypical chest pain	MDCTA	Mid	55	No	NR
Zalamea *et al*[5], 2009	2	Series	F; F	70; 54	Atrial fibrillation; Smoker	Dyspnea on exertionChest pain, nausea, diaphoresis	MDCTA	Mid-distal; Mid-distal	40-50; 55	No; No	No ablation; NR
Andrade *et al*[6], 2010	1	Case report	M	46	Strong family history	No	MDCTA	Mid	25	No	NR
Lee *et al*[8], 2010	1	Case report	F	57	Hypertension, hyperlipidemia	Atypical chest pain	MDCTA	Mid	38	No	Discharged
Renapurkar *et al* [12], 2010	1	Case report	F	49	Family history	Atypical chest pain	MDCTA 64 DS	Mid	10	No	NR
Chou *et al*[19], 2011	1	Case report	M	56	Diabetes, hypertension	Chest tightness	MDCTA	PL	NS	No	Symptoms persistence
Christopher and Duraikannu[7], 2011	1	Case report	F	48	No	Chest pain, dyspnea, palpitation	MDCTA	Mid	15	No	NR
Bansal *et al*[10], 2011	2	Series	NS	NS	NS	NS	MDCTA	Segment 3; Segment 2	13.2; 15.6	NS	NS
Zeina[17], 2011	1	Case report	M	59	Multiple	Chest pain	MDCTA 64	Distal	40	No	NR
Waniewska *et al* [24], 2012	1	Case report	F	62	NR	Atrial flutter, atrial fibrillation, fainting, hypotension	MDCTA	Distal	50	No	RFA
Opolski *et al*[9], 2014	14	Series	M:F = 2:12	54 (mean)	Diabetes, hypertension, hyperlipidemia, smoker, family history	Atypical chest pain, stable angina pectoris, syncope, dyspnea, palpitations, arrhythmia	MDCTA	Segment 3 (47%); Segment 2 (40%); Segment 1 and 4 (13%)	29 (mean)	No	Conservative approach
Bunkiewicz *et al* [13], 2015	1	Case report	F	78	Hypertension, previous acute coronary syndrome	Not specific chest pain, low tolerance of physical effort, dry cough	MDCTA	Mid	20	No	UNK
Buckley *et al*[16],	17	Series	NS	NS	NS	NS	MDCTA	NS	NS	NS	NS

2017											
Krishnan *et al*[4], 2017	6	Autoptic series	M	69 (mean)	NS	UNK	Postmortem examination	Type I: Mid; Type II: Mid; Type III: Anterior branch	Type I: 22 (mean); Type II: 36; Type III: UNK	No	Mortem
Ganga *et al*[20], 2019	1	Case report	M	45	NR	Atypical chest pain	MDCTA	Mid	45	No	NR
Bouhuijzen *et al* [18], 2019	1	Case report	F	64	NR	Atypical chest pain	MDCTA	NS	40	No	
Hossain *et al*[2], 2019	7	Series	M:F = 71.4:28.6	67.3(mean)	Chest pain (25%), shortness of breath (33%)	Pre-TAVR	MDCTA	NS	33.4 (mean)	No	No coronary intervention
Mahmoud *et al* [22], 2020	1	Case report	F	61	NS	Chest pain	MDCTA	Mid	39	NS	NR
Junco-Vicente *et al* [21], 2020	3	Series	1M; 2F	NS	NS	Chest pain	MDCTA	Mid	27.7 (mean)	No	UNK
Marrone *et al*[26], 2020	1	Case report	F	48	Aortic valve disease	NR	MDCTA	Distal	49	No	NR
Ganga *et al*[1], 2021	21	Series	M:F = 1.3:1	53.7 (mean)	NR	NR	MDCTA	Mid (16/21); Distal (5/21)	14.85 (mean)	No	NR
Frey *et al*[23], 2022	1	Case report	M	55	Hypertension, hypercholesterolemia, smoker, obesity	Atypical angina, dyspnea	MDCTA	Mid (posterior)	40	No	Conservative approach
Borges *et al*[25], 2022	1	Case report	M	66	NS	Palpitation, tachycardia, dyspnea	MDCTA	Mid	30	No	NR
Barbiero *et al*	1	Case report	M	54	Hypertension, hyperlipidemia, smoker	Atypical chest pain	MDCTA	Mid	25	No	Medical treatment

F: Female; M: Male; MDCTA: Multi-detector computed tomography angiography; NR: Not reported; NS: Not specified; PL: Posterior lateral; RFA: Radiofrequency ablation; TAVR: Transcatheter aortic valve replacement; UNK: Unknown; DS: Dual source.

Association between the intra-cavitary course of the RCA and other coronary anomalies have been described, such as with the intramuscular course of the LAD coronary artery or with the anomalous origin of the left circumflex (commonly known as LCX) coronary artery from the right aortic sinus[9]. Patients with intra-cavitary course of the RCA were usually asymptomatic, and its discovery was incidentally encountered during an MDCTA coronary study conducted for other reasons (*i.e.*, atypical chest pain, chest tightness, dyspnea, palpitation, atrial flutter or fibrillation, arrhythmia, fainting, hypotension, or syncope) (Table 1).

An intracavitary course of the RCA has a higher probability of iatrogenic damage than myocardial bridging because of the risk of direct injury at the abnormal vessel segment during surgical manipulation or endoatrial procedures (*i.e.*, ablation, catheterization, or electrode implantation). Therefore, although it is usually considered an asymptomatic variant, its early recognition is crucial to avoid vessel



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Figure 1 Multi-detector computed tomography angiography showed the anomalous intra-atrial course of the mid right coronary artery. A: Curved planar reformatting showed the entire course of the right coronary artery (RCA) with a mid-segment with an intra-atrial course; B: Volume rendering technique showed the entire course (green line) of the RCA; C: Cross-sectional images showed the intra-atrial segment of the RCA, which was completely surrounded by blood in the right atrium; D: Curved planar reformatting showed the entire course of the RCA with a mid-intra-atrial course of the artery.

catastrophic lesions during such procedures[2].

CONCLUSION

MDCTA is a less invasive and less user-dependent method than conventional angiography and can accurately depict the coronary vasculature and its variants of origin, termination, or course[2]. The recognition of an intra-atrial course of the RCA by MDCTA could facilitate avoidance of potential hazards during surgical and/or interventional procedures.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Barbiero G, Argiolas A, and Maiolino G performed the patient exam; Barbiero G performed the literature review and wrote the first draft of the manuscript; all authors read and approved the final manuscript.

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MINIREVIEWS

Spontaneous coronary artery dissection: A review of diagnostic methods and management strategies

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Abstract

Spontaneous coronary artery dissection (SCAD) is a rare non-atherosclerotic cause of acute coronary syndromes defined as non-iatrogenic, non-traumatic separation of the coronary artery wall. The most common profile is a middle-aged woman between 44 and 53 years with few cardiovascular risk factors. SCAD is frequently linked with predisposing factors, such as postpartum, fibromuscular dysplasia or other vasculopathies, connective tissue disease and hormonal therapy, and it is often triggered by intense physical or emotional stress, sympathomimetic drugs, childbirth and activities increasing shear stress of the coronary artery walls. Patients with SCAD usually present at the emergency department with chest discomfort, chest pain, and rapid heartbeat or fluttery. During the last decades, the most common problem of SCAD was the lack of awareness about this condition which has led to significant underdiagnosis and misdiagnosis. However, modern imaging techniques such as optical coherence tomography, intravascular ultrasound, coronary angiography or magnetic resonance imaging

have contributed to the early diagnosis of the disease. Treatment of SCAD remains controversial, especially during the last years, where invasive techniques are being used more often and in more emergent cardiac syndromes. Although conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases, revascularization could also be suggested as a method of treatment in specific indications, but with a higher risk of complications. The prognosis of SCAD is usually good and long-term mortality seems to be low in these patients. Follow-up should be performed on a regular basis.

Key Words: Spontaneous coronary artery dissection; Non-atherosclerotic coronary artery disease; Angiographic classification; Percutaneous coronary intervention

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Core Tip: Spontaneous coronary artery dissection (SCAD) is a non-atherosclerotic cause of acute coronary syndromes defined as non-iatrogenic, non-traumatic separation of the coronary artery wall. During the last decades, the most common problem in SCAD was the lack of awareness of the disease which led to significant underdiagnosis and misdiagnosis. However, modern imaging techniques such as optical coherence tomography, intravascular ultrasound, coronary angiography or magnetic resonance imaging have contributed to the early diagnosis of SCAD. Although conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases, revascularization could also be suggested as a method of treatment in specific indications.

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INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a rare non-atherosclerotic cause of acute coronary syndromes (ACS) defined as non-iatrogenic, non-traumatic separation of the coronary artery wall[1]. It usually occurs in young and middle-aged women with few cardiovascular risk factors. Recent studies have shown SCAD to be the underlying cause of myocardial infarction (MI) in 22%-43% of women < 50 years and approximately 21%-27% of pregnancy-associated MI[2-4]. In Canada, SCAD was responsible for 24% of women < 50 years with MI[5] while in Japan this percentage was 35%[3]. In a French series, SCAD was reported in 36% of women under 60 years with ACS and one or few conventional cardiovascular risk factors[6]. Finally, a smaller Australian registry found a prevalence of SCAD of 23% in women under 60 years presenting with ACS[7].

During the last decades, the most common problem in SCAD is the lack of awareness about this condition among healthcare providers, despite the fact that the first case report of this syndrome was a female patient back in 1931[8]. This awareness led to significant underdiagnosis and misdiagnosis in cardiology departments. However, more and more cases are now being identified due to the increased awareness and earlier use of invasive angiographic methods in patients with acute chest pain presenting to emergency departments. Modern imaging techniques such as optical coherence tomography (OCT), coronary angiography or magnetic resonance imaging (MRI) have also contributed to the early diagnosis of the disease. SCAD is not as rare as previously thought. It was supposed to be the main cause for 0.1% to 0.4% of all ACS but these percentages have increased up to 4% over the last years[2,9]. In sudden cardiac deaths, SCAD was reported in 0.5% of cases after autopsy[10]. It is frequently linked with predisposing factors, such as postpartum, fibromuscular dysplasia (FMD) or other vasculopathies, connective tissue disease and hormonal therapy, and it is often triggered by intense physical or emotional stress, sympathomimetic drugs (cocaine, amphetamines), childbirth and activities increasing the intra-abdominal and intra-thoracic pressure (coughing, retching, vomiting) and, thus, shear stress of the coronary artery walls[11].

Treatment of SCAD remains controversial, especially during the last years, where invasive techniques are being used more often and in more emergent cardiac syndromes. Conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases. However, the high rate of technical complications in SCAD treated with primary percutaneous coronary intervention (PCI), has been shown to be associated with adverse clinical outcomes[12,13].

The aim of the present review was to demonstrate the existing knowledge regarding the diagnostic methods and the treatment strategies of the underdiagnosed syndrome of SCAD, and highlight the role of primary PCI.

EPIDEMIOLOGY AND PATHOGENESIS OF SCAD

Although SCAD was primarily considered a disease of young adults, nowadays, the most usual patient is a middle-aged woman between 44 and 53 years with few cardiovascular risk factors[14,15]. There is evidence from a Canadian series that female patients with SCAD are older, with less isometric exercise and higher emotional stress compared to male patients[16]. Clinical presentation and outcomes of SCAD may be similar, not only in white patients, but also in other populations such as Hispanic Americans and Blacks[17]. The fact that most case reports include white patients could be explained by the fact that it may be underestimated in other populations or patients belonging in these populations may not present at the emergency department on time. Patients with SCAD usually have lower levels of hypertension, hyperlipidemia or tobacco use compared with patients who have atherosclerotic acute MI [18]. However, the prevalence of these factors is similar between different ages and sex[18]. Hypertension ranges from 32% to 37% while hyperlipidemia from 20% to 35%[14,15]. The prevalence of SCAD in patients presenting with ACS has risen up to 4% and is the underlying cause of up to 35% of all ACS cases in women ≤ 50 years[2,9].

Pregnancy has a strong association with SCAD. In pregnant women, where the percentage of SCAD-associated MI is up to 27%[4,19], dissection may be a consequence of increased physiological hemodynamic stress or high progesterone levels, leading to weakening of the coronary arterial wall[20]. SCAD episodes are presented either antepartum or post-partum, and specifically, early post-partum (within the first 6 wk of childbirth), late post-partum (from 6 wk to 1 year), and very late post-partum (1 to 2 years)[20]. The most common period of an episode is the first week after childbirth[21]. Women with post-partum SCAD tend to be older at first childbirth and multigravidas compared to non-post-partum SCAD women[21]. Hemodynamic changes affecting cardiac parameters could lead to higher levels of shear stress and, as a result, vessels including the aorta and coronary arteries present structural alterations[22].

Secondary iatrogenic dissection is also a major cause of additional risk in patients with already established SCAD undergoing invasive treatment. Increased risk of secondary iatrogenic dissections during coronary angiography (2%), non-SCAD angiography (0.2%) and PCI (14.3%) in SCAD patients has been previously observed in case series[23].

There is still a gap in the literature regarding the understanding of the potential underlying mechanism of non-atherosclerotic SCAD. Two potential theories regarding the initiation of the coronary artery wall have been proposed. The first theory indicates sudden disruption of the coronary artery wall caused by an intimal tear[24,25]. Specifically, the intimal tear results in separation of the inner intimal lining from the outer vessel wall, allowing blood to enter into the false lumen and create an intramural hematoma within or between one of the three layers (intima, media, or adventitia)[24,26]. Pressure-driven expansion of the hematoma causes propagation of the dissection plane with formation of a true lumen, and a thrombus containing a false lumen. The second theory suggests spontaneous rupture and bleeding of the vasa vasorum within the vessel wall, followed by intramedial hemorrhage[24,25,27]. Intramural hematoma (IMH), which compresses the true lumen, causes ischemia of the myocardium, being thus, the primary cause of ACS with SCAD[1]. Occlusion of the lumen may also be worsened by thrombi in the true or false lumen having, however, a small pathophysiologic role compared to IMH [28].

SCAD may affect either normal vessels or vessels with weakened arterial wall architecture due to predisposing arteriopathies. As a result, dissection of the coronary artery walls could be extensive both anterograde and retrograde[1,29,30].

RISK FACTORS

This syndrome is mainly caused by a combination of factors including sex, hormonal fluctuations, underlying arteriopathies, genetics, and environmental, physical and emotional precipitants. As already mentioned above, pregnancy is a strong predisposing factor of SCAD in women[21]. However, a number of additional factors have been associated with the onset of SCAD in more than half of patients. Extreme physical or emotional stress is probably the most important predisposing factor. Triggering factors leading to a Valsalva-like increase in thoracoabdominal pressure or raising catecholamines, including cocaine exposure or sympathomimetic drugs, intense physical activity, coughing, retching, vomiting and bowel movement, in combination with underlying predisposing arteriopathies, can increase cardiocirculatory shear stress resulting in SCAD[11,15,31,32]. Specifically, emotional stressors seem to appear more often in women, whereas physical stressors have been reported in men among precipitants[16,29].

A significant risk factor of SCAD is FMD. The first case series of concomitant SCAD and extracoronary FMD was reported back in 2011[33]. Since then, high prevalence of FMD has been observed in 72% to 86% of SCAD patients who were routinely screened[11,34]. FMD is an idiopathic, nonatherosclerotic and noninflammatory systemic vasculopathy characterized by unique angiographic findings reflective of perturbations in the structure of the arterial wall leading to luminal stenosis, especially in small and medium-sized arteries[35]. Although the pathophysiology of FMD causing SCAD remains unknown, it is suggested that fibrosis of the vasa vasorum leads to coronary vessel wall ischemia and proliferation of myofibroblasts resulting in dissection[36]. Apart for stenoses, FMD has variable arterial manifestations including aneurysms and dissections. Multifocal FMD, characterized by multiple stenoses in an artery, is the most common type in adults, mainly affecting women. The difference between multifocal and focal FMD is that the first corresponds with medial fibroplasia, perimedial fibroplasia, and medial hyperplasia on histopathology while the second with adventitial and intimal disease[35,37]. A previous study[38] showed that the predominant arteries involved in FMD are renal (66.67%), iliac (44.44%), carotid (37.04%), and vertebral (33.33%). As a result, the prevalence of FMD may be even higher when screening is performed in patients with hypertension[38,39]. FMD and SCAD are directly associated, as prevalence of FMD among patients with SCAD is > 50%[40,41].

Long-term exposure to exogenous estrogen or progesterone has been shown to cause long-term changes in coronary arterial architecture, being thus, a significant risk factor for SCAD[11].

A relation between systemic inflammation and SCAD seems to exist[42]. Frequent chronic inflammatory systemic diseases including systemic lupus erythematosus, inflammatory bowel disease and sarcoidosis are suggested to have a potential relationship with SCAD[43-45]. A potential vasculitic inflammatory mechanism could be the activation of eosinophils from the adventitial and peri-adventitial layers a mechanism which leads to the establishment of SCAD[46]. There are data supporting this hypothesis which shows the presence of peri-arterial eosinophils in patients with SCAD compared to patients with iatrogenic or traumatic dissections where eosinophils are absent[47].

Specific connective tissue disorders such as Marfan and Ehler-Danlos type 4 syndromes also seem to have a relation with SCAD, with a reported frequency between 1% and 2%[11]. Some connective tissue disorders such as Marfan syndrome are associated with mutations in a single gene (FBN1), whereas others such as hypermobility type Ehlers–Danlos syndrome are thought to be multifactorial[48]. Defective fibrillin protein caused by mutations in the FBN1 gene causes structural and functional perturbation of connective tissues may predispose individuals to SCAD[49]. However, no specific connective tissue disorders or extracoronary vascular phenotypes in patients with SCAD have been observed[48]. A recent study[50] highlighted the role of extracellular matrix dysfunction in SCAD. Specifically, in this large cohort, across all patients with SCAD, rare disruptive variants were found within 10 collagen genes among individuals with SCAD compared with 2506 constrained genes expressed in the coronary artery[50]. Furthermore, patients with SCAD were 1.75-fold more likely to carry disruptive rare variants within fibrillar collagen genes[50]. Other collagen vascular disorders that have been proposed to be associated with SCAD are Alport syndrome and Nail-patella syndrome[51,52].

Thyroid dysfunction could be another possible risk factor for SCAD. In hypothyroidism, the lack and impairment of thyroid hormones might lead to impairments in the structure of the artery wall, making coronary arteries more prone to SCAD[46]. In a previous study, investigators showed that the prevalence of hypothyroidism was significantly higher (26%) in patients with SCAD compared to patients with ACS[53]. In the same study, patients with both SCAD and hypothyroidism had more distal lesions and more tortuous coronary arteries. However, more data is required to support this finding.

Finally, the role of genetics in SCAD is a complex issue. Most recent studies have involved genetics as a predisposing factor in SCAD. SCAD has not been shown to be strongly familial, but it is more likely that cases within families are scattered and independent of specific genes. However, a recent study[54] highlighted the PHACTR1/EDN1 gene as directly associated with SCAD and other cardiovascular conditions such as coronary artery disease. The authors showed that patients who carried the rs9349379-A allele had an increased risk of FMD and SCAD[54]. This association requires further investigation.

CLINICAL SYMPTOMS

There is a wide spectrum of clinical presentation and severity of SCAD. Patients with SCAD usually present at the emergency department with chest discomfort as the most common symptom[55], chest pain, and rapid heartbeat or fluttery. Less frequent symptoms include pain to the arms or neck, nausea or vomiting, unusual or extreme tiredness, shortness of breath and back pain[16]. A percentage between 24% and 87% of patients with SCAD demonstrate STEMI alterations in the ECG and elevation of cardiac enzymes[7,13,56,57]. A smaller percentage of patients, present complications such as ventricular arrhythmias (3% to 10%), cardiogenic shock (< 3%) and sudden cardiac death (< 1%)[11,13,30]. Another characteristic of SCAD is reduced left ventricular ejection fraction (EF) (< 50%), observed in almost 44%–49% of patients. However, there are usually significant improvements in the EF after treatment of

the arterial dissection[13,58]. In Canada, patients with SCAD expressed their chest pain either as radiation to the arm (approximately 50%) and/or neck (approximately 22%), dyspnea (approximately 19%) and pain in the back (approximately 12%) or as nausea and vomiting (approximately 23%) and hyperhidrosis (approximately 21%)[55]. However, in a minority of patients, chest pain could also be atypical[55].

DIAGNOSTIC METHODS AND ANGIOGRAPHIC CLASSIFICATION

Accuracy and early diagnosis are the most important factors for the management of SCAD. Coronary angiography is the gold standard and the first-line imaging technique for patients presenting with ACS. Administration of intracoronary nitrates, intracoronary imaging when safe and available, and/or follow-up noninvasive or invasive coronary imaging may be helpful in order to distinguish SCAD from other etiologies of ACS[18].

The main limitation of coronary angiography is that the 2-dimensional luminogram does not allow us to display the arterial wall[24,26]. As a result, further imaging techniques are required in order to set a definitive diagnosis. Intracoronary imaging, including OCT and intravascular ultrasound (IVUS) (Figure 1), is the supplementary method that improves SCAD diagnosis and has the possibility to display the arterial wall layers compared to coronary angiography[24,26]. Important disadvantages are that it is not widely available, it is often associated with additional risks and higher costs and, it requires instrumentation of the coronary artery, a situation which in SCAD could pose a challenge. Coronary computed tomography angiography has lower spatial resolution compared with conventional angiography and presents challenges in the evaluation of lumens and walls of small coronary arteries [9].

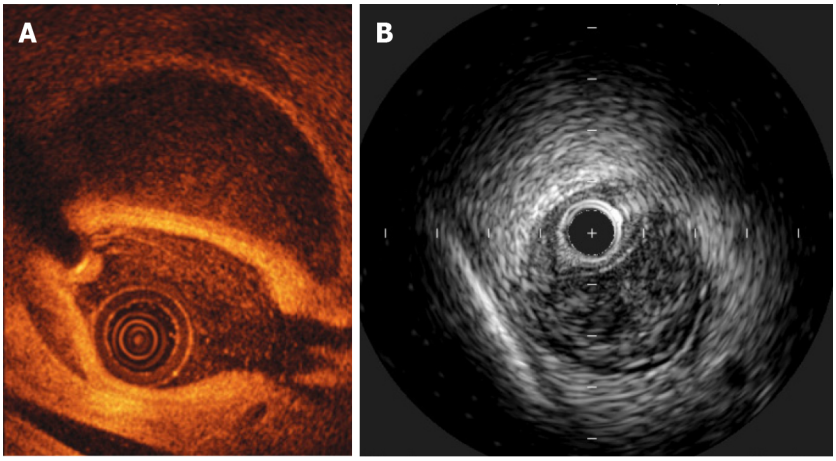
Optical coherence tomography, with an axial resolution of 15 μm, is a supplementary intracoronary imaging method for the diagnosis of SCAD that provides higher spatial resolution[40]. Despite this important advantage, OCT requires blood clearance using a high-pressure contrast injection, a situation that could lead to a further extension of the dissection, and particularly of the false lumen[59]. Nevertheless, the reduction of depth penetration, which is by definition limited in OCT, could lead to safe and accurate diagnosis[6,60]. OCT could also provide specialists with very significant information regarding the true lumen, characteristics related to the false lumen such as the type, size, and the point of extension, as well as its relation with side-branches[60]. In order to locate the characteristic crescentic shape of the false lumen, meticulous image analysis and evaluation are necessary. The practical usefulness of OCT in SCAD patients requiring coronary revascularization is to assure us, before any intervention, the location of the guidewire in the right lumen; thus, avoiding stenting of the false lumen that could cause hazardous complications[61,62].

IVUS, with an axial resolution of 150 μm, is also a supplementary method in SCAD diagnosis, and is able to differentiate atherosclerotic plaques from SCAD[27,59,63,64]. This method clearly illustrates and differentiates the two lumens and can show the severity of false lumen thrombosis. This technique readily depicts the true and the false coronary lumens and is also able to demonstrate the extent of false lumen thrombosis. IVUS presents great advantages over OCT. The major advantages are that pressurized contrast injection to clear blood from the lumen is not required and depth penetration is superior, enabling full imaging through the thrombus of the vessel wall up to the exterior elastic lamina [59]. The primary drawback of IVUS is its poor spatial resolution, making it difficult to identify small structures related to the disease, such as the intimal-medial membrane and localized fenestrations linking the two lumens[65,66].

MRI is another new diagnostic method for patients with SCAD. Specifically, MRI can diagnose SCAD when its underlying diagnosis cannot be initially recognized on angiography[67]. The characteristic findings of MRI in patients with SCAD are (1) late gadolinium enhancement which could be transmural, affected by myocardium, subendocardial, and with patchy enhancement; (2) microvascular obstruction; and (3) IMH[67,68]. Cardiac magnetic resonance (CMR) imaging demonstrating delayed gadolinium enhancement in an area with suspected dissection could help in the confirmation of SCAD. However, normal CMR imaging may not exclude SCAD. A substantial minority of patients with angiographically-confirmed SCAD do not have CMR evidence of infarction[18,68].

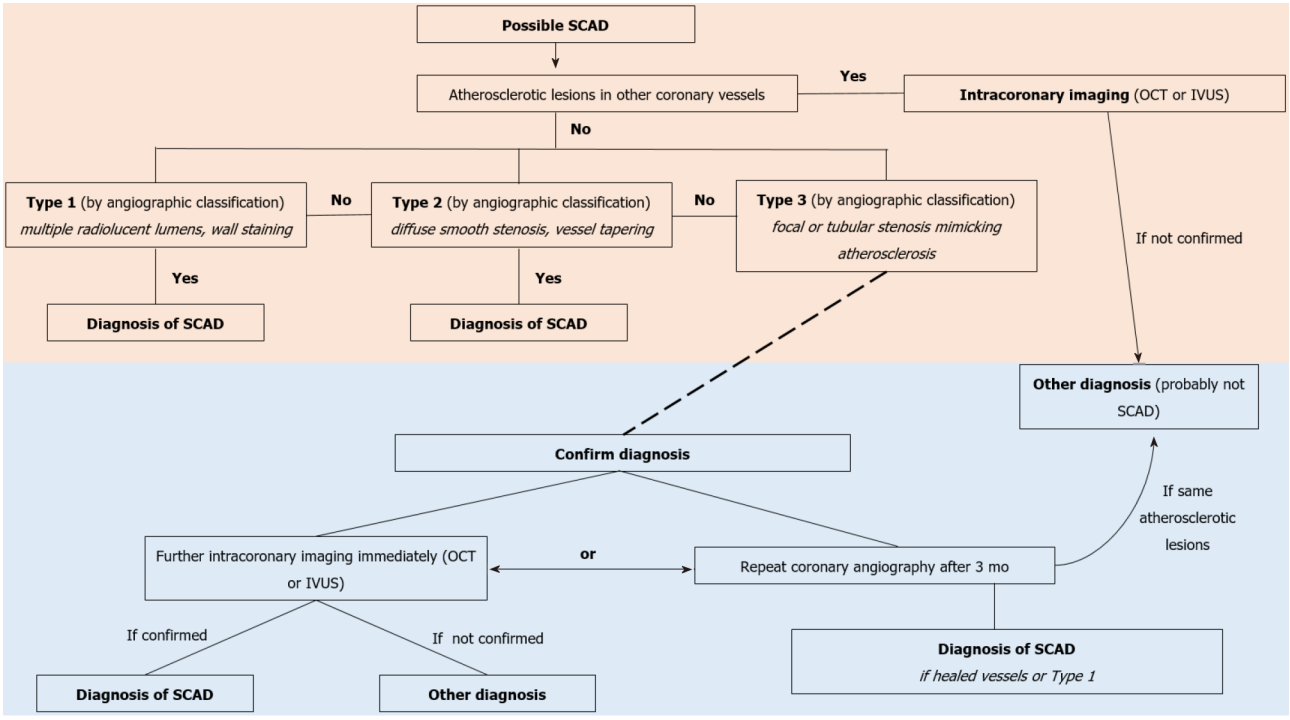
An important key-point in the differential diagnosis of SCAD would be the discrimination between non-atherosclerotic SCAD and coronary artery dissection caused by atheromatic plaque rupture in patients with atherosclerosis or catheter-induced iatrogenic dissections. The absence of atheroma or calcification in patients with non-atherosclerotic SCAD causes more fragile arterial walls and it is difficult to limit the expansion of the dissection[24]. Therefore, patients in this category often present more extensive dissections, while non-affected coronary artery segments appear smooth on angiography[24]. A proposed diagnostic algorithm from our Institution is demonstrated in Figure 2.

The classification of SCAD is based on angiographic imaging techniques. There are 3 widely approved types of SCAD[7] (Figure 3): Type 1 describes the pathognomonic appearance of arterial wall contrast staining with multiple radiolucent lumens with or without dye hang-up or slow contrast clearing[30]. Type 2 describes diffuse smooth stenoses of varying severity and length (typically > 20



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Figure 1 Intravascular imaging techniques in spontaneous coronary artery dissection. A: Optical coherence tomography; B: Intravascular ultrasound.



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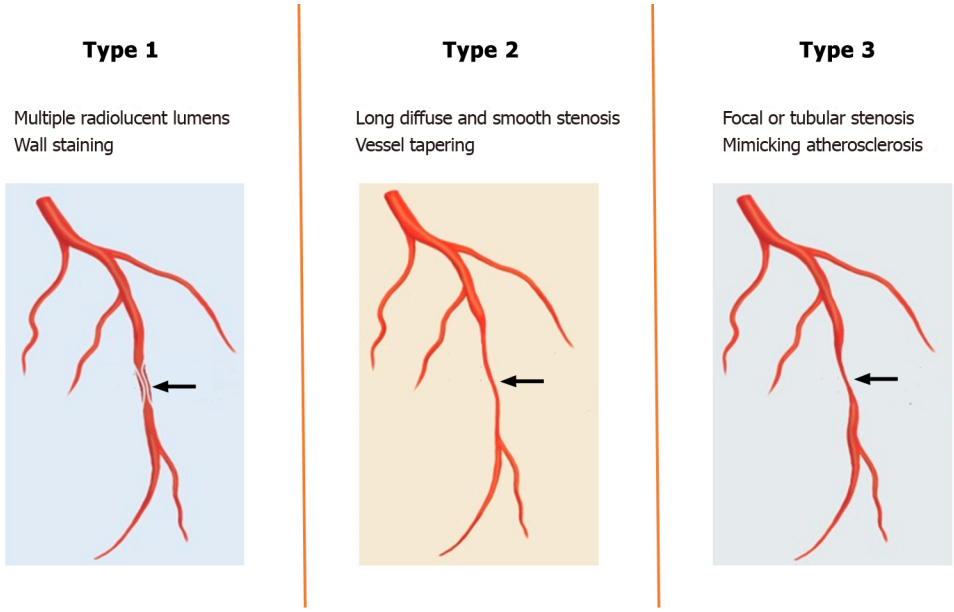
Figure 2 Flowchart diagram for the diagnosis of spontaneous coronary artery dissection. OCT: Optical coherence tomography; IVUS: Intravascular ultrasound; SCAD: Spontaneous coronary artery dissection.

mm). It usually has abrupt changes in the arterial caliber from the normal diameter to diffuse smooth narrowing. The diffuse narrowing is bordered by normal artery segments proximally and distally to the IMH in type-2A variant, while it extends to the apical tip of the artery in type-2B variant[24]. Type 3 describes a focal or tubular (typically < 20 mm) stenosis mimicking atherosclerosis requiring supplementary techniques to diagnose IMH or double-lumen, such as OCT and IVUS[24].

The most common angiographic type of SCAD is type 2, observed in approximately 67% of dissected arteries[7,11,40,69]. The left anterior descending artery is the most frequently affected (32%-46%)[7,11,40,69].

THERAPEUTIC STRATEGIES

One of the most controversary issues of modern cardiology is the management strategy of SCAD. There



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Figure 3 Types of spontaneous coronary artery dissection based on angiographic imaging techniques.

are no randomized controlled trials to compare the effect of medical therapies and revascularization strategies in these patients in order to contribute to the determination of the optimal management of SCAD. It also remains unclear whether guideline-indicated medical therapies administered for ACS would be beneficial in SCAD[70]. Therefore, management strategies are usually based on expert opinions. There is a special category of patients with SCAD, often presenting with cardiogenic shock. Pregnancy-associated SCAD is associated with dissection of more prominent epicardial vessels, leading to extensive myocardial injury and life-threatening arrhythmias[21]. As a result, these patients typically present with ACS complicated by acute heart failure or cardiogenic shock[21]. The therapeutic approach in these patients may include immediate hemodynamic support with mechanical circulatory support, extracorporeal membrane oxygenation, intra-aortic balloon pump (IABP), and left ventricular assist device (LVAD), in combination with revascularization or even cardiac transplantation[71,72]. Case reports have demonstrated beneficial effects of these therapeutic approaches in pregnant women with SCAD and cardiogenic shock[73].

Conservative management

The aim of conservative management in the acute phase of SCAD is to restore or preserve myocardial perfusion and cardiac function. Medical therapy includes beta-blockers and aspirin. The beneficial effect of beta-blockers in reducing shear stress of the coronary artery walls is associated with lower risk of recurrence, especially in patients with significant impairment of left ventricular systolic function[1,40]. Other medical therapies related to the reduction of arterial pressure and protection of the myocardium, such as angiotensin converting enzyme, angiotensin receptor blocker or mineralocorticoid receptor antagonist, are also indicated in SCAD[74,75].

The use of antiplatelets and anticoagulants, as well as the duration of treatment, remain controversial in SCAD. Patients who undergo stenting have an indication to receive dual antiplatelet therapy for 12 mo and lifelong monotherapy (usually aspirin) while acute dual antiplatelet therapy (usually with aspirin and clopidogrel) is suggested for patients managed conservatively[34,40,74,75]. The indication for acute administration of anticoagulants is only during revascularization while the indication for chronic use is in the case of left ventricular thrombus or thromboembolism[65]. However, all the above approaches remain questionable and further evidence is required.

The role of lipid-lower therapies is unclear and controversial. Statins could be recommended for routinely use after MI and in patients with pre-existing dyslipidemia[40,76]. SCAD is characterized by a general lack of atherosclerosis, and, therefore, statins may not be effective in patients with a normal lipidemic profile.

Thrombolysis is contraindicated in the acute management of SCAD as it might extend dissection and cause coronary rupture, leading to cardiac tamponade[77,78]. Adverse outcomes related to thrombolytics, including extension of dissection or hematoma, have been reported in SCAD[79].

Revascularization

Percutaneous coronary intervention is associated with poor success rates (50%-70%) due to the

increased risk of potential coronary complications including iatrogenic catheter-induced dissections, extension of dissections, and failure to enter into the true lumen[61,80]. Furthermore, there is an increased risk of proximal and/or distal false lumen propagation during stent deployment[44,81] and major side branch restriction or occlusion by propagation of the hematoma[59]. Secondary iatrogenic dissection is a major risk for patients undergoing invasive treatment. Increased risk of secondary iatrogenic dissections during coronary angiography (2%), non-SCAD angiography (0.2%) and PCI (14.3%) has been reported in SCAD patients[23]. Another study also demonstrated an increased percentage of secondary dissections related to catheterization maneuvers in patients with SCAD (5%) [12]. Taking all these factors into consideration, meticulous co-axial catheter technique and avoidance of aggressive catheterization maneuvers are suggested for patients with an indication for revascularization, while a conservative approach would be the preferred strategy in clinically stable SCAD patients with no evidence of ongoing ischemia[11,13]. Moreover, in SCAD patients, catheterization through femoral access would be preferable than radial access. Data have shown a 3-fold higher risk for catheter-induced iatrogenic dissection in patients with SCAD undergoing coronary angiography by radial access compared to femoral access[11,23].

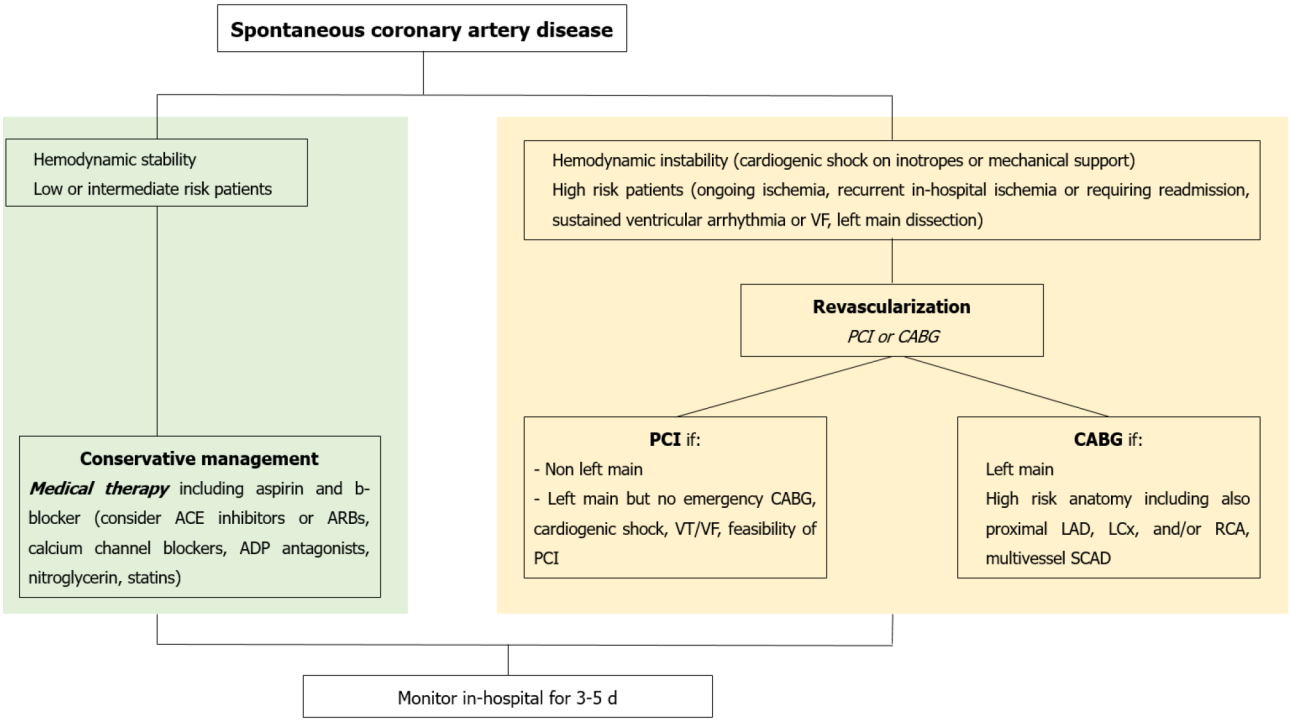
There are specific indications for revascularization. Patients with hemodynamic instability, ongoing or recurrent ischemia, ventricular arrhythmias, or left main dissection should be considered for PCI[1, 9]. A necessary condition for PCI is the suitable anatomy of the coronary arteries. Meticulous catheter wire and guide-wire manipulation, avoidance of deep catheter engagement, noncoaxial positioning of the catheter tip, catheter dampening, and/or strong contrast injections are measures that should be implemented in order to minimize complications[13,82]. All medical procedures should be undertaken with extreme attention in order to prevent catheter-induced dissection. Less conventional interventional approaches include minimal plain old balloon angioplasty to restore flow[83], longer stents to lower the possibility of further extension of the hematoma[59], and other similar techniques[84-87].

Coronary artery by-pass grafting (CABG) could be considered for patients with left main dissections with ongoing ischemia, extensive dissections, in cases where PCI failed and in patients who are not anatomically suitable for PCI[1,59]. CABG as a treatment strategy for SCAD is usually associated with promising in-hospital outcomes[12]. However, there are no clinical trials to prove the beneficial effect of CABG compared to PCI. In contrast, retrospective studies have shown high rates of graft failure at follow-up[12]. There are only case reports suggesting CABG over PCI in peripartum SCAD in order to avoid complications or sudden cardiac death due to extension of the dissection and aneurysm formation [88]. Although CABG has not been shown to prevent recurrent SCAD[12], it still remains an important therapeutic strategy, providing coronary blood flow and myocardial perfusion in critically ill patients. Despite concern for inadequacy of distal targets in diffusely dissected vessels, successful graft anastomoses are usually achieved in every primary vessel and almost all secondary vessels in all patients treated with CABG during index hospitalization, including patients initially managed conservatively or with PCI[12]. A potential risk of CABG is the fact that dissected coronary artery tissues are profoundly fragile, unlikely to hold suture, and prone to anastomotic complications[18]. A medical history of connective tissue disorders may increase the risk. Another possible complication of CABG in patients with SCAD is the high rates of bypass conduit failure due to the fact that healing of the native coronary arteries results in increasing competitive flow[12,18]. There is still not enough evidence on whether arterial or venous grafting demonstrates better outcomes in patients with SCAD. Thus, the use of reliable and immediately high-flow venous conduits could be suggested, particularly in hemodynamically unstable patients with large territories of myocardium on ongoing ischemia[18].

A proposed management algorithm for SCAD is shown in Figure 4.

PROGNOSIS AND FOLLOW-UP

The prognosis of SCAD is usually good and patients surviving SCAD demonstrate low long-term mortality[11,12,13]. Specifically, 49.7% to 89.7% of patients with SCAD received medical therapy as initial treatment, and 2.6% to 8.5% of conservatively treated patients eventually required revascularization during the index hospitalization[11,12,13]. Revascularization with PCI is the initial treatment for SCAD in 16.7% to 47.1% of patients[11,12,13]. Reported PCI success rates vary from 36.4% to 72.5%, which is significantly lower than the success rates in control subjects with atherosclerotic ACS[11,12,13]. Emergency CABG is required in 2.2% to 7.4% of patients who initially received medical therapy or PCI. An initial CABG revascularization approach was used in 0.6% to 3.7%, and initial success was high in this small group of patients, ranging from 87.5% to 100%[11,12,13]. During a follow-up of 2 to 3 years, major adverse cardiac events related to recurrent SCAD were reported in 10% to 30% of cases[3,11,29, 40]. At longer-term follow-up, major adverse cardiac events predominantly related to recurrent SCAD were reported in 15% to 37% at 5 to 7 years, while the estimated rate of major adverse cardiac events was approximately 50% at 10 years[3,11-13,29]. Conservative therapeutic strategies including medical therapy have shown excellent long-term prognosis at 6 years with event-free survival rates between 88% and 94%[89]. Another case series in United States reported a 10-year survival of 92%[29]. Similarly, a case series in Italy reported a 94.4% 6-year survival[13] while, in Canada, mortality was estimated at



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Figure 4 Proposed management algorithm for spontaneous coronary artery dissection. VF: Ventricular fibrillation; ACE: Angiotensin converting enzyme; ADP: Adenosine diphosphate; CABG: Coronary artery by-pass grafting; VT: Ventricular tachycardia; PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; LCx: Left circumflex coronary; RCA: Right coronary artery; SCAD: Spontaneous coronary artery dissection.

1.2% in 3.1 years[40]. Studies with a small number of SCAD patients, such as the Swiss series and the Japanese series, either did not demonstrate deaths in 63 patients at a median 4.5-year follow-up[56] or demonstrated a single death among 63 patients who were followed up for 34 mo[3], respectively. However, recurrent dissections and high rates of target vessel failure are significant factors that caused major adverse cardiac events ranging from 14.6% to 47.4% in SCAD patients who underwent PCI in the above case series[3,13,29,40]. SCAD recurrence was 17% in United States patients within a 4-year follow-up, approximately 29% within 10 years, and the period between the two events was at 2.8 years[29]. The corresponding percentage in the Canadian case series was 10.4% within 3.1 years, while the percentage of a new MI event was approximately 17%[40]. The Japanese series study showed recurrent SCAD of 11% after 1 mo from the first episode, during their 34-mo follow-up[3]. In the Swiss series study, 3 patients had recurrent SCAD out of 63 patients followed-up for a median of 4.5 years[56]. Finally, the Italian series study reported a 4.7% recurrence rate over a median 22-mo follow-up[13].

Follow-up of SCAD patients should be performed every year with imaging methods including simple techniques such as echocardiography and cardiac magnetic resonance imaging, more complex techniques such as computed tomography-peripheral angiography or magnetic resonance-angiography, and invasive techniques such as coronary angiography[59]. Coronary computed tomography angiography was shown to be a valuable and useful method, without complications, for noninvasive follow-up of patients with SCAD, especially in those with large-caliber coronary arteries[57,90,91]. A significant limitation of coronary computed tomography angiography is the poor visualization of SCAD lesions in distal coronary arteries or side branches, or of vessel caliber < 2.5 mm[11,92]. For all patients, either treated conservatively or those who underwent PCI, a follow-up angiography in the catheter laboratory is suggested 6 mo after the event, in cases where coronary computed tomography angiography is not feasible or misdiagnosing. Repeat angiograms can be performed by the femoral or radial approach during a short hospital stay or on an ambulatory basis[93]. Patients should also have outpatient appointments at the referring hospital or with cardiologists in private practice twice within the first year of the event; typically, 1 to 3 mo and 12 mo after the event. Thereafter the appointments depend on the clinical status of each patient[93]. Other non-invasive follow-up techniques including cardiopulmonary exercise stress test and echocardiography should be conducted every year. In pregnancy, pregnant women with a medical history of SCAD should be referred to specialized medical centers for assessment, counseling for the potential increased risk of dissection and complications during pregnancy, and follow-up by a multidisciplinary team that includes maternal-fetal medicine specialists, cardiologists with experience managing SCAD, and obstetric anesthesiologists[83]. In patients with systemic arteriopathy, an extracoronary dissection or an aneurysm, subsequent use of alternative imaging methods that do not expose the patient to ionizing radiation such as magnetic

resonance angiography and duplex ultrasonography should be considered[94]. Major adverse cardiac events should be registered in all patients with SCAD at follow-up, especially in the first 5 years.

EXERCISE AND LIFESTYLE AFTER SCAD

In most SCAD patients, especially those with recurrence or noncoronary aneurysms or dissections, it is suggested thay they avoid extreme endurance training, exercise until exhaustion, elite competitive sports, or vigorous exertion in extremes of ambient temperature. Additionally, patients should avoid lifting or carrying heavy objects that require straining or prolonged Valsalva maneuvers[18]. The onset of SCAD symptoms has been correlated with physical activity in up to 32% of patients after SCAD[95]. After the onset of chest pain, patients should be immediately evaluated according to proposed algorithms in previous articles[18].

High levels of psychological distress including depression, anxiety, and post-traumatic stress disorder are associated with post-SCAD patients, especially women. Psychological support is always recommended in patients with cardiovascular diseases[96].

CURRENT DEVELOPMENTS AND FUTURE PERSPECTIVES

The current progress in early recognition and appropriate therapeutic management of SCAD has improved the understanding of the pathophysiology background of the disease, its association with potential risk factors and the role of genetics. Diagnostic management includes high-resolution diagnostic methods such as OCT, IVUS, cardiac MRI and duplex ultrasonography. Progress has also been noted in the therapeutic strategies of the disease. Life-saving technologies, especially in patients with hemodynamic instability, including mechanical circulatory support systems, extracorporeal membrane oxygenation, IABP, and LVADs, as well as new revascularization techniques and progress in cardiac transplantation have increased survival rates and reduced complications in these patients.

However, data remain retrospective, observational, and often based on case reports. Collaborative evaluations across medical centers are further required. National registries and continuous follow-up programs at 1, 3, 6 and 12 mo, with or without intravascular imaging, would provide more evidence for the disease, leading thus, to more comprehensive points of view regarding accurate diagnosis of SCAD among AMI and chest pain, appropriate indications and optimal techniques for revascularization, optimization of medical therapy, individualization of risk factors for recurrent SCAD and better development of genetic model systems for better understanding of genetic variations of SCAD. Invasive approaches with the use of bioresorbable vascular scaffolds should be encouraged in proximal/middle vessel lesions, occurring in larger vessels (≥ 3.0 mm vessel diameter) and in cases where patients are still symptomatic or hemodynamically unstable[97,98]. Finally, the establishment of new accurate scores for the diagnosis and therapeutic management of SCAD is mandatory.

CONCLUSION

SCAD is a rare cardiovascular disease which mostly affect women (approximately 90%), but there are limited data regarding diagnosis and treatment. The increased awareness of SCAD during the last decade has improved our knowledge regarding the potential mechanisms of the disease. Alertness and education are the most important alliances of the medical community in the early and accurate diagnosis of SCAD, especially among women, and its treatment strategies. Coronary angiography is the gold standard treatment method in unstable patients with symptoms of acute ischemia. OCT and IVUS are supplementary intracoronary imaging techniques in the diagnosis of SCAD, and they should be performed before each intervention in order to increase safety and reduce secondary iatrogenic dissections related to stenting. Further randomized controlled trials in medical centers, investigating different diagnostic methods and different therapeutic approaches, are required.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cryoballoon ablation outcomes for paroxysmal atrial fibrillation

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Abstract

BACKGROUND

Cryoballoon ablation (CBA) is recommended for patients with paroxysmal atrial fibrillation (AF) refractory to antiarrhythmic drugs. However, only 80% of patients benefit from initial CBA. There is growing evidence that pretreatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation. The role of ACEIs and ARBs in patients with paroxysmal AF in CBA remains unknown. We decided to investigate the role of ACEIs and ARBs in preventing the recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

AIM

To investigate the role of ACEIs and ARBs in preventing recurrence of AA following CBA for paroxysmal AF.

METHODS

We followed 103 patients (age 60.6 ± 9.1 years, 29% women) with paroxysmal AF undergoing CBA 1-year post procedure. Recurrence was assessed by documented

AA on electrocardiogram or any form of long-term cardiac rhythm monitoring. A multivariable Cox proportional hazard model was used to assess if ACEI or ARB treatment predicted the risk of AA recurrence.

RESULTS

After a 1-year follow-up, 19 (18.4%) participants developed recurrence of AA. Use of ACEI or ARB therapy was noted in the study population. Patients on ACEI/ARB had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEI or ARB therapy did not prevent recurrence of AA following CBA (P = 0.72). Similarly, on Kaplan–Meier analysis pretreatment with ACEI/ARB did not predict the time to first recurrence of AA (P = 0.2173).

CONCLUSION

In our study population, preablation treatment with an ACEI or ARB had no influence on the recurrence of AA following CBA for paroxysmal AF.

Key Words: Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Paroxysmal atrial fibrillation; Cryoballoon ablation; Outcome

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Core tip: We investigated the role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in preventing recurrence of atrial arrhythmias following cryoballoon ablation (CBA) for paroxysmal atrial fibrillation (AF). Outcomes of 103 patients were evaluated in a retrospective chart review. Preablation treatment with an ACEI or ARB had no influence on recurrence of AA following CBA for paroxysmal AF. To our knowledge, this study is the first of its kind to examine the effect of ACEI/ARB use in this exclusive subset of patients.

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INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia that represents an evolving, global epidemic[1]. It is estimated that the number of Americans afflicted by AF will increase from the current 2.3 million to more than 10 million by 2050[2]. Due to a substantial increase in incidence and prevalence of AF over the past few decades, it presents a significant economic burden on the health care system[3]. In 2014, in the United States alone, an estimated 599790 emergency department visits, 453060 hospitalizations, and 21712 deaths were associated with AF as a primary medical diagnosis. Furthermore, the mean cost per hospitalization for patients with a primary diagnosis of AF was $88194[4].

Even though cryoballoon ablation (CBA) is beneficial in patients with paroxysmal AF refractory to antiarrhythmic drugs, only 80% of patients benefit from initial CBA[5-8]. Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEIs and ARBs decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation (RFA) [9]. The role of ACEIs and ARBs in patients with paroxysmal AF in CBA remains unknown. In this study, we aimed to investigate the role of ACEIs and ARBs in preventing recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

MATERIALS AND METHODS

Study design and definitions

We performed a single-center, retrospective, cross-sectional study in a community-based tertiary care center in Worcester, MA, USA. Paroxysmal AF was defined as nonsustained episodes of AF converting

to sinus rhythm in < 7 d. Patients were required to be on an ACEI or ARB for a minimum duration of 4 wk. Institutional review board approval was obtained before initiation of the study.

Inclusion and exclusion criteria

To be included in this study, participants had to be aged ≥ 18 years and have had CBA as a first or repeat procedure for paroxysmal AF between January 2015 and April 2018. We excluded all patients with a diagnosis of permanent and persistent AF. Following inclusion data on baseline demographics, concomitant comorbidities, clinical, laboratory, echocardiographic, pharmacological and ablation procedural details and outcome details were obtained by trained physicians from chart review.

Cryoablation procedure

All CBA were conducted under general anesthesia. Two sheaths (7 and 9 Fr) were placed in the left femoral vein following ultrasound-guided vascular access. With the fluoroscopic guidance, an intracardiac echocardiography (ICE) catheter was advanced into the right atrium and a decapolar mapping catheter was positioned within the coronary sinus. A trans-septal sheath was placed through the right femoral vein approach. Heparin was administered intravenously for an activated clotting time > 300 s to prevent intraprocedural thromboembolic events. Trans-septal access to the left atrium was obtained under fluoroscopic and ICE guidance. The trans-septal sheath was exchanged for a 12 Fr Flexcath sheath (Medtronic, Minneapolis, MN, USA) which was then utilized to advance a 28-mm Arctic Front Advance Cryoballoon ablation catheter (Medtronic) with the Achieve spiral mapping catheter into the left atrium. An electroanatomic map of the left atrium and all pulmonary veins was performed utilizing 3-dimentional mapping software (Abbott Cardiovascular, Santa Clara, CA, USA), guided by a three-dimensional computed tomography recreation of the left atrium. Each of the pulmonary veins were then isolated using CBA. During the right-sided pulmonary vein ablation, the decapolar catheter was withdrawn to the superior vena cava to pace the diaphragm and allow for monitoring of phrenic nerve injury. For pulmonary veins with incomplete isolation following CBA, local RFA was performed as needed to provide complete isolation. All pulmonary veins have demonstrated a bidirectional conduction block and a postablation voltage map was created using the mapping software.

Follow up for ablation success

The patients with paroxysmal AF undergoing CBA were followed for 1 year postprocedure for any development of AA. The recurrence of AA was assessed through a medical records review by documented self-reported patient symptoms, supplemented by an electrocardiogram or any form of documented long-term rhythm monitoring such as a cardiac event or a Holter monitor. A 3-mo blanking period was used postablation to allow for recurrence of AF after the initial procedure, with the exception for symptomatic patients with early recurrence that required electrical cardioversion or repeat ablation.

Statistical analysis

We reported continuous variables as mean with standard deviation and categorical variables as frequency and percentage. A multivariable Cox proportional hazard model was used to assess if ACEI or ARB treatment predicted the risk of AA recurrence. For the multivariate analysis, we utilized two models. In the first model, analysis was adjusted for nonmodifiable variables including age and gender. In the second model, analysis was adjusted for both nonmodifiable (Model 1) and modifiable variables including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), heart failure (HF), chronic kidney disease stage ≥ 3, and at least moderate degree of any valvular heart disease. The χ^2 test was used to analyze the significance of the categorical variables and Student's *t*-test was used to analyze the significance of continuous variables. To look for the association between ACEI/ARB use and recurrence of AA, we used the multivariable Cox- proportional analysis and calculated hazard ratio (HR) and 95% confidence interval (CI). We used the Kaplan–Meier method to obtain survival curves and a log-rank test for their comparison. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all these statistical analyses. $P < 0.05$ was considered to be statistically significant.

RESULTS

Between January 2015 and April 2018, 103 patients undergoing CBA as a first or repeat procedure for paroxysmal AF were included in this study. They were divided into two groups based on the use of ACEIs/ARBs at the time of CBA. Their baseline characteristics are presented in Table 1. Out of the 103 patients, 42 were receiving ACEIs/ARBs at the time of CBA. The mean age was similar in both groups (61.7 ± 8.6 years in the ACEI/ARB group *vs* 59.9 ± 9.5 years in the other group). Patients in the ACEI/ARB group were more likely to be male (78.6% *vs* 65.6%) and have hypertension (86% *vs* 54.1%) and CAD (26.2% *vs* 9.8%). Out of the 42 patients, 21 (58%) were taking ACEIs and 15 (42%) were taking ARBs. In the ACEI group, all patients were taking lisinopril. In the ARB group, 87% of patients were taking losartan. The mean dose for lisinopril was 16 mg orally daily and the median dose was 10 mg

Table 1 Baseline characteristics of study participants

Characteristics	No ACEI / ARB	ACEI / ARB	*P* value
mean ± SD or *n* (%)	*n* = 61	*n* = 42	
Age (yr)	59.9 ± 9.5	61.7 ± 8.6	0.32
Male	40 (65.6%)	33 (78.6%)	0.15
Baseline heart rate	70 ± 15.7	63 ± 17.8	0.06
Body mass index (kg/m^2)	30.9 ± 76.6	32.3 ± 6.9	0.33
Coronary artery disease	6 (9.8%)	11 (26.2%)	0.028
Congestive heart failure	6 (9.8%)	9 (21.4%)	0.10
Diabetes mellitus	9 (14.8%)	12 (28.6%)	0.09
Hypertension	33 (54.1%)	36 (85.7%)	< 0.001
Valvular heart disease	25 (41.0%)	14 (33.3%)	0.43
Hyperlipidemia	40 (65.6%)	31 (73.8%)	0.37
CHA2DS2VASC score	1.5 ± 1.4	2.0 ± 1.3	0.08
Recurrence of AA	9 (14.8%)	10 (24.4%)	0.22

P value as calculated by *t*-test for continuous and χ^2 for categorical variables. SD: Standard deviation; AA: Atrial arrhythmia; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

orally daily. For patients taking losartan, the mean and median doses were 57 and 50 mg orally daily, respectively.

At 1-year follow-up, 19 (8.4%) patients developed recurrence of AA (Figure 1). The role of ACEIs and ARBs in preventing the recurrence of AA following CBA for paroxysmal AF was assessed using a multivariable Cox proportional hazard model (Table 2). In the initial model adjusted for age and sex, ACEI/ARB use did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.78, 95%CI 0.72–4.42, *P* = 0.66). In a second model adjusted for CAD, congestive HF, diabetes mellitus, hypertension, and valvular heart disease, ACEI/ARB use still did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.37, 95%CI 0.51–3.7, *P* = 0.72). On Kaplan–Meier analysis, ACEI/ARB use did not predict the time to first recurrence of AA (Figure 2, *P* = 0.2173) in these patients.

DISCUSSION

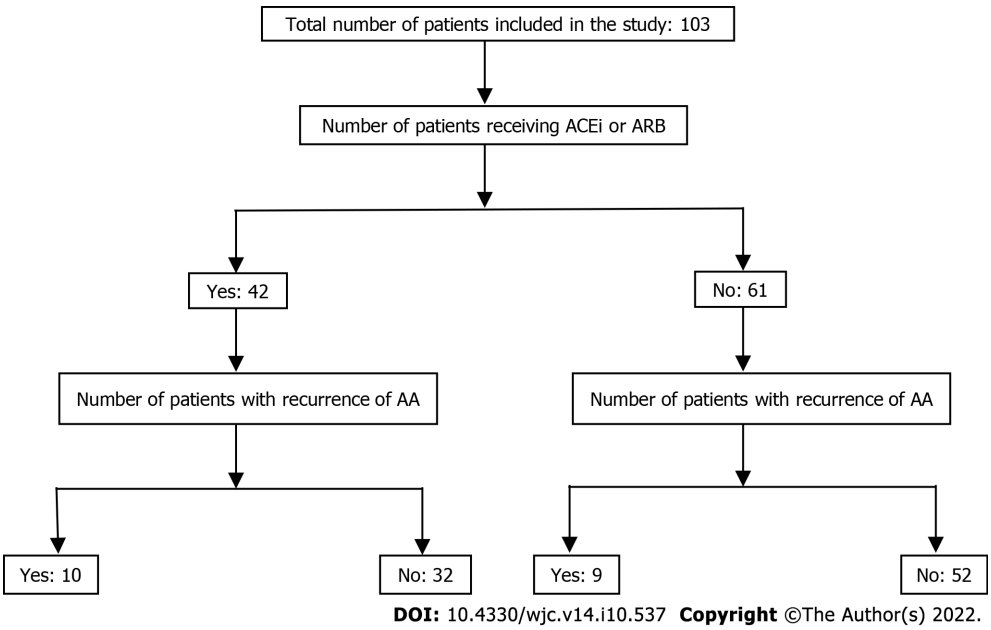
In paroxysmal AF patients undergoing CBA, the use of preprocedural ACEI or ARB had no effect on the recurrence of AA at 1 year follow-up. To our knowledge, this study is the first of its kind to examine the effect of ACEI/ARB use in this subset of patients. It is important to note that the ACEI/ARB group of patients that underwent CBA for paroxysmal AF had significantly higher prevalence of hypertension and CAD, which are known to contribute to myocardial fibrosis. Additionally, both hypertension and CAD contributed to increased left ventricular compliance and left atrial filling pressure. Subsequent left atrial enlargement further promotes AA. These comorbidities, however, were adjusted for in multivariate analysis in Model 2 shown above.

The pulmonary veins are the most common substrate for AF initiation[10,11]. Isolated firing of the atrial myocardium can lead to AF initiation initially as an ectopic focus subsequently progressing to a single-circuit re-entry, and eventually to a multiple-circuit re-entry[12,13]. The process correlates with the duration of AF as it progresses from paroxysmal to persistent, and eventually permanent AF5. Myocardial remodeling is one of the key factors in the pathophysiology of AF and is defined as a group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury[14]. Additionally, myocardial remodeling can be classified into electrical and structural remodeling. which in turn, can be physiological (adaptive) or pathological[15]. There are several ways in which remodeling could lead to arrhythmia development. The first mechanism involves ion channel changes such as inactivation of sodium ion channels, changes in calcium and potassium ion channels, and alteration in the sodium/calcium exchanger function[5,16-18]. Another mechanism includes changes in the junctional intercellular communication, particularly in protein connexin that is responsible for contact between adjacent cells and electrical coupling[19]. Finally, there is structural cardiac remodeling that involves cell death and fibroblast proliferation that promotes extracellular matrix production, and, eventually, fibrosis[20,21]. Fibrotic lesions impede

Table 2 Multivariate adjusted Cox-proportional hazard model of atrial arrhythmia recurrence after cryoablation by angiotensin converting enzyme inhibitors/angiotensin receptor blockers

Outcome of interest	ACEI/ARB HR (95%CI)	No ACEI/ARB HR (95%CI)	*P* value
Recurrence of AA		Ref	
Model 1[a]	1.78 (0.72, 4.42)	1.00	0.66
Model 2[b]	1.37 (0.51, 3.72)	1.00	0.72

[a]Model 1 adjusted for age and sex.
[b]Model 2 adjusted for model 1 + coronary artery disease, congestive heart failure, diabetes mellitus, hypertension and valvular heart disease.
AA: Atrial arrhythmia; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HR: Hazard ratio; CI: Confidence interval.



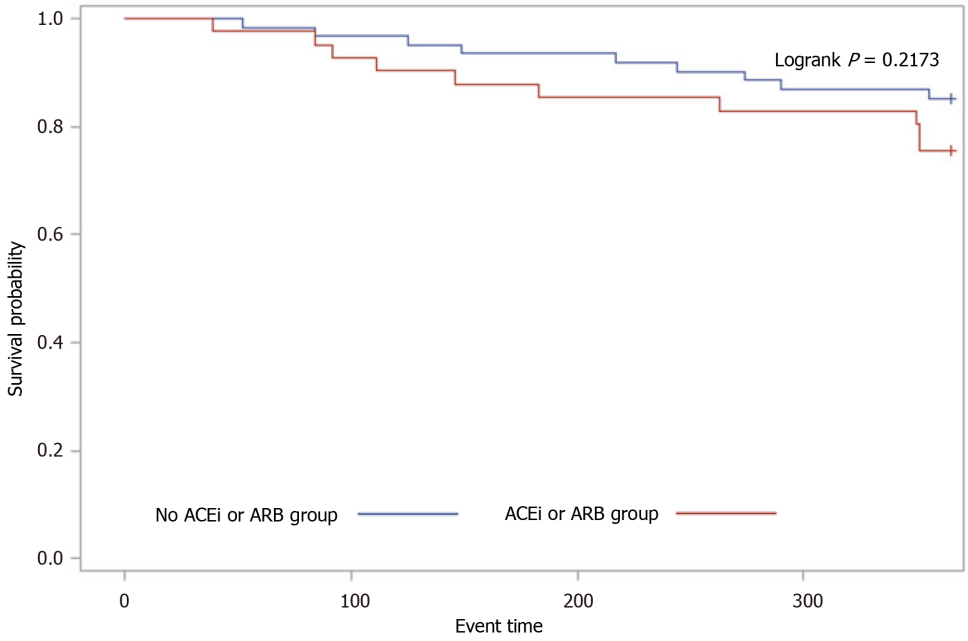
DOI: 10.4330/wjc.v14.i10.537 **Copyright** ©The Author(s) 2022.

Figure 1 STROBE diagram showing flow of patients in the study. ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AA: Atrial arrhythmia.

electrical propagation and eventually promote mechanisms for re-entrant arrhythmias[15].

In recent times, there has been a renewed interest in investigating the role of the renin–angiotensin–aldosterone system in AF. There are several ways hypothesized in which ACEIs and ARBs can potentially affect clinical outcomes. These drugs not only have direct effects on the functional remodeling or electrical properties but also indirect effects by controlling hypertension and HF symptoms which are known risk factors for AF[22]. Atrial myocardium is sensitive to increased hemodynamic stressors due to volume and pressure overload from hypertension and HF. These stressors can in turn promote electrical alterations such as decreased resting potential and delayed afterdepolarizations contributing to increased myocardial excitability[23]. Additionally, increased hemodynamic load and myocardial mechanical stretch can activate genetic pathways that rapidly augment the secretion of angiotensin II[24]. Angiotensin II can successively contribute to arrhythmogenicity by promoting an increase net inward calcium current in affected cardiomyocytes and by inducing myocardial hypertrophy and fibrosis[25]. Increased fibrosis of the atrial myocardium is known to be associated with AF[5,20]. G protein-coupled receptor agonists like angiotensin II induce cellular differentiation processes and activation of fibroblasts, and the development of interstitial fibrosis through activation of extracellular signal-regulating kinases (ERKs). These findings were confirmed in a small study by Goette *et al*[26] where patients with AF undergoing cardiac surgery were found to have a significant increase in atrial fibrosis along with an increased expression of ERK1 and ERK2 in atrial interstitial cells.

The use of ACEIs and ARBs has also been shown to be associated with a decreased AF burden in certain population groups. Anné *et al*[27] investigated 196 patients undergoing RFA for atrial flutter and evaluated outcomes associated with the use of an ACEI or ARB. Predictably, more than half of these patients eventually developed AF, but it was found that the use of an ACEI/ARB was associated with reduced incidence of AF after atrial flutter ablation (P = 0.04)[27]. Furthermore, the use of ARBs was



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Figure 2 One-year Kaplan–Meier Survival curve of atrial arrythmia recurrence after cryoablation by angiotensin-converting enzyme inhibitors / angiotensin receptor blockers use. AA: Atrial arrhythmia; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

evaluated in conjunction with antiarrhythmic medications and showed better outcomes in comparison to antiarrhythmics alone. In a prospective randomized trial by Madrid *et al*[28], 159 patients were randomized to either amiodarone or amiodarone plus irbesartan to evaluate the role of ACEI in maintaining sinus rhythm in persistent AF. Patients in the irbesartan plus amiodarone combination group had a significantly higher rate of sinus rhythm maintenance at 360 d in comparison to the group on amiodarone alone.

In patients with HF and AF, preablation use of an ACEI resulted in an improved ablation success rate in nonparoxysmal AF with low ejection fraction. In a single center, Mohanty *et al*[9] investigated 703 consecutive patients with preserved left ventricular ejection fraction (LVEF > 45%) and 345 patients with reduced EF (< 45%) undergoing RFA for AF. At 24 ± 7 mo of follow-up, in patients with nonparoxysmal AF and reduced EF, the ACEI pretreatment group had lower recurrence of AF post-RFA compared to the non-ACEI group (76% *vs* 64%, $P = 0.015$). Among paroxysmal AF patients regardless of LVEF, ACEI use was not observed to be associated with improved RFA outcomes (80% *vs* 77%, $P = 0.82$). These findings are similar to our study, which demonstrated that in patients with paroxysmal AF the use of an ACEI or ARB did not affect outcomes and event-free survival following CBA. Currently, the guidelines do not recommend the use of ARB or ACEI for the sole purpose of preventing the recurrence of AF, due to a lack of substantial literature supporting it. However, there is growing evidence that in patients with nonparoxysmal AF undergoing RFA, the use of ACEIs or ARBs decreases the recurrence of AF.

Our study had its inherent limitations. Firstly, it was a single center retrospective study with a small sample size limiting the generalizability of outcomes. Secondly, the study population was underpowered for the detection of benefits in patients with paroxysmal AF. Thirdly, we examined an exclusive population of patients with paroxysmal AF and not persistent AF who are known to have a higher degree of electrical and structural remodeling with the potential for superior benefits with ACEIs/ARBs. Since this was a small retrospective study, we could not perform a power analysis. Lastly, our patient population within the ACEI/ARB group had a higher rate of hypertension and CAD. Although these factors were accounted for in the multivariate analysis, we did not collect the data on whether CAD was optimally treated or required a revascularization procedure. Despite these limitations, our study is the first of its kind to examine the role of ACEI/ARB use in an exclusive population of paroxysmal AF patients undergoing CBA.

CONCLUSION

In paroxysmal AF patients undergoing CBA, the use of ACEIs or ARBs was not associated with decreased recurrence of AA. Larger, multicenter, controlled studies, particularly in patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, HF or valvular disease are necessary to fully evaluate the effect of ACEIs, ARBs, or angiotensin receptor

neprilysin inhibitors such as sacubitril/valsartan in patients undergoing CBA for AF.

ARTICLE HIGHLIGHTS

Research background

Cryo-balloon ablation (CBA) is recommended for patients with paroxysmal atrial fibrillation (AF) refractory to antiarrhythmic drugs. However, only 80% of patients benefit from initial CBA.

Research motivation

Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEIs and ARBs decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation.

Research objectives

To investigate the role of ACEIs and ARBs in preventing the recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

Research methods

We performed a single-center, retrospective, cross-sectional study. All patients aged 18 years or older, with a diagnosis of paroxysmal AF, undergoing CBA as a first or repeat procedure between January 2015 and April 2018 were included. We followed these patients with paroxysmal AF undergoing CBA for 1 year post-procedure. Recurrence was assessed by documented AA on electrocardiogram or any form of long-term cardiac rhythm monitoring.

Research results

After 1-year follow-up, out of 103 patients, 19 (18.4%) developed recurrence of AA. Of these, 42 patients were receiving ACEIs/ARBs at the time of CBA. 21 (58%) patients were taking ACEIs and 15 (42%) ARBs. Patients on ACEIs/ARBs had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEI or ARB therapy did not prevent the recurrence of AA following CBA (P = 0.72). Similarly, on Kaplan–Meier analysis pretreatment with ACEIs/ARBs did not predict the time to first recurrence of AA (P = 0.2173).

Research conclusions

In paroxysmal AF patients undergoing CBA, the use of ACEIs or ARBs was not associated with decreased recurrence of AA.

Research perspectives

Future studies, particularly in patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, heart failure or valvular disease are necessary to fully evaluate the effect of ACEIs, ARBs, or angiotensin receptor neprilysin inhibitors such as sacubitril/valsartan in patients undergoing CBA for AF.

FOOTNOTES

Author contributions: Al-Seykal I and Bose A contributed to the conceptual design of the study; Al-Seykal I, Bose A, Mishra A and Hashmath Z independently screened the medical records and extracted the data; Chevli P did the statistical analysis; Al-Seykal I, Mishra A, Hashmath Z and Sharma N contributed to write-up and submission of the study; Bose A, Mishra A, and Laidlaw D reviewed the final manuscript; all authors reviewed and agreed with the final content of the article.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of MetroWest Medical Center.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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SYSTEMATIC REVIEWS

Virulent endocarditis due to *Haemophilus parainfluenzae*: A systematic review of the literature

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Abstract

BACKGROUND

Haemophilus parainfluenzae (HPI) belongs to the HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) group of organisms. The HACEK group of organisms are a part of the oropharyngeal flora and can cause invasive opportunistic infection such infective endocarditis (IE) in hosts with compromised immunological barriers.

AIM

To perform a 20-year systematic review of the literature characterizing the clinical presentation, epidemiology and prognosis of HPI IE.

METHODS

We performed a systematic review of Medline, Pubmed, Scopus and Embase from 2000 to 2022 to identify all cases of HPI IE.

RESULTS

Thirty-nine adult cases were identified. HPI IE was found to affect males slightly more than females and is common in patients with predisposing risk factors such as underlying valvular abnormalities. It mostly affected the mitral valve and had an indolent course; significantly sized vegetations (> 1 cm) developed in most cases. Central nervous system septic embolization was common. It had a favorable prognosis compared to staphylococcal and streptococcal IE.

CONCLUSION

Clinicians should be attentive to the indolent course of HPI IE and the presence of

predisposing risk factors in order to allow for timely management.

Key Words: *Haemophilus parainfluenzae*; Infective endocarditis; Mitral valve; Vegetation

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Core tip: This review and illustrative case show a temporal change in the epidemiology of *Haemophilus parainfluenzae* (HPI) infective endocarditis in 2000–2022. Compared with a review of 26 HPI endocarditis cases from 1984–1995 by Darras-Joly *et al*, this review reported younger mean age, similar rate of infection in both genders, shorter time to diagnosis, higher association with intravenous drug use (IVDU), higher rate of embolic events in general, and tricuspid and pulmonic valve involvement. The rate of mitral valve involvement has remained steady over the past three decades, while there has been a decrease in the rate of aortic valve involvement. There has been a decrease in valvular vegetation rates and incidence of congestive heart failure as complications, while the mortality rate remained similar. These findings indicate improvement in diagnosis and treatment of HPI over the past three decades; however, they also suggest an increase in its virulence and an association with the rising rate of IVDU highlighted by the involvement of the right-sided heart valves.

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INTRODUCTION

Infective endocarditis (IE) remains a significant cause of morbidity and mortality. The incidence has increased from 5–7 cases per 100000 of the population in 2000 to 15 cases per 100000 person-years in 2011[1-3]. Common risk factors include an immunocompromised state, intravenous drug use (IVDU), underlying valvular disorders, prosthetic valves, and implanted cardiac devices[1-3]. The microbiology of IE is important and affects clinical presentation and prognosis[1-3]. Skin flora, including *Staphylococcus*, *Enterococcus* and *Streptococcus* spp., are the most common causative organisms in IE, accounting for 80%–90% of cases, with a mortality rate as high as 30%[1-3].

Although less common, the oropharyngeal flora is also an important cause of IE, particularly the HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) group[1,4-6]. This group has been identified in 1.5%–2% of all IE cases, with a mortality rate of 2%[4-6]. They are fastidious Gram-negative bacilli known for their slow growth in routine blood culture media, which may cause a delay in diagnosis[4,5]. Reported risk factors for the development of HACEK group IE include recent dental procedures and abnormal heart valves[4,5]. The most common organism implicated is *Aggregatibacter* spp[4,6]; however, IE due to *Haemophilus parainfluenzae* (HPI) is gaining increasing attention in the literature. Here, we present an illustrative case of endocarditis in a healthy young man with no predisposing risk factors, and a systematic review of HPI IE cases reported in the literature within the last 20 years to characterize its clinical presentation, epidemiology and prognosis.

Illustrative case

A 25-year-old man with no significant past medical history presented to the emergency department with a 2-mo history of worsening frontal headache and 1 wk of fever and watery diarrhea. Physical examination was significant for a fever of 39.1 °C, heart rate of 109 beats/min, blood pressure of 118/63 mmHg, and holosystolic murmur auscultated at the cardiac apex. Laboratory results were remarkable for white blood count (WBC) count of 12.9 K/L (normal: 4–11), hemoglobin 8.5 g/dL (normal: 13.5–17.0), mean corpuscular volume 77 fL (normal: 78–100), relative distribution width of 16.2% (normal: 11–15), procalcitonin 2.33 ng/mL (normal: 0.49), C-reactive protein 218 mg/L (normal: 4.9), and erythrocyte sedimentation rate 56 mm/h (normal: 0–15). Intravenous (IV) vancomycin, ceftriaxone and acyclovir were initiated due to concern for meningitis. Chest radiograph and head computed tomography were negative for acute abnormalities. A lumbar puncture was performed, with cerebrospinal spinal fluid (CSF) analysis positive for WBC count of 231/mm^3 (normal: 0–5), with 67% neutrophils and 21% lymphocytes, glucose 51 mg/dL (normal: 40–70), and protein f 49.9 mg/dL (normal: 15–40). CSF herpes simplex virus polymerase chain reaction was negative, and acyclovir was discontinued.

Blood cultures on hospital day 4 showed Gram-negative rods, which speciated to HPI on hospital day 6. CSF cultures remained negative, and antibiotics were de-escalated to IV ceftriaxone for HPI bacteremia. Additionally, esophagogastroduodenoscopy, colonoscopy and subsequent biopsies were normal. Iron studies were significant for serum iron of 9 g/dL (normal: 40–190), transferrin 119 mg/dL (normal: 200–390), transferrin saturation 6% (normal: 15–50), total iron binding capacity 167.8 g/dL (normal: 250–435), and ferritin 1083 ng/mL (normal: 25–506).

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) revealed two mobile echodensities on the atrial side of the mitral valve, consistent with vegetations on the A2 and P2 segments of the mitral leaflets (Figure 1), with an anterior leaflet perforation and a severe mitral regurgitation (Videos 1 and 2). Magnetic resonance imaging (MRI) of the brain revealed a 1.0 0.5 cm ring enhancing lesion in the right parietal lobe with surrounding vasogenic edema, suggestive of an abscess secondary to septic emboli (Figure 2A). Repeat MRI brain at 4 wk revealed near resolution of the right parietal lobe lesion (Figure 2B). After completing 8 wk of ceftriaxone, he underwent mitral valve repair with edge-to-edge repair of A1 and P1 segments. Postoperative TEE revealed adequate A1 and P1 fusion. The postoperative course was complicated by left-sided proximal muscle weakness and paresthesia, which resolved within 48 h. He completed cardiac rehabilitation successfully and had no further complications.

MATERIALS AND METHODS

Data sources and searches

Two authors (AO and DK) independently searched Medline, Pubmed, Scopus, Embase and Reference Citation Analysis from January 1, 2000 to March 30, 2022 using the following keywords: *Haemophilus parainfluenzae* and infective endocarditis. An independent search was conducted by a qualified librarian using similar terms. Only articles published in English were included.

Article selection

Inclusion criteria included IE due to HPI, patients aged > 18 years, positive blood or pathology specimens for HPI, and clinical and echocardiographic evidence of IE. Articles not meeting these criteria were excluded. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[7] (PRISMA 2009 Checklist).

Data extraction

Extracted data included patient demographics (age and gender), symptoms at initial presentation, comorbidities (prior valvular disorder, structural heart defects, recent dental, and gastrointestinal or genitourinary procedures), affected valves, severity of valvular damage, patient management, and complications.

Data analysis

We conducted a qualitative systematic analysis using descriptive statistics. A meta-analysis could not be performed due to the differences among individual cases and the small sample sizes (*i.e.* 1 patient) included in the case reports.

RESULTS

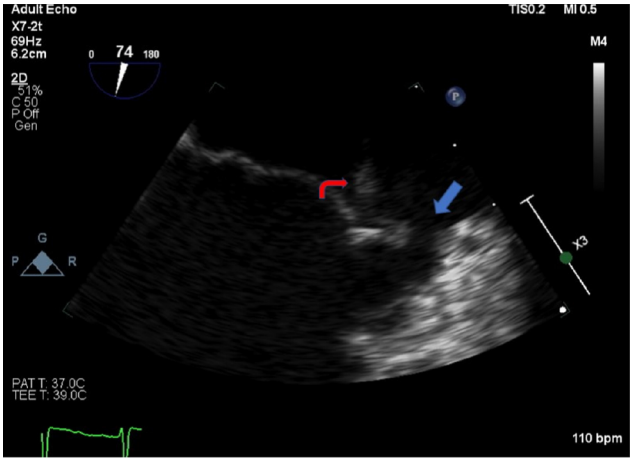
Search results and article inclusion

Our initial search generated 383 articles. After excluding 221 duplicates, the remaining 162 articles were screened for inclusion (Figure 3). Of these, 39 articles[8-46] were systematically reviewed. The remaining articles were excluded because they were irrelevant to the topic (36 articles), discussing IE with organisms other than HPI (52 articles), review articles on HACEK organisms and IE (13 articles), pediatric case reports on HPI IE (12 articles), or not published in English (3 articles).

Patient characteristics

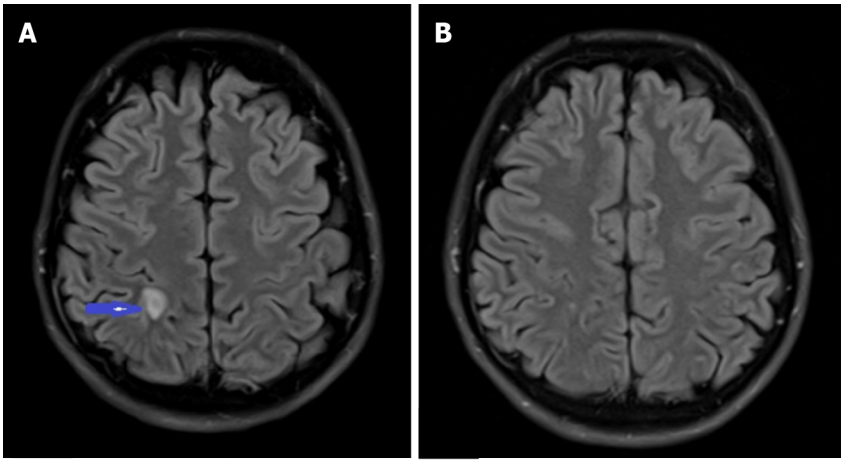
Age and gender: A total of 39 patients were identified. The mean age was 39 years, with a range of 18–69 years. There was a slight predominance towards men (52.5%).

Predisposing risk factors for IE: Approximately 10% of the patients reported a history of IE. About 17.5% had a history of valve replacement (4 with bioprosthetic valves, 2 with mechanical valves, and 1 with unspecified valve type). Twenty percent had mitral valve disorders (3 with mitral valve prolapse, 2 with rheumatic heart disease, and 1 with mitral regurgitation). Eighteen percent had aortic valve disorders (3 with bicuspid aortic valve and 3 with aortic stenosis). Current IVDU was reported in 17.5%. Approximately 10% had poor dentition. Thirteen percent had a history of pacemaker and implanted



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Figure 1 Zoomed mid-esophageal view on transesophageal echocardiography, showing an echodensity attached to the A2 segment of the anterior leaflet of the mitral valve (red arrow) with evidence of leaflet perforation in the A1 segment (blue arrow).



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Figure 2 Septic embolus in the brain. A: T2-weighted MRI brain showing a 1.0 cm × 0.5 cm ring enhancing lesion (blue arrow) in the right parietal lobe with central diffusion restriction and mild surrounding vasogenic edema; B: Repeat MRI brain with near complete resolution of the ring enhancing lesion. MRI: Magnetic resonance imaging.

cardiac defibrillator placement. Two patients had a recent gastrointestinal or genitourinary tract procedure. Three patients were immunocompromised, 2 of which were pregnant (Table 1). Seven of the 39 patients had no predisposing risk factors.

Presenting symptoms and signs: The most common presenting symptom was fever, reported in most patients (36 patients), followed by fatigue (25 patients). Seven patients had shortness of breath, and four reported weight loss. Twenty-eight of 39 patients also presented with one or more manifestations of septic emboli, including embolic stroke (20 patients), septic pulmonary embolism (4 patients), renal emboli (2 patients), and splenic infarct (3 patients). Cutaneous manifestations were noted including Janeway lesions (3 patients), splinter hemorrhages (4 patients), petechiae or purpura (2 patients), or Osler nodes (1 patient) (Table 1).

Valve involvement: Valvular regurgitation was by far the most common abnormality; reported in 28 patients. Of these, 14 had severe regurgitation, eight had moderate regurgitation, and two had mild regurgitation. Mitral regurgitation and stenosis were reported in one case, and mitral valve prolapse was reported in one case. The mitral valve was the most common valve to be affected; noted in 28 patients. Eight patients had aortic valve involvement. The tricuspid valve was affected in seven patients, and only one patient had pulmonary valve involvement (Table 1).

Echocardiography: TTE was the main diagnostic modality, utilized in 36 (90%) patients, followed by TEE for confirmation in 33 patients. Valvular vegetations were reported in 23 patients, with an

Table 1 Compares the characteristics of infective endocarditis caused by *Haemophilus parainfluenzae* in this systematic review with the review by Darras-Joly *et al*[58]

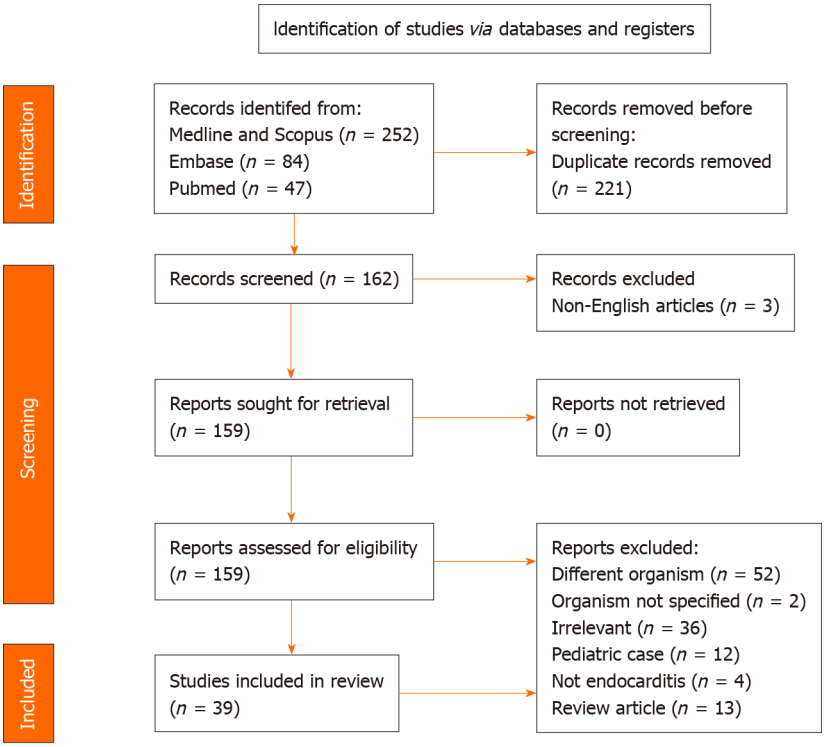
Characteristics		Present review, *n* (%)	Previous review, *n* (%)
Mean duration from sx to dx		18.9 (3-49) d	28.2 (5-80) d
Demographics	Age, yr (range)	39 (18-69)	43.9 (21-79)
	Male-to-female ratio	Approximately 1:1	Approximately 2:1
Predisposing risk factors	History of IE	4 (10)	1 (3.8)
	Valve disorder and/or replacement	10 (25)	18 (69.2)
	IVDU	8 (20)	1 (2.4)
	Poor dentition	4 (10)	NR
	Cardiac devices	5 (13)	4 (15.4)
	History of recent GI/GU procedure	2 (5)	NR
	Immunocompromised	3 (8)	3 (7.1)
Symptoms and signs	Fever	36 (90)	40 (95.2)
	Fatigue	24 (60)	NR
	Vegetations	24 (60)	19 (73.1)
	Abscesses	7 (17.5)	2 (7.7)
	Embolic events	29 (73)	15 (35.7)
	CNS	20 (50)	9 (21.4)
	Lungs	4 (10)	2 (4.8)
	Spleen	3 (7.5)	2 (4.8)
	Kidney	2 (5)	1 (2.4)
Valves affected	Mitral	29 (73)	19 (73)
	Aorta	8 (20)	8 (30.7)
	Tricuspid	7 (17.5)	1 (3.8)
	Pulmonic	1 (2.5)	0 (0)
	Multiple valves	6 (15)	3 (11.5)
Outcomes	Recovery with antibiotics and/or surgery	35 (88)	NR
	CHF	3 (8)	13 (30.9)
	Death	2 (5)	2 (4.8)

CHF: Congestive heart failure; dx: Diagnosis; GI: Gastrointestinal; GU: Genitourinary; IVDU: Intravenous drug use; IE: Infective endocarditis; sx: Symptoms; NR: Not reported.

estimated mean size of 1.9 cm. Cardiac abscesses were reported in 17.5%, but abscess size was reported in only one of the cases as 1.6 1.8 cm. The abscess locations included the aortic root, mitral–aortic intervalvular fibrosa, near a prosthetic aortic valve, left ventricular endocardium, and myocardium. Three patients developed a fistulous connection between the atrium and ventricle. Valvular perforation was reported in 2 cases.

Treatment: The majority (28 patients) were treated both medically and surgically. Nine patients underwent valve repair, while six underwent replacement. Two patients underwent pacemaker removal. Eleven patients had unspecified surgical intervention. Sixty-two percent of patients were treated with ceftriaxone. Ten percent received other antibiotics including levofloxacin, ciprofloxacin, gentamicin, cefotaxime and rifampin. The antibiotic therapy utilized in the remaining 28% of patients was not specified.

Outcome: Two patients reportedly developed congestive heart failure (CHF) and two patients died. The remaining 35 patients recovered adequately.



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Figure 3 PRISMA flow chart highlighting article search and selection.

DISCUSSION

HPI is a part of the oropharyngeal and genitourinary tract flora and has been implicated as a cause of opportunistic infections such as meningitis, IE, and septic arthritis[47]. It is a fastidious Gram-negative coccobacillus and belongs to the genus *Haemophilus* which consists of the *H. influenzae*, *H. parainfluenzae* and *H. ducreyi* groups[47]. They require beta-nicotinamide adenine dinucleotide (NAD) and/or heme to supplement *in vitro* growth[47]. An important differentiating feature of HPI is its ability to synthesize heme and hence does not require heme supplementation to grow[47].

The virulence of HPI is not well characterized[47,48]. In general, the *H. parainfluenzae* group has some degree of resistance to beta-lactam antibiotics, particularly penicillins[47,48]. Isolates have been identified that are multidrug resistant to tetracyclines, fluoroquinolones and macrolides[47]. The mechanisms behind this resistance are due to mutations in the penicillin-binding protein, Tet, DNA gyrase, topoisomerase, and 50s ribosomal protein genes[47,49]. The antibiotics with adequate minimum inhibitory concentration on HPI include levofloxacin, cefditoren, cefotaxime and cefpodoxime, although other antibiotics such as aminoglycosides and chloramphenicol may have adequate effect[50,51]. Culturing HPI involves addition of patients' blood samples to a brain–heart infusion with 5% beef extract broth, which is incubated at 37 °C for up to 14 d[52]. Gram-negative coccobacilli are identified *via* Gram stain and inoculated onto a peptone–protease agar[52]. Paper discs containing NAD and heme are applied to the agar which incubates overnight[52]. HPI is then identified based on its sole reliance on the presence of NAD for growth[52]. Additionally, the 16S rRNA polymerase chain reaction and mass spectrometry are reliable means of differentiating *Hemophilus* spp. and the HACEK organisms without culturing[18].

In our review, the majority of patients had at least one predisposing risk factor for IE, such as a history of IE, an underlying valve disorder, a prosthetic or mechanical valve or a cardiac device, poor dentition, recent dental procedure within 2 wk, IVDU, or an immunocompromised state (including use of steroids or pregnancy). This is important for clinicians to recognize, as eradication or control of the predisposing factor may help prevent recurrent HPI infection.

The average duration between symptom onset and diagnosis was 18.9 d, and surgical intervention (due to the presence of large vegetations ~2 cm) was required in most of the patients (69%). These features highlight the indolent course of HPI IE and signify the need for prompt diagnosis, which may reduce the need for surgical intervention. The resolution of IE with cephalosporin, aminoglycoside and fluoroquinolone antibiotics suggests that the majority of HPI bacteria in the past 20 years are not multidrug resistant.

The risk of embolic events in IE is common with *Staphylococcus aureus*, *Candida* spp., and HACEK organisms[51]. The reported incidence ranges between 28% and 66% for *S. aureus*, with central nervous

system (CNS) embolism being the most common[53,54]. In this review, ~70% of embolic complications were in the CNS. This is notable as previously, *Kingella* spp. appeared to have the highest rate of CNS embolism of all HACEK organisms, with a rate of 20%–30%[55]. Embolic events have been associated with worse prognosis in IE, with the risk proportional to vegetation size > 10 mm[53,54]. The indolent or subacute course of HPI IE may explain why the mortality remains lower compared to IE involving other organisms, despite significant vegetation size. The in-hospital mortality rates of *S. aureus* and *Streptococcus* spp. IE are 20%–30% and 11%, respectively[53,56]. The mortality rate of HPI IE in this review was 5%. Of the HACEK organisms that cause IE in adults, *Actinobacillus actinomycetemcomitans* (a member of the *Aggregatibacter* spp.) and *Cardiobacterium* spp. have the highest reported mortality rates of 18% and 10%, respectively[57,58]. While both are associated more with aortic valve endocarditis[57,58], HPI more commonly affects the mitral valve.

Our findings and the illustrative case show a temporal change in the epidemiology of HPI within 2000–2022. Compared to a review of 26 HPI endocarditis cases from 1984 to 1995 by Darras-Joly *et al* [58], this review reported a younger mean age, similar rate of infection in both genders, shorter time to diagnosis, higher association with IVDU, higher rate of embolic events, and tricuspid and pulmonic valve involvement. The rate of mitral valve involvement has remained steady over the past three decades, while there has been a decrease in the rate of aortic valve involvement. Valvular vegetation rates and CHF incidence have decreased, while the mortality rate remained similar (Table 1). These findings might indicate the improvement in the diagnosis and treatment of HPI over the past three decades. However, the increased involvement of right-sided valves suggests an increase in its virulence and an association with the rising rate of IVDU. Notably, the review by Darras-Joly *et al*[58] was not systematic because it was limited to cases in France. To the best of our knowledge, this is the first systematic review HPI IE to be published in the English language literature.

Our patient's presentation of subacute IE highlights the typical features of HPI IE. It is indolent, has a predilection for the mitral valve, and is commonly associated with septic emboli involving the CNS. However, multiple features were present suggesting HPI may be more virulent in the current era, including the patient's absence of risk factors, HPI induced leaflet perforation (which was not noted in our review), and valvular destruction requiring surgery.

Limitations

A noteworthy limitation of this review is that it did not account for unreported cases of HPI IE; therefore, we cannot ascertain an exact incidence and prevalence.

CONCLUSION

This systematic review of reported adult HPI IE cases spanning the last two decades highlights the subacute course of HPI IE, its preference for the mitral valve, and favorable prognosis compared to IE caused by the other HACEK organisms, *Staphylococcus*, and *Streptococcus*. Clinicians should be attentive to its indolent course and the presence of predisposing risk factors in order to allow for timely management.

ARTICLE HIGHLIGHTS

Research background

Existing data indicate that the incidence of infective endocarditis (IE) continues to rise steadily. Although components of the skin flora including *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. are the most implicated organisms particularly in virulent IE, the oropharyngeal flora including the HACEK group of are a significant cause of IE.

Research motivation

An interesting presentation of *Haemophilus parainfluenza* (HPI) IE in a 25-year-old man with no significant past medical history and no predisposing risk factor for IE was the basis for this systematic review. It aimed to determine if there have been temporal changes in the presentation and prognosis of IE caused by HPI over the past two decades.

Research objectives

To characterize the risk factors, signs and symptoms, echocardiographic findings and the prognosis of IE caused HPI.

Research methods

A search of Medline, Pubmed, Scopus and Embase was conducted to identify the cases of HPI IE

published in 2000–2022. A systematic review of these cases was performed to analyze the trends in the presentation and prognosis of HPI IE.

Research results

This systematic review of 39 HPI IE cases in the English literature highlights the slight male predominance of the disease, the nonspecific presentation with constitutional symptoms, the predilection for the mitral valve, a high rate of central nervous system embolic events and a lower mortality rate compared to IE caused by microbes of the skin flora.

Research conclusions

HPI IE is an indolent disease that requires a high index of suspicion to diagnose and is associated with a favorable prognosis with timely intervention.

Research perspectives

We have illustrated a case and conducted a two-decade systematic review of the HPI IE cases published in the English language literature. In doing so, we have highlighted its indolent course, presentation and prognosis. We have also compared our findings with those of a review of HPI IE cases between 1984 and 1995; in doing so, we have enumerated some temporal changes in this disease entity. These include a younger mean age of presentation, identical rate of infection between males and females, improvement in diagnosis, a higher rate of embolic events and an increasing association with intravenous drug use.

FOOTNOTES

Author contributions: Olagunju A and Mookadam F designed the research; Olagunju A, Kenny D, Martinez J, Gideon P, and Unzek S performed the research; Olagunju A, Kenny D and Mookadam F analyzed the data; Olagunju A, Kenny D, Martinez J and Mookadam F wrote the paper.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: 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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LETTER TO THE EDITOR

Is Takotsubo cardiomyopathy still looking for its own nosological identity?

Riccardo Scagliola, Gian Marco Rosa

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Abstract

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of myocardial infarction with non-obstructive coronary arteries. Further investigations are needed in order to define TCM with the most appropriate disease taxonomy.

Key Words: Takotsubo cardiomyopathy; Myocardial infarction with non-obstructive coronary arteries; Disease classification

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Core Tip: Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of myocardial infarction with non-obstructive coronary arteries. These issues need to be confirmed by further investigations, in order to define TCM with the most appropriate disease taxonomy.

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TO THE EDITOR

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Current revised Mayo Clinic diagnostic criteria for TCM include: (1) The presence of transient left ventricular wall motion abnormalities (either hypokinesis, akinesis or dyskinesis) with or without apical involvement; (2) usually extending beyond a single epicardial vascular distribution; (3) in the absence of obstructive coronary artery disease on coronary angiography; (4) associated with new electrocardiographic abnormalities or modest troponin increment; and (5) in the absence of pheochromocytoma or myocarditis[1]. Subsequently, the International Takotsubo Diagnostic Criteria (interTAK Diagnostic Criteria) provided the following additional criteria in order to improve the identification of TCM: (1) Cases with wall motion abnormalities related to the distribution of a single epicardial coronary artery should not be considered an exclusion criteria of TCM; (2) pheochromocytoma, as well as neurologic disorders (*i.e.* subarachnoid hemorrhage, ischemic stroke or transient ischemic attack) are recognized as secondary causes of TCM, and (3) the presence of coronary artery disease does not represent an exclusion criterion of TCM[2]. This latter additional finding and the contextual detection of obstructive epicardial coronary lesions make the distinction between acute coronary syndrome and TCM more challenging in clinical practice[3]. In this regard, whether TCM should be classified as a distinct subset of myocardial infarction with non-obstructive coronary arteries (MINOCA) is still controversial. In a comprehensive review by Vidal-Perez *et al*[3], TCM was included within the wide nosological spectrum of MINOCA. However, emerging clinical and pathophysiologic findings in the literature have progressively raised doubts concerning this current taxonomy. In a retrospective analysis conducted by Lopez-Pais *et al*[4] on a large multicenter registry, patients with TCM showed a different clinical profile compared to those belonging to the other subsets of MINOCA. Specifically, TCM was more frequently detected as an intercurrent complication during hospitalization for other causes, and was characterized by a much more aggressive acute phase and by a better long-term prognostic outcome, compared to patients affected by the other forms of MINOCA. Additionally, when present, some electrocardiographic findings can also help to distinguish between TCM and the other subsets of MINOCA. In particular, the absence of Q waves or reciprocal changes of ventricular repolarization, a ratio between ST-segment elevation in leads V_4-V_6 and V_1-V_3 > 1 and the presence of ST-segment depression in lead aVR in the absence of ST-segment elevation in lead V_1 have been reported to detect TCM with a high predictive accuracy[5,6]. Furthermore, different pathophysiological processes have been shown to be involved in developing reversible wall motion abnormalities which characterize TCM, compared to the rest of MINOCA subsets (Table 1). Although microvascular dysfunction has been hypothesized to be involved in the pathogenic mechanisms of TCM, it seems to represent a mere epiphenomenon compared to the catecholaminergic surge related to sympathetic hyperactivity, which is mediated by both the central and autonomic nervous system in response to psychophysical or environmental stressors[7]. Specifically, direct catecholamine toxicity and the effects of norepinephrine spillover from the cardiac sympathetic nerve terminals, have been shown to be the greatest responsible mechanisms of wall motion abnormalities detected in TCM, as demonstrated by the congruent distribution of cardiac nervous terminals to the affected segments of the myocardial wall[8]. This is reflected in a typical histopathological pattern called myocytolysis, which is characterized by areas of early myofibrillar damage, hypercontracted sarcomeres and a mononuclear inflammatory response. These histological features are distinct from those noted in the rest of patients with MINOCA (which were instead characterized by atonic myocytes, with no myofibrillar damage and polymorphonuclear infiltrates), and were not primarily induced by vasoconstriction, but by a direct effect of catecholamines on cardiac β-adrenergic receptors (like other conditions related to the catecholamine surge, as in the case of pheochromocytoma or subarachnoid hemorrhage)[9,10]. As reported by Santoro and coworkers, histologic findings confirm how TCM and acute coronary syndromes are sustained by two different inflammatory patterns. In particular, high levels of anti-inflammatory interleukins detected in TCM (particularly IFN-α and IFN-γ) have been shown to be related to the presence of M2 macrophages surrounding the impaired myocardial tissue, and to their capability in removing damaged cells and preserving healthy tissue, thus favoring a complete functional recovery in this subset population[11]. Finally, the presence of transient and reversible transmural myocardial edema involving the dysfunctional wall segments on T2-weighted imaging, in the absence of late gadolinium enhancement, represents a pathognomonic hallmark provided by cardiac magnetic resonance in TCM patients, compared to the rest of MINOCA subjects[12]. In conclusion, several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of MINOCA. These issues need to be confirmed by further investigations, in order to define TCM with the most appropriate disease taxonomy.

Table 1 Characterizing the differences between Takotsubo cardiomyopathy and myocardial infarction with non-obstructive coronary arteries

	Takotsubo cardiomyopathy	MINOCA
Clinical findings	A more aggressive acute phase despite a better long-term cardiovascular prognosis	A less aggressive acute phase despite a worse long-term cardiovascular prognosis
Main pathophysiologic mechanisms	Sympathetic hyperactivity and a direct effect of catecholamines on β-adrenergic receptors of cardiomyocytes	Coronary plaque disruption; Coronary vasospasm; Spontaneous coronary artery dissection; Microvascular dysfunction; Coronary thromboembolism
Histopathologic lesions	Areas of myofibrillar damage with hypercontracted sarcomeres and mononuclear infiltrates	Absence of myofibrillar damage with atonic sarcomeres and polymorphonuclear infiltrates
Location of myocardial lesions	Around intracardiac nervous terminals	Around cardiac vessels
Inflammatory patterns	Increased levels of anti-inflammatory interleukins, able to remove damaged cells and preserve healthy myocardial tissue	Increased levels of pro-inflammatory interleukins, able to promote coronary plaque disruption and microvascular impairment
CMR findings	Transient and reversible transmural myocardial edema on T2-weighted imaging in the absence of late gadolinium enhancement	Late gadolinium enhancement (either subendocardial or transmural) with or without myocardial edema on T2-weighted imaging

CMR: Cardiac magnetic resonance; MINOCA: Myocardial infarction with non-obstructive coronary arteries.

FOOTNOTES

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LETTER TO THE EDITOR

Euglycemic diabetic ketoacidosis: A rare but serious side effect of sodium-glucose co-transporter 2 inhibitors

Nenad Lakušić, Ivana Sopek Merkaš, Ana Marija Slišković, Dora Cerovec

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Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication and from recently established therapy in chronic heart failure patients. A rare, but potentially life-threatening complication of SGLT2 inhibitor use is euglycemic diabetic ketoacidosis. We described a case of a middle-aged male patient with type 2 diabetes who developed metabolic ketoacidosis after a few days of empagliflozin administration. SGLT2 inhibitor related ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. There are multiple possible risk factors and mechanism that might contribute to the pathogenesis of ketoacidosis. It is implied that SGLT2 inhibitor use and prescription by non-diabetologists (cardiologists, nephrologists, family physicians, *etc.*) will continue to grow in the future. It is important to inform the general cardiac public about this rare but serious side effect of SGLT2 inhibitors.

Key Words: Sodium-glucose co-transporter 2 inhibitors; Euglycemic diabetic ketoacidosis; Chronic heart failure

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Core Tip: Sodium-glucose co-transporter 2 inhibitors have recently become an established treatment for most chronic heart failure (CHF) patients (with and without diabetes), and it is important for the cardiologist to know their side effects, including those that are rare, but serious, like euglycemic ketoacidosis. In this way, an unwanted outcome of CHF treatment can be avoided.

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TO THE EDITOR

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication which decrease the reabsorption of glucose in the renal tubules, causing urinary glucose excretion and thereby modestly lowering elevated blood glucose levels in patients with type 2 diabetes. The SGLT2 receptors are expressed in the proximal tubule of the kidney and mediate reabsorption of 90% of the filtered glucose load. By their mechanism of action, SLGT2 inhibitors also modestly decrease blood pressure (osmotic diuresis) and weight (reduction in adipose tissue as well as calorie loss through glycosuria)[1].

According to the latest European Society of Cardiology guidelines on chronic heart failure (CHF)[2], SGLT2 inhibitors (empagliflozin, dapagliflozin) are equally used along with other established therapy for CHF. They can be used in patients with reduced, but also preserved (empagliflozin) ejection fraction of left ventricle, with or without diabetes[3]. The SGLT2 inhibitors achieve beneficial effects by lowering blood pressure, stimulation of natriuresis and diuresis, neurohormonal effect, improvement of cardiac energy metabolism, reduction in inflammation, *etc.*[4]. SGLT2 inhibitors improve cardiovascular outcomes and have a similar effect as a group of drugs in preventing HF and chronic kidney disease progression (class effect), efficacy in secondary prevention of atherosclerotic cardiovascular disease events (empagliflozin and canagliflozin) and in preventing cardiovascular mortality (empagliflozin)[5].

Euglycemic diabetic ketoacidosis[6] is a known and rare complication of SGLT2 inhibitor use and can potentially lead to a life-threatening situation, especially if not recognized in time[7]. Shortly, we would like to describe a case of middle-aged male patient with type 2 diabetes, without CHF, who developed metabolic ketoacidosis after a few days of empagliflozin administration.

The patient is a 42-year-old male with a history of type 2 diabetes treated with metformin for three years, which he took very irregularly. One week before hospitalization, he was administered the combination of empagliflozin 12.5 mg/metformin 1000 mg twice daily. Two days after starting the medication he reported nausea and diarrhea, then vomiting with a feeling of fatigue and malaise. Diabetic ketoacidosis (ketonuria 8 mmol/L, arterial blood gas (ABG) analysis-pH 7.23, glucose 9.7 mmol/L) was diagnosed and the patient was urgently hospitalized. Parameters of renal function and serum kalium level were within referent range. Metabolic acidosis was successfully managed after two days of standard treatment (prompt fluid resuscitation with crystalloid solutions and monitoring of electrolyte and ketones, low-dose intravenous insulin) and omission of empagliflozin from further therapy. On the third day of treatment, the patient was discharged from the hospital with new recommended therapy-basal and fast-acting insulin and metformin.

Diabetic ketoacidosis is a complex metabolic disorder characterized by hyperglycemia, acidosis, and ketonuria, which usually develops in patients with diabetes when insulin levels are too low (absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones, *i.e.*, glucagon, cortisol, *etc.*). In the absence of insulin, lipolysis is stimulated instead of glycogenolysis for energy production, consequently increasing ketone levels followed by their accumulation in the blood leading to acidosis. Diabetic ketoacidosis most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood glucose levels[8]. Increased risk of ketoacidosis was described among SGLT2 patients and several mechanisms might contribute to the pathogenesis-SGLT2 inhibitors decrease glucose level by an insulin-independent mechanism, increase the rates of lipolysis in adipose tissue and ketogenesis in the liver (increasing circulating ketone body levels), increase plasma glucagon levels, increase preproglucagon gene expression by acting directly upon pancreatic α-cells, and also SGLT2 inhibitors could decrease renal clearance of ketone bodies (*e.g.*, phlorizin-a nonselective inhibitor of SGLT1 and SGLT2, which increase renal tubular reabsorption of acetoacetate), *etc*[9]. Ketone body levels are elevated in patients receiving SGLT2 inhibitor treatment (and in patients with HF) so it is important to emphasize that failing myocardium in diabetic heart and in HF patients is unable to optimally use traditional substrates (free fatty acid, glucose) but can effectively use ketone bodies as an alternative for energy production. Changes that may include critical effects of SGLT2 inhibitors are those in shifting metabolism from fat/glucose oxidation to ketone bodies and thereby improving

myocardial and renal function[10].

The incidence of ketoacidosis in patients using SGLT2 inhibitors is about 2 per 1000 treated patients [11]. It is important to emphasize that SGLT2 inhibitor–associated ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. Some of the risk factors for developing ketoacidosis in patients treated with SGLT2 inhibitors are prior diabetic ketoacidosis, hemoglobin A1C above 10%, recent hypoglycemia, low baseline serum bicarbonate levels, use of digoxin and medications for dementia[11] or concomitant therapy with pioglitazone[12]. Given that thiazolidinediones, including pioglitazone, can cause fluid retention, as such are contraindicated in patients with NYHA class III and IV heart failure, and are not recommended in patients with symptomatic heart failure[2].

Patients with CHF are a complex group of patients with numerous comorbidities that require specific and differentiated treatment and close monitoring[13]. Since SGLT2 inhibitors have recently become an established treatment for most CHF patients with and without diabetes[2], and their use and prescription by non-diabetologists (cardiologists, nephrologists, and family physicians, *etc*.) will continue to grow in the future. Indeed, there are recommendations and suggestions that SGLT2 inhibitors and beta-blockers might be the first line of treatment for patients with CHF with reduced ejection fraction of left ventricle[14].

Therefore, the main purpose of this letter is to inform and warn the general cardiac public about this rare but serious side effect of SGLT2 inhibitors. In case of nausea, vomiting, or malaise in patients taking SGLT2 inhibitors, prompt response and diagnostic screening are necessary. Serum ketones and ABG analysis should be obtained in any patient presenting these symptoms, and SGLT2 inhibitors should be discontinued if acidosis is confirmed. In this way, serious side effects and an unwanted outcome of CHF treatment can be avoided.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk stratification of patients who present with chest pain and have normal troponins using a machine learning model

Muhammad Shafiq, Diego Robles Mazzotti, Cheryl Gibson

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Abstract

BACKGROUND

Risk stratification tools exist for patients presenting with chest pain to the emergency room and have achieved the recommended negative predictive value (NPV) of 99%. However, due to low positive predictive value (PPV), current stratification tools result in unwarranted investigations such as serial laboratory tests and cardiac stress tests (CSTs).

AIM

To create a machine learning model (MLM) for risk stratification of chest pain with a better PPV.

METHODS

This retrospective cohort study used de-identified hospital data from January 2016 until November 2021. Inclusion criteria were patients aged > 21 years who presented to the ER, had at least two serum troponins measured, were subsequently admitted to the hospital, and had a CST within 4 d of presentation. Exclusion criteria were elevated troponin value (> 0.05 ng/mL) and missing values for body mass index. The primary outcome was abnormal CST. Demographics, coronary artery disease (CAD) history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking were evaluated as potential risk factors for abnormal CST. Patients were also categorized into a high-risk group (CAD history or more than two risk factors) and a low-risk group (all other patients) for comparison. Bivariate analysis was performed using a χ^2 test or Fisher's exact test. Age was compared by *t* test. Binomial regression (BR), random forest, and XGBoost MLMs were used for

prediction. Bootstrapping was used for the internal validation of prediction models. BR was also used for inference. Alpha criterion was set at 0.05 for all statistical tests. R software was used for statistical analysis.

RESULTS

The final cohort of the study included 2328 patients, of which 245 (10.52%) patients had abnormal CST. When adjusted for covariates in the BR model, male sex [risk ratio (RR) = 1.52, 95% confidence interval (CI): 1.2-1.94, $P < 0.001$)], CAD history (RR = 4.46, 95%CI: 3.08-6.72, $P < 0.001$), and hyperlipidemia (RR = 3.87, 95%CI: 2.12-8.12, $P < 0.001$) remained statistically significant. Incidence of abnormal CST was 12.2% in the high-risk group and 2.3% in the low-risk group (RR = 5.31, 95%CI: 2.75-10.24, $P < 0.001$). The XGBoost model had the best PPV of 24.33%, with an NPV of 91.34% for abnormal CST.

CONCLUSION

The XGBoost MLM achieved a PPV of 24.33% for an abnormal CST, which is better than current stratification tools (13.00%-17.50%). This highlights the beneficial potential of MLMs in clinical decision-making.

Key Words: Machine learning; Chest pain; Risk stratification; Risk factors; Cardiac stress test; Cardiac catheterization

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Core Tip: For patients with chest pain, current stratification tools result in unwarranted investigations due to low (13.0%-17.5%) positive predictive values (PPVs). This retrospective cohort study aimed to create a machine learning model (MLM) for risk stratification of patients with chest pain with a better PPV. Demographics, coronary artery disease history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking were the covariates. The XGBoost MLM achieved a PPV of 24.33% for an abnormal cardiac stress test, which is better than current stratification tools. This model highlights the potential use of MLMs in clinical decision-making.

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INTRODUCTION

The annual cost of cardiovascular disease and stroke has been estimated to be more than $200 billion in the United States[1]. Chest pain, in particular, led to over 40 million hospital visits from 2006-2016 and had an associated cost of $6.2 billion from 2014-2016[2]. For each hospital admission, the average cost has been reported to be $11700 per patient in the United States[3]. This cost represents a significant burden on the patients and the healthcare system and emphasizes the need for a better stratification tool to safely identify patients who present with chest pain for early discharge without unnecessary testing.

Patients who present with chest pain are considered to be low risk if their probability of a major adverse cardiac event is < 1%, according to clinical practice guidelines of the American College of Cardiology and American Heart Association[4]. The two most widely used stratification tools that calculate the probability of major adverse cardiac event include the history, electrocardiogram (ECG), age, risk factors, and initial troponin pathway accelerated diagnostic protocol (HEART pathway-ADP) and the emergency department assessment of chest pain score (EDACS)-ADP[5-8]. The HEART pathway-ADP and EDACS-ADP have demonstrated excellent sensitivity and a negative predictive value (NPV) of 99%, as recommended by the American College of Cardiology and the American Heart Association[5-8]. However, both the HEART pathway-ADP and EDACS-ADP have low positive predictive values (PPVs) of 13.0% and 17.5%, respectively[7,9]. This low PPV leads to unnecessary additional testing, such as serial laboratory tests and cardiac stress tests (CSTs). Furthermore, the main focus of these two stratification tools has been the 30-d outcome of acute myocardial infarction (AMI) and all-cause mortality.

Many medical devices are already using artificial intelligence and machine learning algorithms[10]. However, these domains are underutilized in clinical decision-making despite their huge potential. The National COVID Cohort Collaborative facilitated the creation of machine learning models (MLMs) for

accurate prediction of coronavirus disease 2019 severity with proven efficacy[11]. The same concept of machine learning can be applied to patients who present with chest pain in the emergency room (ER), and the use of patient data points (such as demographics and risk factors) can build predictive models with better specificity and PPV.

Stewart *et al*[12] reported in a recent systematic review of 23 studies that MLM outperformed traditional risk stratification scores for chest pain. Although the outcome varied among the included studies, data and the specifics of the MLMs, such as hyperparameters, were not shared, which complicates replication and validation[12]. Most recently, Doudesis *et al*[13] published the myocardial-ischemic-injury-index (MI^3) algorithm with high PPV (70.4%) and NPV (99.8%) for myocardial infarction. They have not provided the specifics of their MLM either.

The HEART pathway-ADP, the EDACS-ADP, and other recently developed MLMs include both normal and abnormal troponin levels in their stratification[7,8,12,14,15]. However, risk stratification is more challenging when the troponin level is normal. In addition, the HEART pathway-ADP and the EDACS-ADP do not address the risk of non-obstructive coronary artery disease (CAD) or the risk of AMI over an extended period of time (over a year). Lastly, recently developed MLMs claim to have better stratification, but essential information about their models have not been shared, limiting the potential for reproducibility. Given these challenges to risk stratification among patients with chest pain and the need to improve patient outcomes and reduce unnecessary healthcare costs, we hypothesized that an MLM could be created to better predict abnormal CST among patients who present with chest pain and have normal troponin values. CST can identify wide spectrum of CAD, including non-obstructive CAD, and it provides risk assessment for 1 year rather than just 30 d. Due to the current enhanced computing capabilities, MLMs have the potential to achieve better PPV and lower false-positive rates, which can reduce unnecessary testing. MLMs can gain the reproducibility needed to build trust through data sharing and transparency, which can further improve risk stratification and deliver the most cost-effective healthcare.

This study aimed to create an MLM that can use patient characteristics to provide risk stratification for further clinical intervention for patients who present with chest pain and have normal troponin values. The hypothesis of this study was that patient characteristics can be used to create MLMs for risk stratification for patients who present to the ER with chest pain and have normal troponin values with a PPV of 25% or more and an NPV of at least 99%.

MATERIALS AND METHODS

Study design

This study used a retrospective cohort design involving de-identified data available in the i2b2 common data model repository of the University of Kansas Medical Center. Database queries for patients observed in the health system between January of 2016 and November of 2021 were conducted using Healthcare Enterprise Repository for Ontological Narration, a search discovery tool that allows cohort building for observational research using de-identified data[16,17]. Institutional Review Board approval was not required because the data was de-identified. Identification and/or definitions of computable phenotypes used in this study are provided in the Supplementary material.

Selection criteria

Inclusion criteria: All patients aged 21 years or older who presented to the ER, had their first troponin test carried out within the first 6 h of arrival to the ER and at least one troponin test completed after 6 h, were subsequently admitted to the hospital, and had a nuclear CST carried out within 4 d of presentation to the ER were included in the study.

Exclusion criteria: Patients with elevated troponin levels (> 0.05 ng/mL) and those with missing body mass index values were excluded. Patients with elevated troponin levels are considered high risk, and hospital admission with further clinical intervention is more appropriate for this class of patients. Without body mass index data, obesity could not be defined as one of the risk factors/covariates in this study.

Risk stratification

CAD history, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, obesity, and smoking history were the risk factors included in this study. For comparison, patients included in the final cohort were also categorized into a high-risk group (CAD history or > 2 risk factors) and a low-risk group (no prior CAD history and ≤ 2 risk factors).

Encounters

Only the first encounter was included in the study for patients with more than one ER encounter that met the above inclusion and exclusion criteria.

Outcome

The outcome of the study was the incidence of abnormal CST. Abnormal CST was defined as CST followed by cardiac catheterization and/or coronary artery bypass graft within 30 d. Cardiac catheterization and coronary artery bypass graft were used as a surrogate to identify abnormal CST in this study.

Statistical analysis

Bivariate analysis: Except for age, the association between the incidence of abnormal CST and sex, race, and risk factors was assessed by χ^2 test or Fisher's exact test. High-risk and low-risk groups were also compared using a χ^2 test, and the risk ratio was calculated. Age was compared by t test. Alpha criterion was set at 0.05.

Binomial regression: Binomial regression (BR) was used to adjust for confounding factors and infer the degree of association between the risk factors and the outcome. All BR assumptions were assessed, including assumptions of no multi-collinearity and no outliers. To ensure model adequacy, Hosmer-Lemeshow goodness-of-fit test was also performed. Alpha criterion both for BR as well as Hosmer-Lemeshow goodness-of-fit test was set at 0.05.

MLMs: BR was also used for prediction, and it used the same predictor variables as for inference. Besides BR, the random forest and XGBoost MLMs were also used. In the random forest MLM, proximity and importance were set as "True". In order to minimize overfitting, the number of trees was set at 25 in training and testing. In the XGBoost MLM, hyperparameters were set as: Booster = "gbtree"; objective = "binary:logistic"; eval_metric = "auc"; eta = 0.1; max.depth = 10; gamma = 0; min_child_weight = 1; and colsample_bytree = 1. In order to minimize overfitting, 25 rounds were used in the XGBoost MLM.

Bootstrapping with replacement was used for internal validation of all the above models. Data were randomly split into training (75%) and testing (25%) during each iteration of bootstrapping. The model with training data was first fitted, and then testing data were applied to assess internal validation during each iteration of bootstrapping. Finally, the results were averaged. In order to produce more precise estimates, 500 iterations were used in bootstrapping for all models, and 95% confidence intervals (CIs) were created. Prediction cutoff values were calibrated manually, and the value with the best metrics (sensitivity, specificity, PPV, and NPV) was then selected for each model. All statistical analyses were performed using R software (version 4.1.2).

RESULTS

The final cohort sample included 2328 unique patients, of which 245 (10.52%) patients had abnormal CST requiring cardiac catheterization and/or coronary artery bypass graft (Figure 1). There were 196 duplicate encounters, which were removed, and only the patient's first encounter was included in the study. The basic demographic characteristics of the patients are presented in Table 1. Male sex and Caucasian race were significantly associated with the incidence of abnormal CST.

In the bivariate analysis, obesity was not significantly associated with abnormal CST. Smoking history was significantly associated with abnormal CST, but the association was weak. As shown in Table 2, all other risk factors were significantly associated with abnormal CST. High-risk patients were found to have a risk ratio of 5.31 (95%CI: 2.75-10.24) for abnormal CST when compared to low-risk patients (Table 3).

Age, race, and obesity were removed from the final BR model because they were not statistically significant, did not have any confounding relationship with other covariates, and their contribution to the prediction was not significant. These three covariates together resulted in an increased area under the receiver operating characteristic curve (AUC) by only 1.35%. The final model met all assumptions of BR, including the assumption of no multi-collinearity and no outliers, and appeared to fit the data adequately (Hosmer-Lemeshow goodness-of-fit test, P = 0.9). Only male sex, CAD history, and hyperlipidemia were statistically significant when adjusted for covariates in the final BR model. Covariates that were included in the final BR model and their estimated risk ratios are shown in Table 4.

Prediction models

BR: The same covariates used for inference in the BR model were also used for prediction. These covariates included sex, CAD history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and smoking history. First, all data were used together, which yielded an AUC of 74.51% (Figure 2A). The internal validation of the BR model yielded similar results (Figure 2B). A prediction cutoff value of 0.2 provided a sensitivity of 45.06%, specificity of 80.46%, a PPV of 21.34%, and an NPV of 92.55%.

Random forest: In the random forest model, all covariates were included. This model showed a much

Table 1 Demographics

Characteristics	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Degree of association (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
Age, mean ± SD	63.02 ± 11.67	61.99 ± 12.46	Mean different: 1.03 (-0.53, 2.59)	0.200
Sex male	153 (62.4%)	965 (46.3%)	RR: 1.8 (1.41, 2.30)	< 0.001
Race				
Caucasian	163 (66.5%)	1182 (56.7%)	RR: 1.8 (1.08, 3.00)	0.020 (combined)
African American	65 (26.5%)	650 (31.2%)	RR: 1.35 (0.79, 2.32)	
Asian	2 (0.8%)	43 (2.1%)	RR: 0.66 (0.16, 2.79)	
Other	15 (6.1%)	208 (10.0%)	Reference	

CABG: Coronary artery bypass graft; CI: Confidence interval; RR: Risk ratio; SD: Standard deviation.

Table 2 Bivariate analysis of the risk factors

Risk factors	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Risk ratio (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
CAD history, yes	216 (88.2%)	1063 (51.0%)	6.11 (4.18, 8.92)	< 0.001
Obesity, yes	136 (55.5%)	1121 (53.8%)	1.06 (0.84, 1.35)	0.620
Diabetes mellitus, yes	112 (45.7%)	760 (36.5%)	1.41 (1.11, 1.78)	0.005
Hypertension, yes	232 (94.7%)	1783 (85.6%)	2.77 (1.61, 4.78)	< 0.001
Hyperlipidemia, yes	236 (96.3%)	1602 (76.9%)	6.99 (3.62, 13.50)	< 0.001
CKD history, yes	88 (35.9%)	540 (25.9%)	1.52 (1.19, 1.94)	< 0.001
Smoking history, yes	153 (62.4%)	1133 (54.4%)	1.35 (1.05, 1.72)	0.020

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; CI: Confidence interval; CKD: Chronic kidney disease.

Table 3 Comparison between the high-risk group and the low-risk group

Risk category	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Risk ratio (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
High risk	236 (96.3%)	1700 (81.61%)	5.31 (2.75, 10.24)	< 0.001
Low risk	9 (3.7%)	383 (18.39%)		

CABG: Coronary artery bypass graft; CI: Confidence interval.

better fit for all data combined (Figure 2C). During internal validation of the random forest model, the AUC dropped significantly (Figure 2D). A prediction cutoff value of 0.18 provided a sensitivity of 13.92%, specificity of 93.66%, a PPV of 20.55%, and an NPV of 90.24 % for the random forest model.

XGBoost: All covariates were used in the XGBoost model. It provided a better AUC for all data combined compared to BR (Figure 2E). Like the random forest model, the AUC dropped significantly during internal validation of the XGBoost model (Figure 2F). A prediction cutoff value of 0.27 was used for the XGBoost model, and it yielded a sensitivity of 30.54%, specificity of 88.51%, a PPV of 24.33%, and an NPV of 91.34%. A comparison of the three models is presented in Table 5.

Table 4 Adjustment of risk factors association with the abnormal cardiac stress test *via* binomial regression

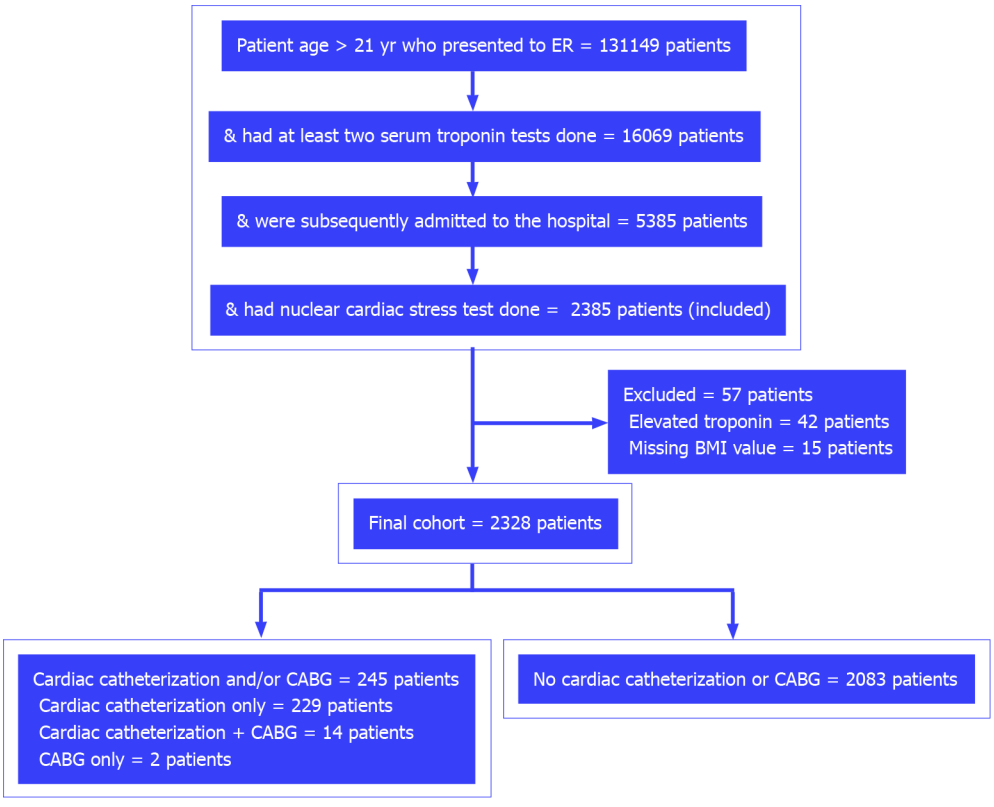
Covariate	Risk ratio	95%CI	*P* value
Sex, male	1.52	1.2, 1.94	< 0.001
CAD history, yes	4.46	3.08, 6.72	< 0.001
Hypertension, yes	1.35	0.82, 2.44	0.280
Hyperlipidemia, yes	3.87	2.12, 8.12	< 0.001
Diabetes mellitus, yes	1.06	0.83, 1.34	0.650
CKD history, yes	1.02	0.80, 1.30	0.860
Smoking history, yes	1.06	0.84, 1.35	0.620

CAD: Coronary artery disease; CI: Confidence interval; CKD: Chronic kidney disease.

Table 5 Comparison of the models for the prediction of an abnormal cardiac stress test

Feature	BR	RF	XGBoost
Prediction cutoff value	0.20	0.18	0.27
Sensitivity (95%CI)	45.06 (44.23, 45.88)	13.92 (13.50, 14.33)	30.54 (29.30, 31.79)
Specificity (95%CI)	80.46 (80.14, 80.79)	93.66 (93.53, 93.80)	88.51 (88.15, 88.86)
PPV (95%CI)	21.34 (21.09, 21.60)	20.55 (20.05, 21.04)	24.33 (23.46, 25.20)
NPV (95%CI)	92.55 (92.42, 92.69)	90.24 (90.14, 90.35)	91.34 (91.12, 91.56)

BR: Binomial regression; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; RF: Random forest.



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Figure 1 Flowchart of the cohort selection. BMI: Body mass index; CABG: Coronary artery bypass graft; ER: Emergency room.

DISCUSSION

This study found statistically significant associations between abnormal CST and several factors, including male sex, CAD history, and hyperlipidemia, among patients with chest pain who presented to the hospital, had normal troponin tests, and completed a CST. The incidence rate of abnormal CST among low-risk patients was only 2.30%, while it was 12.19% among high-risk patients. NPV for all MLMs in this study did not reach the recommended value of 99%. However, the XGBoost MLM in this study provided a much better PPV of 24.33%.

Both the HEART pathway-ADP and EDACS-ADP have excellent sensitivity and NPV (99%), but the PPV (13.0% and 17.5%, respectively) is considerably low. This likely leads to unnecessary clinical intervention[7,8]. Despite the retrospective nature and limited explanatory variables in modeling in this study, the XGBoost MLM resulted in an increased PPV (24.33%). Patients who had CAD with the need for revascularization and who did not follow up within 30 d could not be identified in the HEART pathway-ADP and EDACS-ADP studies. Likewise, further clinical intervention was not completed for low-risk patients, who were subsequently discharged in the HEART pathway-ADP and EDACS-ADP studies. Therefore, no objective data exists to suggest that those discharged patients did not have CAD (such as non-obstructive CAD). Nevertheless, in our study, nuclear CST was part of the inclusion criteria to ensure there was objective data on CAD for all patients. Therefore, the inclusion criteria were stricter for our study.

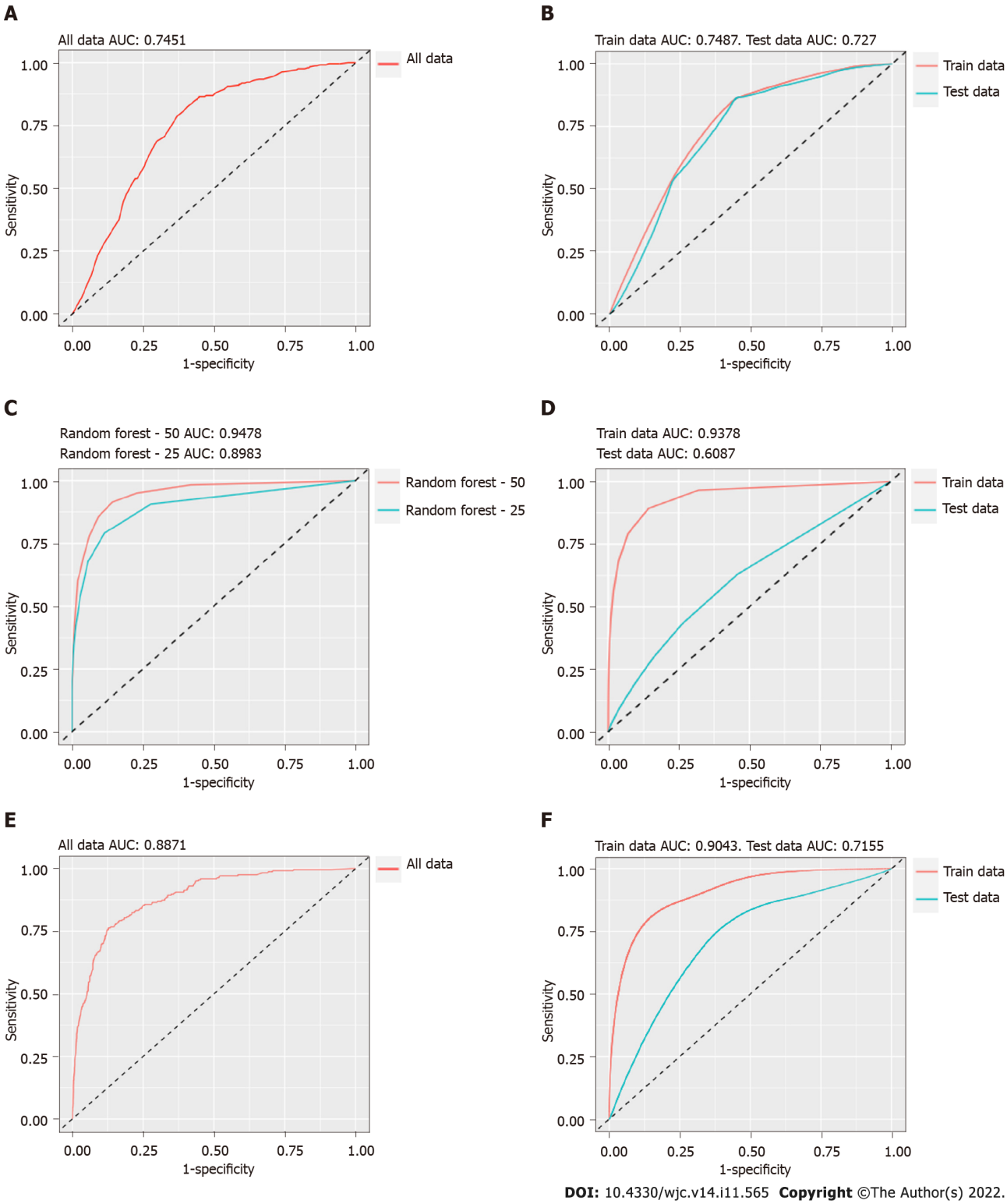
In the HEART pathway-ADP and EDACS-ADP, ECG and all troponin tests (normal and abnormal) were predictor variables[7,8]. If a patient has elevated troponin values, then the resulting clinical decision is to recommend further clinical intervention the majority of the time. However, it is challenging to identify patients who have normal troponin values and need further clinical intervention. This study undertook the challenge of including only patients with normal troponin values, which is another reason that the selection criteria for this study cohort was restricted. However, it mirrors real-life clinical practice and the challenges that come with it. ECG was not included in this study and is a significant limitation. Since it was a retrospective study based on de-identified data, access to actual ECG data was not possible. Machine readings of the ECG are available. However, due to the poor PPV of machine readings for abnormal findings on ECG, machine readings were not included[18,19]. Incorporating incorrect interpretations of ECG machine readings could have resulted in erroneous results and conclusions.

There has been increased interest in using MLMs and artificial intelligence in clinical decision-making in the past 8-10 years[12,14,15]. For patients who presented with chest pain to the ER, Stewart *et al*[12] conducted a systematic review of 23 studies that used MLMs to stratify these patients. There is significant heterogeneity in the studies included in this systematic review with differences noted in study design, type of MLM used, selected outcomes, comparisons made, data sharing, and validation. Despite the limitations, Stewart *et al*[12] reported that MLMs outperformed traditional risk stratification scores. Using high-sensitivity serum troponins, Doudesis *et al*[13] recently developed the MI^3 using gradient boosting MLM with sex, age, serial serum troponin concentrations, and the time interval between the serum troponin sampling as their parameters. This model also included both normal and abnormal troponin assays. MI^3 has reported a PPV of 70.4% for myocardial infarction if the MI^3 score was > 49.6 and an NPV of 99.8% if the MI^3 score was < 1.6. The specifics of their gradient boosting MLM have not been shared.

Zhang *et al*[14] conducted a study using MLMs for chest pain stratification, which shares some similarities in methodology to our study. The retrospective arm of their study was based on data from the electronic medical records. They excluded patients who had no follow-up data and did not include ECG for technical reasons (with no further explanation). The main differences in the study by Zhang *et al*[14] and our study included different outcomes (30-d AMI and all-cause mortality *vs* abnormal CST, respectively), different number of explanatory variables (14 *vs* 10, respectively), troponin values (all values *vs* only normal values, respectively), and the use of different MLMs.

Zhang *et al*[14] reported a robust sensitivity, specificity, and PPV of 92.90%, 88.50%, and 90.80%, respectively, for the 30-d risk of AMI during internal validation[14]. They observed similar sensitivity, specificity, and PPV for 30-d risk of all-cause mortality (77.50%, 99.99%, and 90.80%, respectively)[14]. This represents one of the best models for risk stratification of patients who present to the ER with chest pain. In comparison, our study had a small sample size, used fewer explanatory variables, and included only normal troponins values, which likely led to lower predictive performance. Despite the robust performance of their MLM, Zhang *et al*[14] have not shared the MLM specifications in order to reproduce and externally validate their model. The heterogeneity of MLMs, lack of data sharing, and current lack of external validation are the major obstacles to widespread adoption of MLMs for risk stratification for patients presenting with chest pain.

Digitization of health records and exceptional computing power have enabled the use of artificial intelligence and MLMs in medicine. Taking advantage of these resources, our study created an MLM and is the first study to our knowledge that used an MLM for risk stratification of abnormal CST. Since abnormal CST can be used as a surrogate for the entire spectrum of CAD, this study promotes the idea that MLMs can be used to risk stratify for all CAD spectrums.



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Figure 2 Receiver operating characteristic curve. A: The binomial regression (BR) model; B: The interval validation of the BR model; C: The random forest models with 25 trees and 50 trees; D: The internal validation of the random forest model; E: The XGBoost model; F: The internal validation of the XGBoost model. AUC: Area under the receiver operating characteristic curve.

There are limitations to this study. First, ECG was not included in the study. ECG can improve both the PPV and NPV. Second, given the clear definitions of the computable phenotypes, the probability of missing a true risk factor or outcome is very low, but it is not zero. Third, we included only ten explanatory variables in this study, which is likely one of the reasons for lower NPV. Similar MLM studies with better predictive performance have incorporated 14 or more explanatory variables. Lastly, this study was a retrospective single-center study. Future studies replicating this study will strengthen the external validity of the current findings.

CONCLUSION

The current study achieved a better PPV for the entire spectrum of CAD (not just AMI) compared to the currently used risk stratification tools. These results highlight the potential of using MLMs in clinical decision-making. The results of this study also advanced the idea that a well-designed prospective study, which incorporates ECG and ensures proper follow-up, can achieve a much better PPV than currently used stratification tools (*i.e.*, the HEART pathway-ADP and the EDACS-ADP) while simultaneously maintaining an NPV of 99% for chest pain presentation to the ER. Data sharing and external validation of these prospective trials will be crucial to the recognition and adoption of MLMs.

ARTICLE HIGHLIGHTS

Research background

Risk stratification tools exist for patients presenting with chest pain to the emergency room and have achieved the recommended negative predictive value (NPV) of 99%. However, the current stratification tools result in unnecessary clinical interventions due to a low positive predictive value (PPV).

Research motivation

Healthcare costs are astronomical in the United States, including for patients who present with chest pain. These costs emphasize the need for a better stratification tool to safely identify patients who present with chest pain for early discharge without unnecessary testing.

Research objectives

This study aimed to create a machine learning model (MLM) for risk stratification of chest pain patients with a better PPV while maintaining an NPV of 99%.

Research methods

This retrospective cohort study used demographics, coronary artery disease history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking as the covariates for the prediction of an abnormal cardiac stress test (CST). Binomial regression (BR), random forest, and XGBoost MLMs were used for prediction. Bootstrapping was used for the internal validation of the prediction models.

Research results

The XGBoost MLM had the best PPV of 24.33%, with an NPV of 91.34% for abnormal CST. The BR MLM had a PPV of 21.34% and an NPV of 92.55%. The random forest MLM had a PPV of 20.55% and an NPV of 90.24%.

Research conclusions

The XGBoost MLM provided a better PPV than currently used stratification tools (24.33% *vs* 13.00%-17.50%). Though the NPV from the XGBoost MLM remained lower than the recommended value of 99%, it highlights the potential use of MLMs in clinical decision-making.

Research perspectives

Data sharing and external validation of the MLMs will be crucial for their recognition and widespread adoption.

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FOOTNOTES

Author contributions: Shafiq M was involved in all aspects of this study, including but not limited to study design, data collection, data analyses, and writing of the abstract and manuscript; Mazzotti DR was involved in study design, data collection, and data analyses; Gibson CA assisted in writing the abstract and manuscript.

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ORIGINAL ARTICLE

Observational Study

Time trends in antithrombotic therapy prescription patterns: Real-world monocentric study in hospitalized patients with atrial fibrillation

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Abstract

BACKGROUND

Since 2010, the European Society of Cardiology has extended prescription criteria for oral antithrombotic therapy (OAT) in atrial fibrillation (AF). Direct oral anticoagulants (DOACs) were upgraded from an IIAa recommendation in 2012 to an IA in 2016. In real-world scenarios, however, OAC prescription is still suboptimal, mainly for DOACs.

AIM

To evaluate OAT temporal prescription patterns in a cohort of patients hospitalized with AF in a Cardiology Department.

METHODS

A retrospective observational study was conducted on a cohort of hospitalized patients in a secondary setting (Trapani, Italy) from 2010 to 2021 with AF as the

main or secondary diagnosis. For 4089 consecutive patients, the variables extracted from the Cardiology department database were: Sex, age, time of hospitalization, antithrombotic therapy (warfarin, acenocoumarol, apixaban, dabigatran, edoxaban, rivaroxaban, aspirin, clopidogrel, other antiplatelet agents, low molecular weight heparin, and fondaparinux), diagnosis at discharge and used resources. Basal features are presented as percentage values for categorized variables and as mean +/- SD for categorized once.

RESULTS

From January 1st, 2010 to October 6th, 2021, 25132 patients were hospitalized in our department; 4089 (16.27%, mean age 75.59+/-10.82) were discharged with AF diagnosis; of them, 2245 were males (54.81%, mean age 73.56+/-11.45) and 1851 females (45.19%, mean age 78.06+/-9.47). Average length of stay was 5.76+/-4.88 days; 154 patients died and 88 were moved to other Departments/Structures. AF was the main diagnosis in 899 patients (21.94%). The most frequent main diagnosis in patients with AF was acute myocardial infarction (1973 discharges, 48.19%). The most frequent secondary cardiac diagnosis was chronic coronary syndrome (1864 discharges, 45.51%), and the most frequent secondary associated condition was arterial hypertension (1010 discharges, 24.66%). For the analysis of antithrombotic treatments, the final sample included 3067 patients, after excluding in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications for prescribed treatments. OAC treatment increased significantly (35.63% in 2010-2012 *vs* 61.18% in 2019-2021, +25.55%, $P < 0.0001$), in spite of any antiplatelet agent use. This rise was due to increasing use of DOACs, with or without antiplatelet agents, from 3.04% in 2013-2015 to 50.06% in 2019-2021 (+47.02%, $P < 0.0001$) and was greater for factor Xa inhibitors, especially apixaban. In addition, treatment with a vitamin K antagonist, in spite of any antiplatelet agent use, decreased from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$), as well as any antiplatelet therapy, alone or in double combination, (49.18% in 2010-2012 *vs* 34.18% in 2019-2021, -15.00%, $P < 0.0001$); and patients not receiving antithrombotic therapy declined with time (14.58% in 2010-2012 *vs* 1.97% in 2021, $P < 0.0001$).

CONCLUSION

Real-world patients with AF are elderly and affected by cardiovascular and non-cardiovascular diseases. The percentage of patients on OAT and DOACs increased. These data suggest a slow, gradual guidelines implementation process.

Key Words: Atrial fibrillation; Antithrombotic agents; Time series; Warfarin; Direct-acting oral anticoagulants; Aspirin

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Core Tip: In this study, the proportion of patients on oral antithrombotic therapy, with or without an antiplatelet agent, increased significantly from 2010 to 2021. This rise was due to increasing use of direct oral anticoagulants, with or without antiplatelet agents. At the same time, there was a gradual decline in the use of vitamin K antagonists, with or without antiplatelet drugs, and of antiplatelet therapy, alone or in double combination, while the proportion of patients not receiving antithrombotic therapy decreased. These data suggest a slow and gradual guidelines implementation process.

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INTRODUCTION

Atrial fibrillation (AF) represents the most common type of sustained cardiac arrhythmia and an emerging epidemic throughout the world, affecting 1%–2% of the adult population[1]. Its prevalence rises steeply from 0.1% in patients < 60 years to approximately 20% in those ≥ 85 years[2,3]. With the progressive aging population and improved survival from other forms of cardiovascular disease[3], both AF prevalence and incidence have been progressively increasing[2,4-6], becoming a significant public health burden.

AF is often associated with increased rates of death, hospitalization, cardiovascular and non-cardiovascular complications, and degraded quality of life, and is a known independent cardiac risk factor (fourfold to fivefold) for ischemic stroke, due to high thromboembolic risk[7-9]. This risk is greater in the elderly (in patients 80-89 years old it reaches 23.5%)[7]. Up to 15%-20% of all strokes are due to AF. AF is often associated with other cardiovascular risk factors or conditions, such as diabetes mellitus, arterial hypertension, chronic coronary syndromes, or heart failure, linked to a further increase in thromboembolic risk[10].

Contemporary registry-based observational studies from various geographical regions have consistently shown that patients with thromboembolic complications, particularly ischemic stroke and systemic thromboembolism (acute mesenteric ischemia, and acute limb ischemia) and AF, have a worse prognosis, more disability, longer hospital stays, more medical and neurologic complications, and greater case fatality rates than those without AF[11]. This increases health-care related costs and reduces quality of life[12]. Stroke prevention is therefore central to the management of AF and is a major public health priority.

Fortunately, among patients with AF, stroke, thromboembolic events and death risk may be up to two-thirds mitigated *via* the usage of oral anticoagulants (OACs), that it is superior to no treatment or antiplatelet agents such as acetylsalicylic acid (ASA), until recently a treatment choice, in patients with different stroke risk profiles[13-17]. The net clinical benefit is almost universal, except for patients with a very low stroke risk.

The European Society of Cardiology (ESC)[18-21] as well as other societies[22-25], in their evidence-based guidelines dedicated to AF, have widened since 2010 the indications for antithrombotic therapy, and now claim OACs as the appropriate treatment for stroke prevention in most patients (namely with additional stroke risk factors, introducing use of the CHA_2DS_2-VASc and HAS-BLED scores for stroke and bleeding risk stratification, respectively. All patients with non-valvular AF (NVAF), except those who are at low risk or with contraindications, require antithrombotic prophylaxis in order to prevent thromboembolism[18-21].

OACs include vitamin K antagonists (VKAs) and, in recent years, direct oral anticoagulants (DOACs). VKAs (in particular warfarin, historically the first-line stroke prevention option and the only available OAC for decades) are effective for preventing stroke by up to two-thirds, regardless of renal function, and with minor costs[26]. The good anticoagulation control with VKAs is assessed by high time in the therapeutic range (TTR). However, previous randomized controlled trials and real-life settings have controversies regarding TTR values[27]. In low TTR values, VKAs were found to be associated with severe complications, and a minimum TTR of 58% should be achieved to expect a net benefit from being on OAC therapy[28]. VKAs have, however, important limitations such as a narrow therapeutic window, requirement for close monitoring and frequent follow-ups, drug–drug and drug–food interactions, unpredictable dose-response effects, and a slow onset and ebbing of action. As a result, in the past years many AF patients received ASA, other antiplatelet agents, or both, or no antithrombotic treatment[6].

Management of AF patients has dramatically improved following the introduction of DOACs, comprising factor Xa inhibitors, such as apixaban, edoxaban, and rivaroxaban, and direct thrombin inhibitors (dabigatran etexilate), first approved in 2010, that showed numerous advantages over warfarin. DOACs rapidly became preferred by both clinicians and patients due to their easier usage: easy dosing schedule, rapid onset of action, more predictable efficacy which allows a fixed-dose regimen, no need for frequent international normalized ratio (INR) controls and fewer interactions with co-medication or with food[29-31]. In terms of stroke and systemic thromboembolism prevention, all DOACs were demonstrated at least to be non-inferior and in some respects superior (*e.g.* fewer intracranial hemorrhages) compared with warfarin in randomized controlled trials[32-35], even in older populations[36]. Recently, there has been a significant price drop in DOACs and meta-analyses of randomized controlled trials[37-39], as well as observational data[40-42] confirm their efficacy and real-life effectiveness. However, DOACs have higher costs and need adjustment based on renal function.

Currently, all four DOACs are approved in Italy. The European Medicine Agency (EMA) authorized dabigatran and rivaroxaban use in 2008 (they became available for use in clinical practice on the Italian market in 2013). The EMA approved apixaban in 2011 (available in Italy since January 2014), and edoxaban (available since June 2015). Since 2013, the Agenzia Italiana del Farmaco authorized (AIFA) them for cardiovascular risk reduction in NVAF[43].

After the release of DOAC, several European and North American scientific societies updated their guidelines, now recommending DOACs as first choice treatment in most patients with NVAF[19-21,24,25]. The changes in guidelines, coupled with the emergence of DOACs, whose use has been steadily increasing over a decade[17], have the potential to transform clinical practice patterns.

It is important, however, that AF guidelines are adhered to, as non-adherence to OACs is associated with increased ischemic stroke and mortality in high-risk patients[44].

Notwithstanding the increasing percentage of patients treated with DOACs[45,46], observational studies and administrative databases widely reported the suboptimal use of OACs for stroke prevention [47-51].

In the past, patients with NVAF remained untreated for several reasons, including overestimation of patient bleeding risk and underestimation of stroke risk by physicians[52], and the presence of comorbidities, mainly in elderly patients[53]. Sociodemographic and economic factors can influence

prescription patterns[54-56]. On the other hand, DOAC prescription is subject to prior authorization in the Italian as well as in other National Health Systems[57,58]. Until recently, regulatory criteria placed DOAC as a second line therapy, limiting their use to patients in which VKA are contraindicated, or with objective difficulties in accessing INR control facilities, or with high intracranial hemorrhage risk[57].

Nevertheless, real-world studies in this population, are still scarce, in particular there is limited evidence on temporal trends of contemporary AF management since the introduction of DOACs[46,59-61], and treatment patterns at single country level are less known. In Italy, since their introduction, the rate of DOAC utilization is one of the lowest in Europe[43,58,61-63]. Thus, an updated analysis of DOAC treatment in Italy for NVAF patients could be useful.

Knowledge obtained from real-world scenarios may suggest strategies to improve the entire AF care process[63]. The questions are: do prescribers follow current guidelines for OACs prescription in AF patients, and has adherence to guidelines changed over time?

In this paper, the authors discuss the actual real-world status and the change, in its temporal trend, in the prescription of antithrombotic treatments in patient with AF consecutively discharged from a Cardiology Unit during an almost twelve-year period. We hypothesized that adherence to OACs prescription according to guidelines recommendations for patients with AF would improve over time.

MATERIALS AND METHODS

Study design and setting

This was a retrospective, single-center, observational study conducted in the Cardiology Unit of S. Antonio Abate Hospital of Trapani (Western Sicily, Italy). This unit takes care of all cardiovascular diseases and is also equipped with a cardiac catheterization and electrophysiology laboratory.

Study population

We reviewed the database of medical records of all patients aged ≥ 18 years who were consecutively discharged from a reference cardiology center from January 2010 to 2021. The following inclusion criteria were applied: any diagnosis of AF (both main and secondary) at discharge from hospital and hospitalization not resulting in death. Patients without indication of prescribed drugs were excluded.

Study variables and definitions

We collected data on demographic and clinical characteristics, including age and sex, main and secondary diagnosis at discharge, diagnostic and therapeutic procedures, and prescribed antithrombotic treatments from the discharge medication list.

The presence of AF was ascertained during the hospital stay by medical history taking, in-hospital diagnosis by 12-lead electrocardiography, or 24-h Holter monitoring.

The discharge diagnosis codes assessed for each patient and the diagnostic and therapeutic procedures were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

We considered: AF, ICD-9-CM code 42731; cardiovascular diseases (angina pectoris, ICD-9-CM codes 4111, 4131 and 4139; acute myocardial infarction, ICD-9-CM code 410; chronic coronary syndromes, ICD-9-CM codes 412, 414, 429, V4581, V4582; cardiomyopathies, ICD-9-CM codes 402 and 425; valvular diseases, ICD-9-CM codes: 394, 396, 397, 424, 394, V433; peripheral vascular disease, ICD-9-CM codes: 433.1, 440.2, 443.9; acute and chronic heart failure, ICD-9-CM codes: 428, 5184; cardiac arrhythmias, ICD-9-CM codes 426, 427, 727.89; endocarditis, ICD-9-CM codes 421, 424; pulmonary embolism, ICD-9-CM code 415; aortic aneurysm, ICD-9-CM code 493, chest pain, ICD-9-CM codes 786, V717), and other concomitant diseases, such as diabetes mellitus, ICD-9-CM code: 250; arterial hypertension, ICD-9-CM codes: 401–404; dyslipidemias, ICD-9-CM code 272; pulmonary diseases (chronic bronchitis, ICD-9-CM code: 491; asthma, ICD-9-CM code: 493; other, 518, 519, 492, 466, 491, 485, 486, 515, 518, V126; sleep apnea, ICD-9-CM codes: 780.51, 780.53, 780.57, 780.54); disorders of the thyroid gland, ICD-9-CM codes: 240–246; cerebrovascular diseases (stroke/transient ischemic attack (TIA)/hemorrhagic stroke, ICD-9-CM codes: 430–436, 438, 442, 4370); dementia, ICD-9-CM code: 290; other cerebral degenerations, ICD-9-CM code: 331; anemia, ICD-9-CM codes 280, 282, 283, 285; obesity, ICD-9-CM code 278; renal diseases, ICD-9-CM codes 584, 585, V560; neoplastic diseases, ICD-9-CM codes: 1419, 1420, 1479, 1512, 1519, 1534, 1537, 1539, 1540, 1541, 1561, 1590, 1599, 1619, 1629, 1749, 179,185, 1882, 1889, 1890, 1970, 1976, 1980, 1985.

In order to evaluate resource usage related to AF management we considered: length of hospital stay; diagnostic test prescription (such as echocardiogram, ICD-9-CM code: 8872; other ultrasound scan tests, ICD-9-CM code: 887; stress tests, ICD-9-CM code: 894; coronary angiography, ICD-9-CM codes: 885, 3721; peripheral angiography, ICD-9-CM code: 884; Holter ECG monitoring, ICD-9-CM code: 895; computed tomography, ICD-9-CM codes: 8703, 8704, 8741, 8742, 8801; and magnetic resonance imaging, ICD-9-CM code: 889); and interventional procedures (such as electrical cardioversion, ICD-9-CM code: 996; cardiac pacemaker implantation, ICD-9-CM codes: 377, 378; automatic cardiac defibrillator implantation, ICD-9-CM code: 379; percutaneous transluminal coronary angioplasty, ICD-9-CM codes: 885, 3721; peripheral percutaneous transluminal angioplasty, ICD-9-CM codes: 004, 0066, 3950; coronary

stenting, ICD-9-CM codes: 004, 360, 377; and peripheral stenting, ICD-9-CM code: 3990).

We searched antithrombotic drug prescription at discharge based on the Anatomical Therapeutic Chemical (ATC) Classification System codes.

The OACs in this study included VKA (warfarin and acenocoumarol) and DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban); antiplatelet drugs (aspirin, clopidogrel, ticlopidine, ticagrelor, and prasugrel), low molecular weight heparin (LMWH) and fondaparinux were also considered. We defined a subject as receiving a VKA prescription if he/she redeemed a discharge prescription with a drug having ATC code B01AA03 (warfarin) or B01AA07 (acenocoumarol). On the other hand, we defined DOAC users as those subjects redeeming prescriptions of dabigatran (ATC code: B01AE07), rivaroxaban (ATC code: B01AF01), apixaban (ATC code: B01AF02), and edoxaban (ATC code: B01AF03).

The patients were then further stratified into the following main categories: (1) Monotherapy with VKAs; (2) monotherapy with DOACs; (3) OAC therapy (VKAs or DOACs); (4) single antiplatelet therapy (SAPT); (5) double antiplatelet therapy (DAPT); (6) double antithrombotic therapy (DAT) (one OAC and one antiplatelet drug); (7) triple antithrombotic therapy (TAT) (DAPT plus OAC); and (8) without therapy.

Drug choice was based on the knowledge and expertise of each prescriber, thus ensuring the collection of real-life data.

Data source and analysis

We retrieved anonymized medical records stored in the Cardiology Unit databases, collected in electronic case report forms (Microsoft Office Access 2013, Redmond, Washington, United States). Data quality was monitored electronically as well as through periodic medical and data quality reviews, on-site monitoring, and audits.

Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. In compliance with privacy laws, the patients' identification codes were encrypted using a unique and anonymous personal identification code. According to the Italian law for confidentiality data, informed consent was not required for using anonymized retrospective information. Each patient, however, signed a written informed consent form at hospital admission, agreeing to the use of his/her data in anonymous form for any aim of medical research. No additional follow-up visits or testing was performed beyond those carried out as part of routine clinical care.

Statistical analysis

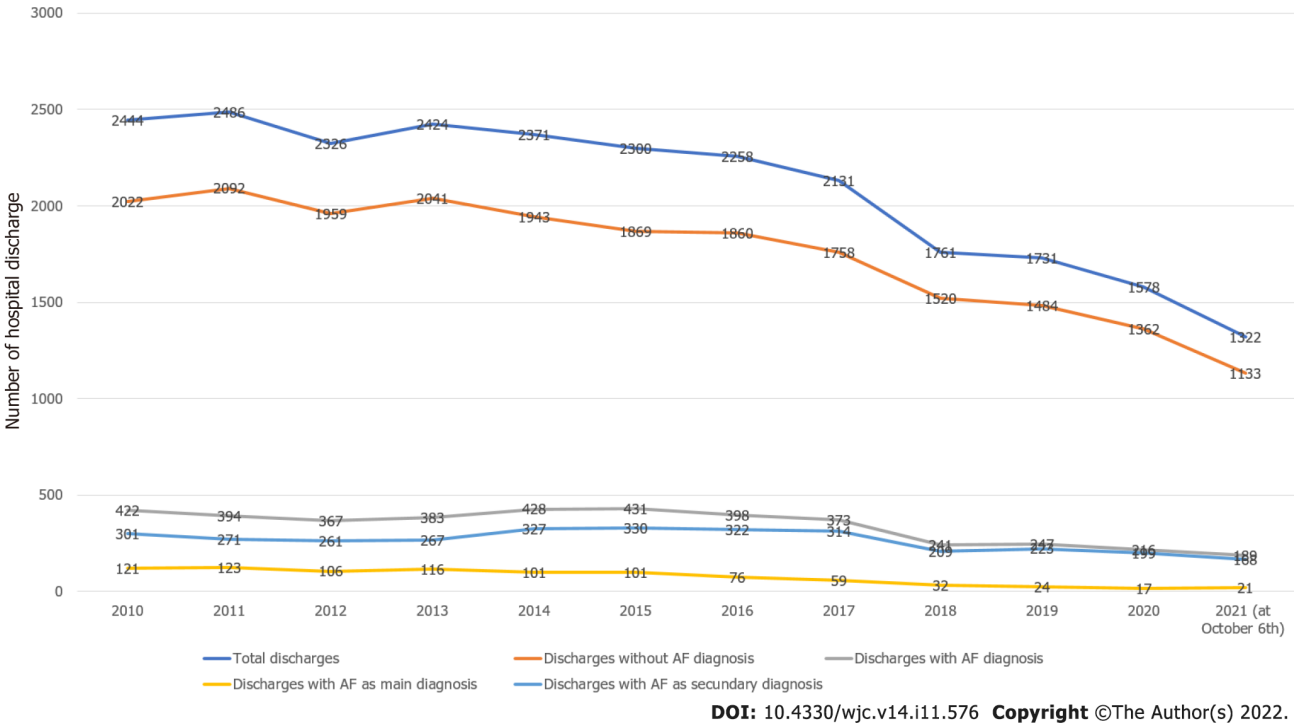
Data cleaning was performed by verifying minimum and maximum values and by analyzing missing data. Data from patients with missing values were not removed from the analyses of general AF patterns but removed from the analysis of treatment patterns.

The analysis provides descriptive statistics to summarize data patterns. Standard descriptive statistical methods were used to analyze the patient's demographics and clinical status, and to evaluate the proportion of treated patients in each drug category. The considered variables were year of discharge, age, sex, length of stay, discharge diagnosis, undertaken diagnostic and therapeutic procedures and prescribed drugs at discharge. Once the database was cleaned, a descriptive analysis was undertaken. Continuous variables were reported as mean and standard deviation (± SD), whereas categorical variables were expressed as absolute and relative frequencies with percentages, as appropriate. Continuous variables were compared using the Student's *t*. Categorical data were compared using the χ^2 test or Fisher's exact test, as appropriate. A two-tailed P value < 0.05 was considered statistically significant. The statistical analysis was performed using Microsoft Office Excel 2013 (Redmond, Washington, United States) and MedCalc (https://wwwmedcalc.org), and graphs were created using Microsoft Office Excel 2013 (Redmond, Washington, United States). The statistical methods of this study were reviewed by the authors themselves.

RESULTS

For the at-discharge analysis, we included data from 25132 discharges from January 1, 2010 to October 6, 2021.

A diagnosis of AF was present in 4089 discharges (16.27%). Figure 1 shows the behavior of hospital discharges in the considered period. Total discharges decreased from 2444 in 2010 to 1532 in 2020 (2021 data were not considered because they were partial) (-37.32%). Discharges without AF diagnosis decreased from 2022 in 2010 to 1362 in 2020 (-30.66%). Discharges with AF diagnosis decreased from 422 in 2010 to 216 in 2020 (-48.81%). The decrease in discharges with AF diagnosis was significantly superior to the decrease in discharges without AF diagnosis (-18.15, P < 0.0001). Discharges with AF as the main diagnosis decreased from 121 in 2010 to 17 in 2020 (-85.95%). Discharges with AF as a secondary diagnosis decreased from 301 in 2010 to 199 in 2020 (-33.88%). The decrease in discharges with AF as the



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Figure 1 Time trends in the number of hospital discharges (total, with and without atrial fibrillation diagnosis); discharges with atrial fibrillation were further divided into the main or secondary diagnosis. AF: Atrial fibrillation.

main diagnosis was superior to the decrease in discharges with AF as a secondary diagnosis (-52.07, $P <$ 0.0001).

Among AF patients, 1851 were females (45.19%) and 2245 males (54.81%), with a male/female ratio of 1.21. The mean age of AF patients was 75.59+/-10.82 years. Mean age was lower in males (73.56+/-11.45) than in females (78.06+/-9.47) ($P < 0.0001$).

AF was the main diagnosis in 899 discharges (21.94%) and the secondary diagnosis in 3190 discharges (88.06%). AF as the secondary diagnosis was observed more frequently than as the main diagnosis (+66.12%, $P < 0.0001$).

Other main diagnoses are shown in Table 1. The prevalence in this table is related to the total sample. The most frequent main diagnosis in patients with AF was acute myocardial infarction. Secondary diagnoses are shown in Table 2. The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have more comorbidities at the same time. The most frequent secondary cardiac diagnosis was chronic coronary syndrome, and the most frequent secondary associated condition was arterial hypertension.

With regard to resource utilization, mean length of stay was 5.76+/-4.88 days in the total sample. Mean length of stay was 3.37+/-2.92 days in discharges with AF as the main diagnosis, and 6.48+/-5.11 days in discharges with AF as a secondary diagnosis. Length of stay was lower in discharges with AF as the main diagnosis ($P < 0.0001$).

Diagnostic and therapeutic procedures are shown in Table 3. The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have received more diagnostic and therapeutic procedures at the same time. The most frequently used procedure was echocardiogram, whereas the most frequently performed intervention was percutaneous transluminal coronary angioplasty (PTCA)/stenting. Healthcare utilization was noticeable in this AF group.

For the analysis of antithrombotic treatments, we excluded in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications for prescribed treatments. The final sample was made of 3067 patients with AF diagnosis and known therapy. Figure 2 shows the flowchart of the study.

Antithrombotic drugs prescribed at discharge are shown in Figure 3. ASA was the most utilized drug (29% of prescribed drugs), followed by warfarin (27%) and clopidogrel (14%). VKAs were prescribed in 29% of total antithrombotic drugs. Among them, warfarin was undoubtedly the most prescribed drug (92.77% *vs* 7.23% of acenocoumarol). DOACs were prescribed in 20% of total drugs. Among them, apixaban was the most prescribed (39% of all DOACs). Antiplatelet agents were prescribed in 45% of drugs. Among them ASA was the most prescribed (63.65%), followed by clopidogrel (31.53%).

Changes over time in the prescribed antithrombotic drugs are shown in Table 4 (absolute numbers). After an initial increase, VKAs prescription progressively decreased. Antiplatelet drugs prescription decreased progressively over time. In contrast, DOAC prescription increased sharply from 0.5% in 2013

Table 1 Other main diagnosis excluding atrial fibrillation in the studied sample

Diagnosis	*n*	%
AMI	1973	48.19
Cardiac arrhythmias	210	5.37
Chest pain	201	4.91
Heart failure	143	3.49
Chronic coronary syndrome	80	1.95
Cardiomyopathies	77	1.88
Peripheral artery disease	74	1.81
Stable angina	55	1.34
Unstable angina	45	1.10
Pericarditis	29	0.71
Valvular heart diseases	27	0.66
Shock	21	0.51
Pulmonary embolism	22	0.49
Other	233	15.65

AMI: Acute myocardial infarction.

to 57% in 2021. The percentage of prescribed OACs increased from 27% in 2010 to 64% in 2021, whereas the percentage of patients without any antithrombotic therapy decreased from 13% in 2010 to 4% in 2021.

In order to avoid an accentuation of year-to-year variability, data on treatment were grouped in 3-year periods, as shown in Figure 4. VKAs prescription decreased from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$). Antiplatelet drugs prescription decreased from 49.18% in 2010-2012 to 34.18% in 2019-2021 (-15.00%, $P < 0.0001$). On the contrary, DOACs prescription increased from 3.04% in 2013-2015 to 50.06% in 2019-2021 (+47.02%, $P < 0.0001$). OAC prescription increased from 35.63% in 2010-2012 to 61.18% in 2019-2021 (+25.55%, $P < 0.0001$), whereas the percentage of patients without any antithrombotic therapy decreased from 14.58% in 2010-2012 to 1.97% in 2021 ($P < 0.0001$).

It should be considered that antithrombotic treatments can be combined variously among patients, particularly as our population sample consisted of a large percentage of acute and chronic coronary heart disease patients. Thus, in Figure 5 we show the behavior over time of various antithrombotic combinations. SAPT, DAPT, VKAs, and no therapy decreased over time, whereas DOACs, DAT, TAT and global OACs increased over time.

Finally, these data have been corrected according to the total number of discharges, as their number is not stable over time, as shown in this study. Figure 6 shows the trend in prescribed antithrombotic therapy during the study period. The more relevant data are the sharp increase in patients treated with DOAC (from 0.78% in 2013 to 52.38% in 2021, $P < 0.0001$) and with OACs (from 34.31 in 2010 to 80.95 in 2021, $P < 0.0001$); conversely, the number of patients not receiving any antithrombotic therapy decreased from 16.67 in 2010 to 4.23 in 2021 ($P < 0.0003$).

DISCUSSION

In this retrospective, single center, contemporary real-world study we examined clinical characteristics, resource utilization, and temporal trends over a twelve-year interval in antithrombotic therapy prescription pattern in a cohort of patients discharged from a cardiology unit with a diagnosis of AF.

Discharges with AF diagnosis decreased over time, and the decrease in discharges with AF as the main diagnosis was significantly superior to the decrease in discharges with AF as the secondary diagnosis. We observed that AF patients were elderly, and predominantly male, with a high prevalence of concomitant cardiac and extra-cardiac diseases. Healthcare utilization in this group of patients was noticeable in terms of both diagnostic and therapeutic procedures.

In terms of antithrombotic treatments, from 2010 to 2021 patients on OAC therapy increased significantly, regardless of antiplatelet drugs use. The increasing use of DOACs, namely factor Xa (FXa) inhibitors (especially apixaban), can explain this phenomenon. Contextually, VKA use, regardless of antiplatelet treatments, declined, like antiplatelet therapy, alone or in double combination, while the

Table 2 Secondary cardiac and extra-cardiac diagnoses in the studied sample

Secondary diagnosis	*n*	%
Cardiac		
Chronic coronary syndromes	1864	45.51
Cardiomyopathies	1221	29.81
Valvular heart diseases	595	14.53
Heart failure	406	9.91
Arrhythmias	119	2.91
Angina pectoris	91	2.22
Extra-cardiac		
Arterial hypertension	1010	24.66
Renal diseases	985	24.05
Diabetes mellitus	932	22.75
Lung diseases	617	15.06
Dyslipidemias	345	8.42
Cerebrovascular & psychiatric diseases	313	7.64
Thyroid diseases	152	3.71
Anemia	166	4.05
Peripheral artery diseases	146	3.56
Obesity	137	3.12
Neoplastic diseases	83	2.03

proportion of patients not receiving antithrombotic therapy decreased.

In this study, a diagnosis of AF was present in 4089 on 25132 discharges from 2010 to 2021. Total discharges decreased (-37.32%) from 2010 to 2020. This phenomenon may be explained by the shift in medical treatments from hospital to territory. Also discharges with and without AF diagnosis decreased from 2010 to 2020 (respectively -48.81% and -30.66%), but the decrease in discharges with AF diagnosis was greater than the decrease in discharges without AF diagnosis (-18.15, $P < 0.0001$). Although the incidence and prevalence of AF are expected to increase due to progressive growth in the number of elderly people in the general population, our sample reflects only patients hospitalized in a cardiology unit. Thus, the decrease in discharges with AF diagnosis may be explained, in general, by the decrease in total hospital admissions and, in particular, by the reduction in admission of patients with a paroxysmal AF, that is now considered inappropriate; in fact, the decrease in discharges with AF as the main diagnosis was significantly superior to the decrease in discharges with AF as the secondary diagnosis (-52.07, $P < 0.0001$). However, AF as a secondary diagnosis was observed more often than as the main diagnosis (+66.12, $P < 0.0001$). This was due to the real-world nature of this observational study, focused on a global sample of patients admitted to a cardiology unit.

We observed that AF patients were elderly (mean age was 75.59+/-10.82 years), as shown in other studies[29,46,52,64,65]. Males accounted for the majority of patients in the whole study group: the male/female ratio was 1.21. This confirms the data from other studies[29,59,65,66]. An opposite trend, with a greater prevalence in women, was observed by Ermini[63]. The mean age was lower in males (73.56+/-11.45) than in females (78.06+/-9.47) ($P < 0.0001$).

The most frequent main diagnosis in patients with AF was acute myocardial infarction. The most frequent secondary cardiac diagnosis was chronic coronary syndrome, and the most frequent secondary associated condition was arterial hypertension. A high prevalence of concomitant cardiac and extra-cardiac diseases was shown, in particular arterial hypertension, diabetes mellitus, heart failure, and coronary artery disease. This profile of comorbidities at baseline was in agreement with previous analyses[46,53,63,67,68]. In the Akershus Cardiac Examination 1950 study, 87.6% of men with AF and 86.4% of women with AF had comorbidities, compared with 74.4% and 66.3%, respectively, without AF [3]. Thus, our subjects reflected real-world clinical practice, including a large proportion of patients with advanced age and many comorbidities.

With regard to resource utilization, mean length of stay was 5.76+/-4.88 days in the total sample. Mean length of stay was 3.37+/-2.92 days in discharges with AF as the main diagnosis, significantly lower than in discharges with AF as a secondary diagnosis (6.48+/-5.11, $P < 0.0001$). The procedure

Table 3 Main diagnostic and therapeutic procedures performed in the studied sample

Procedures	*n*	%
Diagnostic		
Echocardiogram	3588	87.60
Coronary angiography	804	19.63
Dynamic ECG monitoring	458	11.18
CT scan	299	7.30
Other echography	212	5.18
Stress test	139	3.39
Therapeutic		
Coronary PTCA/stenting	941	22.97
PM implantation	258	6.30
ICD implantation	90	2.20
Peripheral vessels angiography	90	2.20
Peripheral vessels PTCA/stenting	60	1.46
Electric cardioversion	56	3.71

PTCA: Percutaneous transluminal coronary angioplasty; ECG: Electrocardiogram; CT: Computerized tomography; PM: Pacemaker; ICD: Implantable cardiac defibrillator.

most frequently used was echocardiogram, whereas the most frequently performed intervention was PTCA/stenting. Thus, healthcare utilization in this group of patients is noticeable in terms of both diagnostic and therapeutic procedures.

Our study was able to show the trends in antithrombotic treatments in AF patients. During the study periods, several guidelines on antithrombotic AF management have been published. In practice, the ESC guidelines progressively extended the indication for OAC, excluded antiplatelet treatment, and gave greater importance to DOACs[18-21].

It is known, however, that real-world guideline implementation is not a simple process. The increasing prevalence of AF and AF-related comorbidities proves the need for comprehensive prevention and management strategies. The challenge is the optimization of therapy for each patient. However, there are still gaps in optimal stroke prevention[17].

Thus, the main purpose of this study was to investigate whether guideline recommendations in terms of antithrombotic treatment were actually applied in clinical practice, by evaluating antithrombotic treatment patterns in Italian patients with a discharge diagnosis of AF. In this setting, several disease-specific, prospective observational studies and registry programs were created to better understand AF populations, their demography, treatments, and clinical outcomes at world[45,46,69-72] and European level[9,10,44,73-76]. In addition, observational data are available from America[6,51,71,77,78], Europe [52,55,58,59,62,79-83], and Asia[53,84-93].

A progressive improvement in the guideline-recommended antithrombotic prophylaxis of stroke in AF patients, mainly in newly diagnosed cases, has been shown by these studies[59]; however, most of them belong to the pre-DOAC era, and there is still much to learn about how DOACs are being used in clinical practice. The present study adds to the few studies that have investigated the prescription pattern of antithrombotic agents in AF patients in recent years: Proietti[76] evaluated patients from Belgium, Denmark, Greece, Italy, Norway, Poland, Portugal, Romania, and the Netherlands; Huisman [45,46] evaluated patients from Asia, Africa/Middle East, Europe, Latin America and North America; and Apenteng[59] studied United Kingdom patients.

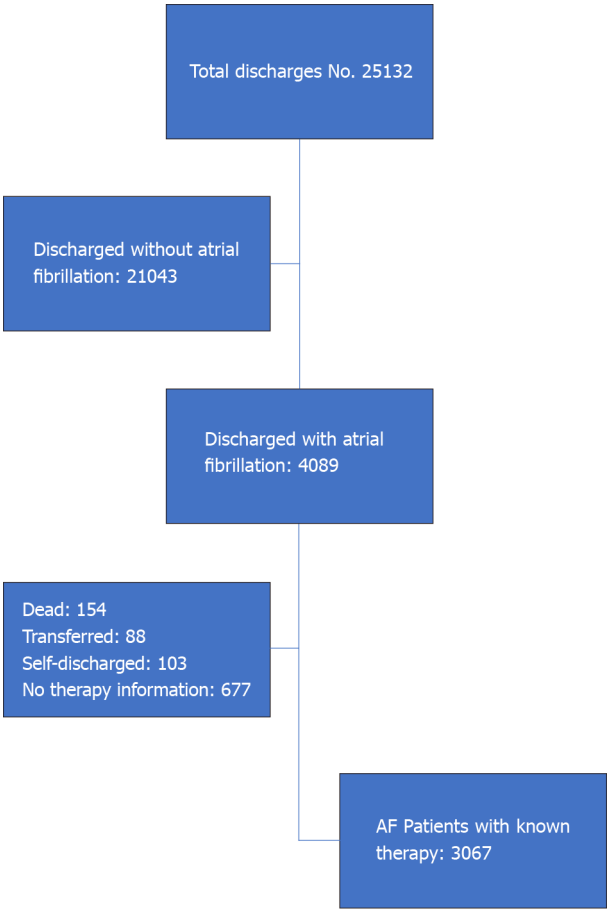
In our study, antiplatelet agents were prescribed in 45% of total drugs. Among them ASA was the most prescribed (63.65%), followed by clopidogrel (31.53%). ASA was also, in total, the most utilized drug, followed by warfarin and clopidogrel. SAPT, however, decreased significantly over time from 49.18% in 2010-2012 to 34.18% in 2019-2021 (-15.00%, $P < 0.0001$). Antiplatelet therapy was also commonly prescribed in other studies, regardless of whether there was coexistent myocardial infarction or coronary artery disease[74,75]. Other studies showed, for example, that antiplatelet agents were used in 30% of all patients with AF[63] and in 36% in the pre-DOAC era[58]. Antiplatelet agents are particularly used in the elderly; in 18.3%, 18.9%, 18.9%, and 18.7% of patients aged 75–< 80, 80–< 85, 85–< 90, and ≥ 90 years, respectively[87]. In other studies, treatment with ASA was also the most common (41.7% of patients in GARFIELD[45,46]), whereas in others was very low (3.3%)[68]. The proportion of patients

Table 4 Changes in prescribed antithrombotic drugs over time in the studied group (absolute numbers)

Yr	Warfarin	Acenocumarole	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Aspirin	Clopidogrel	Ticlopidine	Ticagrelor	Prasugrel	LMWH	Fondaparinux	No therapy
2010	32	3					41	35	1			2		17
2011	93	3					82	30				2		24
2012	100	11					99	47				1		58
2013	177	12		2			191	73	7	7	1	17	4	65
2014	114	7		10			108	28		12		7	4	41
2015	149	12		18	11		138	40	5	13	1	20	1	55
2016	127	6		29	25	3	138	48		13	5	26		34
2017	116	17	18	24	46	16	95	63		7		9	6	30
2018	56	4	20	45	54	21	52	43		4		3	1	7
2019	43	4	40	40	67	21	68	55		2		3	2	2
2020	31	1	19	30	55	27	49	46		5		7	5	7
2021	15	2	29	17	46	41	35	35				4	2	8

LMWH: Low molecular weight heparin.

treated with antiplatelet agents other than ASA was low (3.4%)[45,46], in contrast to the high clopidogrel use in our data. These differences may be explained by the fact that we studied unselected cardiology patients with high prevalence of acute and chronic coronary syndromes, and in whom antiplatelet therapy was still prescribed routinely with or without oral anticoagulation. Minor use of antiplatelet agents over time as sole therapy for stroke prevention in AF is a common finding and other studies showed a downward trend from 36% to 17% (in GARFIELD-AF)[70], from 18% to 8% (in the ORBIT-AF program)[71], from 6.1 to 2.5%[80], from 36,5% to 10,5%[59], and from 36% to 25%[58]. It is increasingly recognized that antiplatelet agents are of little benefit and have a not insignificant risk, although 2010 ESC guidelines still endorsed aspirin for patients at intermediate stroke risk according to $CHADS_2$ risk stratification[18]; however, in the 2012 update[19] antiplatelet drugs were to be considered only in patients refusing any OAC. In the 2014 AHA/ACC/HRS treatment guidelines[24] aspirin was still considered an option for AF patients with moderate stroke risk. Conversely, the 2019 AHA/ACC/HRS guidelines[25] suggested that NVAF patients, regardless of their stroke risk, should not be treated with antiplatelet drugs monotherapy, unless an OAC is contraindicated; thus, high risk patients would be considered undertreated whenever only ASA is used. However, antiplatelet therapy continues in part to be inappropriately prescribed instead of OAC[68]. A reason of the persistence of antiplatelet agents use may be that anticoagulant prophylactic therapy is especially difficult in patients in whom a high thromboembolic risk coexists with contraindications for OAC treatment, such as the



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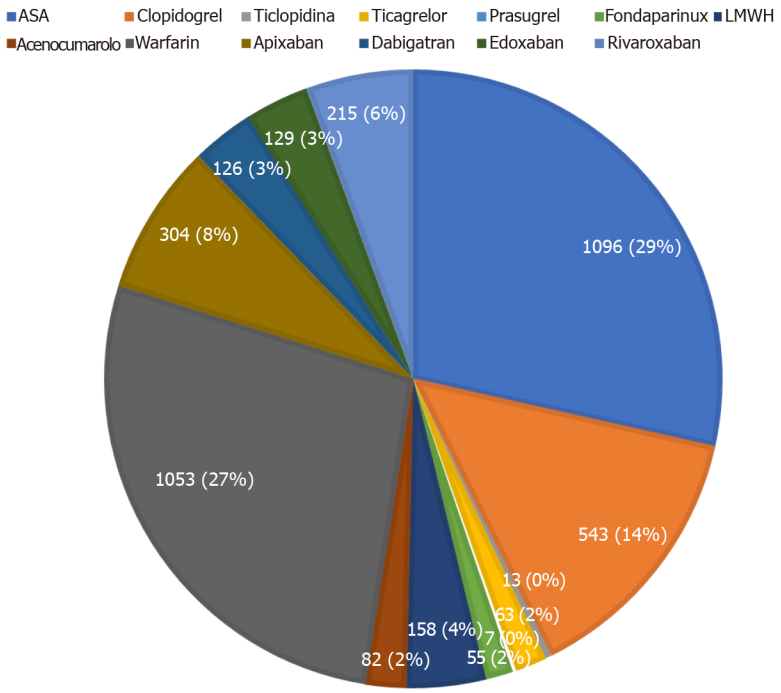
Figure 2 Study flowchart.

elderly. OAC underuse, associated with antiplatelet therapy prescription, regardless of a known atheromatous disease, has been reported by Averlant *et al*[94] in elderly AF patients. In addition, in the post-DOAC era, patients who are receiving antiplatelet drugs have more comorbidities[58].

We observed that DAPT also decreased over time from 13.72% to 2.12%. In ACS patients treated with percutaneous coronary intervention (PCI), a DAPT is recommended to reduce stent thrombosis risk[67]. This reduced use of DAPT is likely due to a greater prescription of DAT or TAT in a population with noticeable prevalence of coronary syndromes.

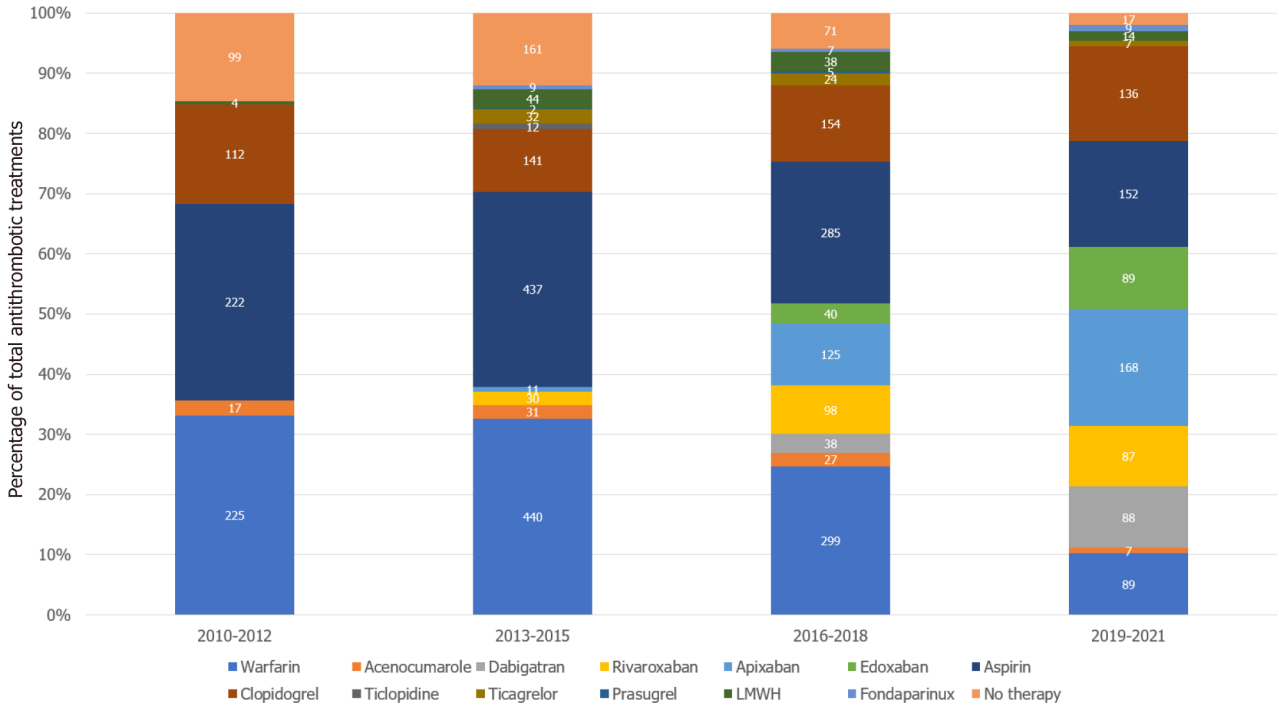
In our study, VKAs were prescribed in 29% of total antithrombotic drugs. Among VKAs, warfarin was undoubtedly the most prescribed drug (92.77% *vs* 7.23% of acenocoumarol). VKAs prescription decreased significantly from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$). In other studies, warfarin was also the most prescribed OAC (from 24.2% to 88.8%[29,64,75,79,90] according to the period and to the country. The PINNACLE study, conducted by the National Cardiovascular Data Registry, showed that only 55% of warfarin-eligible patients actually received that drug[77]. A gradual decrease in warfarin use was also observed in GARFIELD-AF[70,79,80], mainly after DOAC introduction. Geographical differences exist, however, in VKA therapy, with a notably greater use of VKAs in China, where it was the fastest growing OAC used[45,46,64], likely for economic reasons. Age and comorbidities (in particular decreased renal function) may guide the choice of warfarin instead of OACs[95]. In the post-DOAC era, patients receiving VKA have more comorbidities[58,87] in comparison to the pre-DOAC era, and are frequently treated with polypharmacy[96]. VKA use is also common in patients with acute and chronic coronary syndromes requiring both OAC and antiplatelet therapy[68,72].

We observed that DOACs represented 20% of the total prescriptions. Apixaban was the most frequently prescribed (39% of all DOACs). The more relevant data from this study are the sharp, statistically significant increase in patients treated with DOAC, from 0.78% in 2013 to 52.38% in 2021, $P < 0.0001$, and from 3.04% in 2013-2015 to 50.06% in 2019-2021, +47.02%, $P < 0.0001$. In 2018, DOAC use surpassed that of warfarin. Our study confirms apixaban as the most used DOAC[52,87,97]; however, other authors have observed the prevalent use of dabigatran[29,65,68] or rivaroxaban[43]. It is difficult to explain these differences, which are likely a consequence of local preferences.



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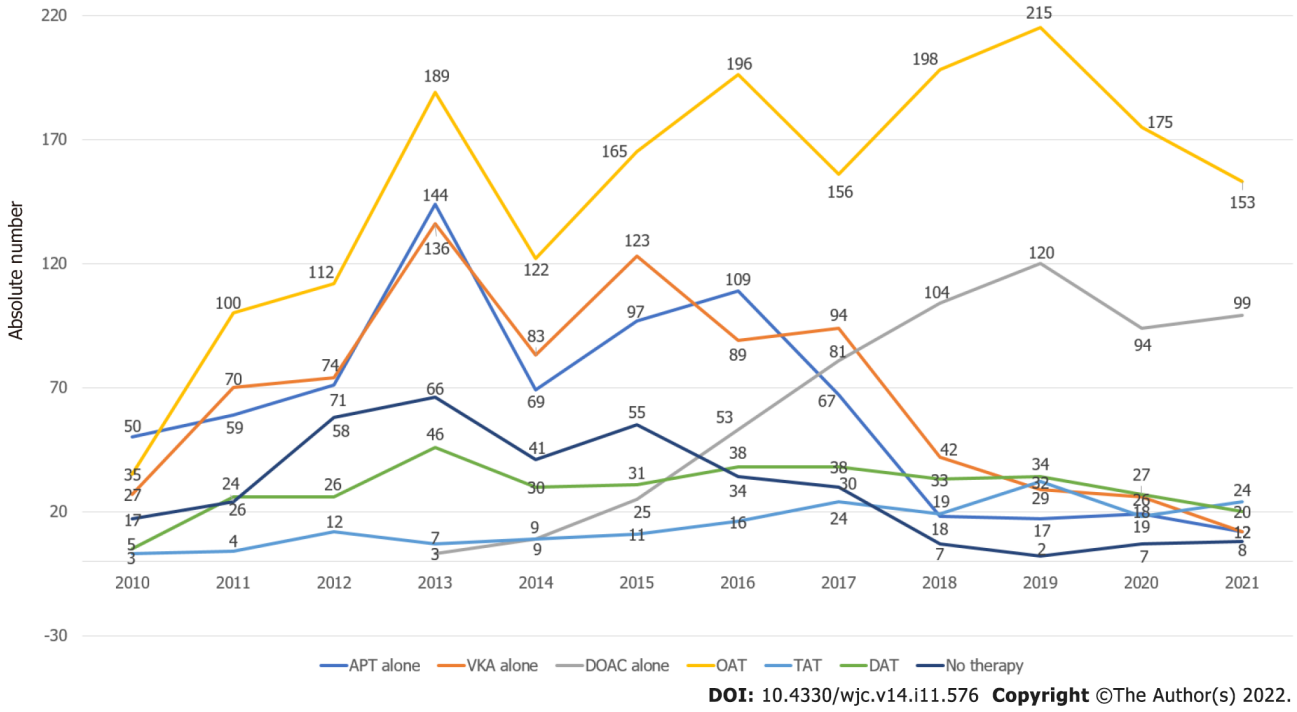
Figure 3 Prevalence of different antithrombotic treatments as a percentage of total antithrombotic treatments. ASA: Acetylsalicylic acid; LMWH: Low molecular weight heparin.



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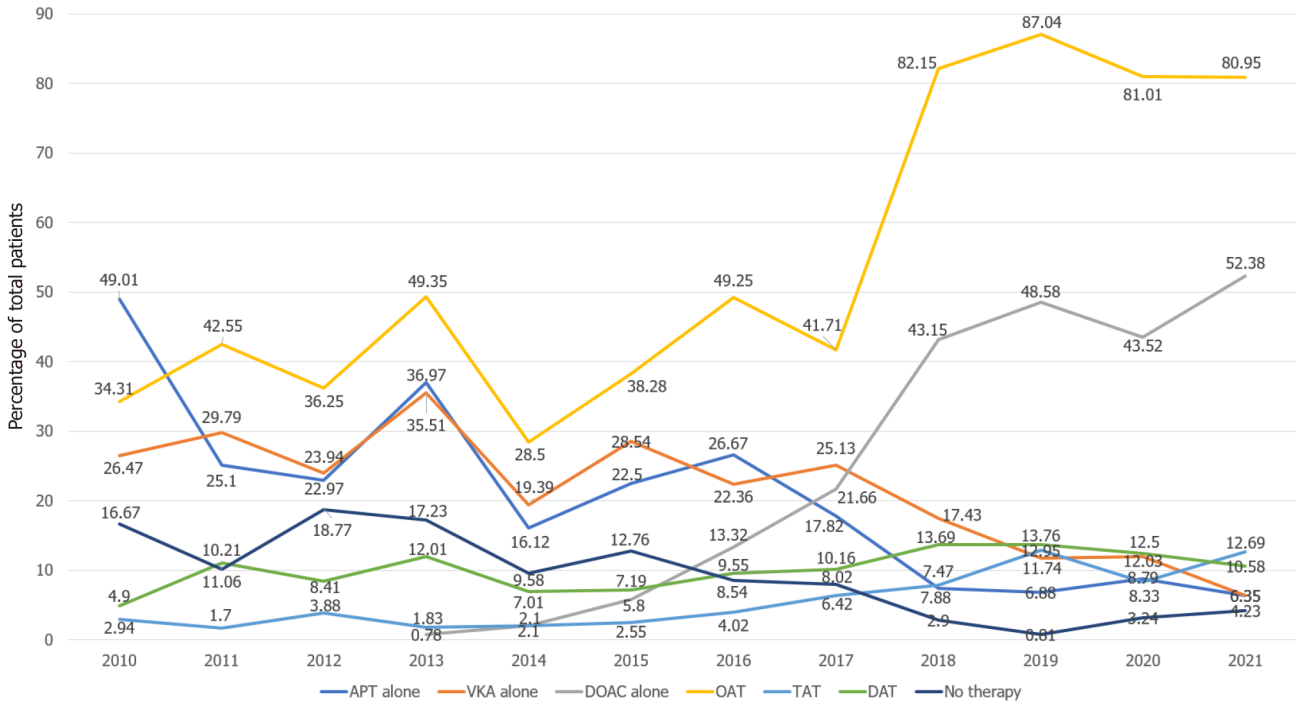
Figure 4 Time trends over three-year periods (from 2010-2012 to 2019-2021) of the prevalence of different antithrombotic treatments as a percentage of total antithrombotic treatments. LMWH: Low molecular weight heparin.

The prescription rate of DOACs for NVAF, after their release in 2011, has increased significantly in recent years, as demonstrated by many other studies, which reported a substantial increase from 14.5% to 70.1%[68,71,80,98,99]. Some of these studies, however, used data from registries of cardiovascular care practices, which may favor enrolment of highly motivated patients under specialist care, and the applicability of these results to the general population may be limited[65]. Actually, DOAC adoption trends are quite variable, with slow integration into clinical practice reported in most countries[98]. A



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Figure 5 Time trends by year (from 2010 to 2021) in prescription of different antithrombotic treatments (absolute number). APT: Antiplatelet treatment; VKA: vitamin K antagonist; DOAC: Direct oral anticoagulant; OAT: Oral antithrombotic therapy; TAT: Triple antithrombotic therapy; DAT: Double antithrombotic therapy.



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Figure 6 Time trends by year (from 2010 to 2021) in prescription of different antithrombotic treatments (as a percentage of total patients). APT: Antiplatelet treatment; VKA: vitamin K antagonist; DOAC: Direct oral anticoagulant; OAT: Oral antithrombotic therapy; TAT: Triple antithrombotic therapy; DAT: Double antithrombotic therapy.

systematic literature review indicates that suboptimal OACs use is a persisting challenge, despite the availability of DOACs[100]. After the launch of the first DOAC in 2011, the proportion of DOACs as OAC increased from 3% in 2012 to 42% in 2016 (P < 0.0001 for the trend)[16]. A marked variability in NOAC use was observed between countries, ranging from 6.1% (in Thailand) to 87.5% (in Switzerland) of all OAC-treated patients[72]. Many countries have some limitations on DOAC usage due to its costs.

In Italy, in particular, reimbursement was possible only after mid-2013 for dabigatran, late 2013 for rivaroxaban, early 2014 for apixaban and late 2016 for edoxaban. In Italy, management with VKAs was better than in other European countries, allowing higher TTR[62]. Some studies aimed to determine the preference criteria in DOACs use. At patient level, prior stroke, transient ischemic attack, thromboembolism, thyroid disease, dyslipidemia, cancer, HAS-BLED ≥ 5, paroxysmal or non-permanent AF, and the presence of comorbidities were positive predictors of DOACs use over VKAs, whereas young age (≤ 64 years) and renal dysfunction (as they must be used with caution in this latter category of patients) were negative predictors of DOACs use over VKAs[57,68,99]. GARFIELD-AF showed that DOACs seemed to be favored for the management of patients with a low stroke risk (CHA_2DS_2-VASc 0 or 1)[72]. However, the extent of anticoagulant selection driven independently by ischemic stroke risk (predictions of treatment benefit) and bleeding risk (prediction of treatment harm) was marginal, as neither score explained much variation in the multivariable adjusted regression model[72,79]. Clinicians may be choosing warfarin in real-world clinical practice for patients with both high stroke risk and bleeding risk, indicating possible concerns about the lack of a reversal agent for the DOACs[29]. This contrasts with the reduced use of dabigatran in our study. DOAC use was more frequent than VKA in men and in the elderly[66,68,70,72], particularly apixaban[97], as they have fewer potential drug interactions in elderly patients. In the ANAFIE Registry, 72% of elderly AF patients receiving anticoagulant treatment were treated with DOACs[86]. However, in some studies DOACs were more frequently prescribed in female and young patients[55]. The rate of DOAC, rather than warfarin, was increased ($P < 0.0001$ for the trend) in patients with AF undergoing PCI[52]. OAC therapy at discharge was prescribed in approximately 30% of patients with AF and ACS requiring PCI (DOACs accounted for approximately half of them)[67].

In our study, both DAT (SAPT plus OAC) and TAT (the combination of OAC and DAPT to prevent both systemic embolism or stroke and coronary thrombosis, especially in the acute phase of the disease) increased over time (respectively from 4.90% in 2010 to 10.58% in 2021 and from 2.94% in 2010 to 12.69% in 2021). These data are in agreement with many other studies[52,59,63,68]. However, our data refer to a general population admitted to a cardiology unit with various diagnoses, while different results have been observed in selected samples such as patients with both AF and coronary artery disease (in particular those with ACS and/or undergoing PCI). Combined antithrombotic regimens present a great challenge in these real-world clinical scenarios. Previous studies have shown that warfarin alone was not sufficient to avoid stent thrombosis, and SAPT or DAPT alone was not adequate to prevent AF-related thromboembolic events; therefore, patients with AF undergoing PCI are typically prescribed multiple antithromboembolic drugs. Before the introduction of DOACs, from 2013 to 2014, only 1.7% of patients were treated using both warfarin and DAPT in the China acute myocardial infarction (CAMI) registry[92]. After DOAC introduction, in patients with ACS the rate of DAT prescription increased over the years (from 41% in 2010 to 59% in 2016, $P = 0.012$ for the trend) whereas TAT prescription decreased (from 14% in 2010 to 5% in 2016, $P = 0.010$ for the trend)[16] and the co-prescription of DOACs and antiplatelet drugs did not change much in recent years[59]. 'Triple therapy' is likely less prescribed by physicians due to concerns regarding bleeding risk. A greater risk-to-benefit ratio of DAT (DOAC plus a P_2Y_{12} inhibitor) in comparison to a VKA-based TAT has been shown in randomized controlled trials[101,102]. The Danish nationwide administrative registries showed that DOACs use exceeded that of warfarin, in any combination with antiplatelet drugs, by 2016[103]. These studies influenced current international guidelines, now favoring, in this setting, a DAT with a DOAC and a P_2Y_{12} inhibitor (especially clopidogrel).

From 2010 to 2021, globally, we observed that OAC was prescribed in 49% of all antithrombotic therapy, but even more we showed an increase in patients treated with OACs (from 34.31% in 2010 to 80.95% in 2021, $P < 0.0001$ and from 35.63% in 2010-2012 to 61.18% in 2019-2021, +25.55%, $P < 0.0001$). In a similar study, Mai[67] reviewed 3813 electronic medical records of patients aged ≥ 18 years, who were hospitalized from 2013 to 2018, which showed that prescription of OACs in patients with AF was low (29.7%). Another study, from 2014 to 2017, showed that 90.1% of patients received an OAC (either as a monotherapy or combined with antiplatelet drugs[68]. In other studies conducted in different temporal and geographical settings the rate of prescription of OACs, both in monotherapy and in association with antiplatelet drugs, varied from 41.2% to 92%[15,60,64,73,103]. These data, on the one hand, indicate how guidelines can be successfully applied in the real world, but, on the other hand, they suggest that OAC underuse persists, despite the growing awareness of anticoagulation benefits in AF[71,80]. OAC use seems especially low in Italy, as reported by the PREFER-AF registry[62]. Our results are in line with previous studies from different populations, demonstrating a recent increase in OAC use[44,46,60,70,104], particularly after the introduction of DOAC [15,59,72,89,91]. The proportion of patients treated with OAC monotherapy increased slowly, but gradually[52]. DOACs availability, together with comprehension of the reduced efficacy of antiplatelet drugs in comparison to OACs, have likely driven, at least in part, this paradigm shift in prescribing practice, notwithstanding an initial reluctance of healthcare payers due to the greater DOAC costs[70]. The prescription of OACs, as well as its temporal trend, is also related to various geographic and clinical patterns. In patients who underwent PCI, the OAC prescription rate increased from 56% in 2010 to 74% in 2016 ($P = 0.041$ for the trend) and OAC monotherapy gradually increased from 2% in 2010 to 9% in 2016 ($P = 0.041$ for the trend)[16]. Another study showed that OAC treatment was prescribed at discharge only in about 30% of patients with AF

and ACS requiring PCI[67]. Among the factors playing a role in OACS underuse, we should consider demographic patterns (*i.e.*, elderly and women), concomitant diseases such as hepatic or renal disease, lack of adherence, physicians' and patients' treatment fears, and lack of access to the healthcare system. With regard to age, for example, patients prescribed OACs at discharge were younger than those not prescribed OACs (mean age 71.7+/-10.6 *vs* 74.6+/-10.2 years)[64]. In the RAMSES prevention strategies trial[85], a national observational registry on Turkish adults with NVAF, OAC therapy was prescribed for 74.8% of participants younger than 80 years and 63% of those aged 80 and older ($P < 0.001$). Comorbidities and other individual-level characteristics may explain this difference in the elderly. Higher CHA_2DS_2-VASc score and lower HAS-BLED score were independent predictors of OAC prescription in participants aged 80 years and older[85]. OAC treatment was prescribed in only half of elderly patients in the Fushimi AF Registry[89]. A retrospective Chinese study showed that OACs were prescribed in only 41.1% of AF patients aged ≥ 65 years[15]. The overall OACs rate in older people, notwithstanding the higher risk of bleeding, was greater (87.3%) in another study[87], and 92% of patients ≥ 75 years old received OAC treatment in the All Nippon AF in the Elderly (ANAFIE) Registry [86], as well as 92% of patients ≥ 80 years old in the OCTOFA study[81]. Other factors, such as lower levels of education, lower income, prior antiplatelet use, having several cardiovascular comorbid conditions (including stroke or transient ischemic attack, hypertension, diabetes, dyslipidemia, valvular heart disease, heart failure, coronary syndromes, carotid stenosis, and peripheral vascular disease) were associated with not being prescribed an OAC[64,75]. OACs use was greater in low bleeding risk patients than in those with both high stroke and high bleeding risk (94.2% *vs* 91.3%, $P < 0.0001$)[88]. However, patients with contraindications to OACS are a minority. For example, in the elderly, only 4% of patients had such contraindications (primarily, active cancer and anemia)[68]. In 86,671 elderly AF patients, only 2% were ineligible for OAC therapy due to absolute contraindications (most often previous intracranial bleeding)[71]; also, OACs were contraindicated in less than 13% of 10130 patients in the ORBIT-AF trial [78].

In our study, LMWH and fondaparinux were used in approximately 6% of total antithrombotic drugs, but they were used in very low percentages as unique treatment throughout the 12-year period. Another study showed that LMWH, not endorsed just from the 2012 ESC guidelines[19], was used in 2.5% of patients[68].

Finally, we showed that the percentage of patients without any antithrombotic therapy, including antiplatelets and LMWH/fondaparinux, significantly decreased from 16.67% in 2010 to 4.23% in 2021 ($P < 0.0003$) and from 14.58% in 2010-2012 to about 1.5% in 2019-2021. These data are consistent with other studies, showing that a total varying from 21.9% to 30.2% did not receive any prophylactic antithrombotic therapy[46,60,70,75,90] with substantial variations across countries. A recent meta-analysis reviewed a total of 11,231 publications, demonstrating in patients with high stroke risk a rate of non-treatment of 23.3% (7.9%-51.1%)[100]. Undertreatment is frequent in female and older patients, notwithstanding their great stroke risk[36,87,93,105]. However, in the DOAC era, non-treatment rates in high-risk patients are lower than in the pre-DOAC era (11.1%, 95%CI 7.9%-40.2% *vs* 33.6%, 95%CI 13.4%-51.1%)[100]. Patients receiving no treatment are generally younger and healthier[70]. However, patients who received no treatment in the post-DOAC era had more comorbidities ($P < 0.01$, respectively)[58].

Strengths and limitations

Our study has several strengths, including the analysis of clinicians' preferences on antithrombotic treatment in a broad spectrum, consecutive, geographically defined population over a long period of time, providing a novel contribution by characterizing OAC prescriptions pattern among patients with AF.

However, our results should be interpreted in the context of the limitations of this study, whose purpose was restricted to the review of analyses of observational data collected through clinical databases, reflecting real-world clinical practice, which presented some limitations.

First, although efforts were made to standardize definitions and reduce missing data, this was a retrospective study with the limitations inherent to observational study design such as selection biases due to residual or not measured confounding factors (*i.e.* sociodemographic, patient preferences, biochemical parameters, and/or clinical confounding variables unavailable in the data, which would have likely impacted on the choice of treatment), all of which may restrict the interpretation of study results. In particular, data on CHA2DS2-VASc and HAS-BLED score were not available in the present analysis.

Second, data on detailed OAC types and the quality control of OAC use prior to hospitalization were not collected, likewise no follow-up was investigated, and therefore the effects of quality of warfarin control and of OAC adherence on outcome could not be evaluated.

Third, as all patients were discharged from a secondary center, the current registry is not free from referral bias. In addition, we studied patients managed only by cardiologists and discharged from a single center. The GARFIELD-AF registry found that patients who are managed in the outpatient setting are more likely to receive DOAC therapy than patients treated in emergency care or in the hospital setting[72].

Finally, we did not exclude valvular AF patients, in which VKA use is mandatory; however, only about 5% of all AF patients had mechanical heart valves or moderate-to-severe mitral stenosis[6] and an even lower proportion was observed in our study.

Thus, the results and conclusions of this study should be interpreted cautiously, as transferability to different contexts is limited.

CONCLUSION

AF has a negative impact on many cardiovascular diseases[106,107], but its most challenging is thromboprophylaxis. Although anticoagulation provides a net clinical benefit in patients with AF, a noticeable gap in antithrombotic prescription between real world and guideline recommendations was shown even in recent studies[108-111]. The long-awaited introduction of DOACs in the field of anticoagulation brought physicians a safer option, and in the last years, several real-world studies have confirmed their effectiveness and safety. The prescription trend of antithrombotic therapy in AF patients has noticeably changed over very recent years.

The main aim of our study was to describe patterns of OAC prescription for stroke prevention in a real-world population of Italian AF patients discharged by a cardiology ward. We demonstrated a significant increase from 2010 to 2021 in the proportion of OAC prescriptions, regardless of antiplatelet drugs use. This increase appears to be the consequence of greater DOACs use, mainly FXa inhibitors. Contextually, VKA use declined gradually regardless of antiplatelet drugs use, and the same phenomenon was shown for antiplatelet therapy alone or in double combination; finally we noted a decrease in the proportion of patients without any antithrombotic therapy.

These findings, in line with findings from other European and global datasets, appear consistent with recent changes in AF management guidelines; this suggests, in Italy, an improvement in adherence to guidelines clinical recommendations. Despite this significant improvement, we should highlight, however, that OAC prescription remains suboptimal over time; thus, a significant proportion of patients with AF still do not receive appropriate treatments for stroke prevention, suggesting that the increasing use of DOACs is not yet closing the gap between scientific evidence, recommendations from academic guidelines and clinical practice in the general population. Thus, an unmet medical need remains among patients with AF. Due to the nature of this study, we cannot, however, provide explanations as to the decision-making processes that underlie these apparent changes in prescriptions.

Improving adherence to AF guideline recommendations regarding OACs treatment requires still further efforts. Clinicians and policy makers should develop more specific educational intervention programs for physicians, to ensure that OACs, especially DOACs, are appropriately prescribed to eligible patients, in particular to vulnerable subgroups by age, socioeconomic status, and presence of comorbid conditions, in order to optimize health resources.

As the burden of disease continues to increase, it remains imperative to implement appropriate use of anticoagulation among AF patients with elevated stroke risk, targeted to local care delivery models, aiming to decrease both the risk of death and potentially preventable cardiovascular events, and associated medical costs for the healthcare systems. We need further studies investigating why OAC treatment in AF patients remains suboptimal, intervening on the relative barriers.

ARTICLE HIGHLIGHTS

Research background

International guidelines extended prescription criteria for oral antithrombotic therapy, in particular for direct oral anticoagulants (DOACs) in atrial fibrillation (AF). However, oral anticoagulant (OAC) prescription is still suboptimal, mainly for DOACs.

Research motivation

Considering the huge clinical impact and healthcare economic burden (in terms of both direct medical costs and indirect productivity losses), there are a number of reasons why it is important to complement experimental data with real-life or observational data, investigating OAC treatment in the real world, and the potential nonadherence to AF treatment guidelines. It is, in fact, important that AF guidelines are followed, as non-adherence to OACs is associated with increased ischemic stroke and mortality in high-risk patients.

Research objectives

We aimed to evaluate temporal prescription patterns of antithrombotic agents in a cohort of patients hospitalized with AF in a Cardiology Department. This should be useful in determining how AF guidelines are followed in the real-world.

Research methods

This was a retrospective, single-center, observational study conducted in the Cardiology Unit of S. Antonio Abate Hospital of Trapani (Western Sicily, Italy). We reviewed the database of medical records of all patients aged ≥ 18 years who were consecutively discharged from January 2010 to 2021. We collected data on demographic and clinical characteristics, including age and sex, main and secondary diagnosis at discharge, diagnostic and therapeutic procedures, and prescribed antithrombotic treatments from the discharge medication list.

Research results

From 2010 to 2021, we showed a significant increase in the proportion of AF patients on OAC therapy, regardless of antiplatelet agent use. The main reason for this increase was due to greater DOACs use, mainly FXa inhibitors. Contextually, VKA use, as well as antiplatelet therapy, alone or in double combination, declined; however, the proportion of patients not receiving any antithrombotic therapy globally decreased.

Research conclusions

These findings, in line with findings from other European and global datasets, appear consistent with recent changes in AF management guidelines; this suggests, in Italy, an improvement in adherence to guidelines clinical recommendations. Despite this, we should highlight, however, that OAC prescription remains suboptimal over time; thus, a significant proportion of patients with AF still do not receive appropriate treatments for stroke prevention, suggesting that the increasing use of DOACs is not yet closing the gap between scientific evidence, recommendations from academic guidelines and clinical practice in the general population.

Research perspectives

Improving the adherence to AF guideline recommendations for stroke prevention with OAC therapy requires further efforts. Clinicians and policy health makers need to develop more specific educational intervention programs for physicians to ensure that OACs, especially DOACs, are appropriately prescribed to eligible patients, in particular to vulnerable subgroups, in order to optimize health resources. We need further studies investigating why OAC treatment in AF patients remains suboptimal, intervening on the relative barriers.

FOOTNOTES

Author contributions: Abrignani MG was responsible for the conception and design of the study, and wrote the first draft of the manuscript; Lombardo A, Braschi A, Renda N, Abrignani V, and Lombardo RM contributed to the design of the study and made critical revisions of the manuscript related to its important intellectual content; and all authors gave final approval of the version of the article to be published.

Institutional review board statement: As this study was a retrospective review of a database with fully anonymized data and without risk of patients' identification, it does not require ethical approval in our Institution. Permission to use patient data from this facility has been obtained from the Head of Cardiology Unit, S. Antonio Abate Hospital of Trapani.

Informed consent statement: Patients were not required to give informed consent for the study as the analysis used anonymous clinical data that were obtained from a database.

Conflict-of-interest statement: All authors have no disclosures or conflicts 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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META-ANALYSIS

Potential for sodium-glucose cotransporter-2 inhibitors in the management of metabolic syndrome: A systematic review and meta-analysis

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Abstract

BACKGROUND

Landmark trials have established the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) in cardiovascular disease including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of diabetes mellitus. However, studies evaluating the role of SGLT2-Is in metabolic syndrome (MetS) are limited.

AIM

This study primarily aimed to evaluate the impact of SGLT2-Is on the components of MetS.

METHODS

Two independent reviewers and an experienced librarian searched Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify placebo controlled randomized controlled trials that evaluated the impact of SGLT2-Is on the components of MetS as an endpoint. Pre- and post-treatment data of each component were obtained. A meta-analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

RESULTS

Treatment with SGLT2-Is resulted in a decrease in fasting plasma glucose (–18.07

mg/dL; 95%CI: -25.32 to –10.82), systolic blood pressure (–1.37 mmHg; 95%CI: -2.08 to –0.65), and waist circumference (–1.28 cm; 95%CI: -1.39 to –1.18) compared to placebo. The impact on high-density lipoprotein cholesterol was similar to placebo (0.01 mg/dL; 95%CI: -0.05 to 0.07).

CONCLUSION
SGLT2-Is have a promising role in the management of MetS.

Key Words: Metabolic syndrome; Sodium-glucose cotransporter 2 inhibitors; Dapagliflozin; Empagliflozin; Cardiovascular disease

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Core Tip: This meta-analysis of randomized, placebo-controlled trials aimed to evaluate the impact of dapagliglozin and empagliflozin on metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III. In doing so, it highlighted a statistically significant improvement in fasting plasma glucose, systolic blood pressure and waist circumference. The effect of dapagliflozin and empagliflozin on high-density lipoprotein cholesterol was similar to that of placebo. In addition to its primary aim, this study also highlighted an improvement in other cardiometabolic parameters including hemoglobin A1C, uric acid and body weight in patients that received dapagliflozin and empagliflozin.

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) are a relatively novel and revolutionary class of medications that reduce the reabsorption of glucose from the proximal tubules in the kidneys[1-4]. Their glycosuric effect led to their initial use in the management of patients with type 2 diabetes mellitus (DM)[1-4]. However, recent large, randomized control trials (RCTs) have highlighted the extension of their benefits to cardiovascular diseases (CVD) including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of DM[5-15]. However, to date, studies on the impact of SGLT2-Is in the management of metabolic syndrome (MetS) and its components remain inadequate. Metabolic syndrome is an emerging pandemic[16-19]. Its prevalence has risen from approximately 25% to 38% between the early 1990s to 2010s in the United States[16-19]. The prevalence has increased by 29.1% in people aged 40-60 years[16-19]. It has been defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III as the presence of 3 of 5 entities: (1) Waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in females; (2) Serum triglycerides (TGL) ≥ 150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) ≥ 130/85 mmHg or on drug treatment for hypertension (HTN); and (5) Fasting plasma glucose (FPG) ≥ 100 mg/dL or on drug treatment for elevated blood glucose[20]. A growing body of evidence exists supporting the association of MetS with the development and progression of CVD[17-20]. In a meta-analysis by Mottillo *et al*[19] a 2-fold increase in the risk of CVD and CV mortality in patients with MetS was noted. DM is a component of the MetS and affords a 2-4-fold increase in CVD Risk[21]. Hence, there is an urgent need to improve the management of MetS, which currently ranges from lifestyle interventions such as physical activity and caloric restriction through dietary modification to pharmacological and surgical approaches that address components of the MetS[4]. The primary aim of this study is to evaluate the impact of the SGLT2-Is on the MetS parameters noted in NCEP ATP III criteria. The secondary aim is to highlight the effect of SGLT2-Is on other cardiometabolic parameters including hemoglobin A1C (HbA1c), body weight (BW) and uric acid (UA). This study is derived from placebo controlled RCTs that have evaluated the impact of these medications on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.

Table 1 Jadad score of included studies

Ref.	Randomization	Blinding	Accountability	Jadad score
Bailey *et al*[24], 2015	2	1	1	4
Bailey *et al*[25], 2013	1	1	1	3
Rosenstock *et al*[26], 2012	1	1	1	3
Wilding *et al*[27], 2014	2	2	1	5
Matthaei *et al*[34], 2015	2	1	1	4
Jabbour *et al*[30], 2014	1	1	1	3
Anker *et al*[15], 2021	2	2	1	5
Sone *et al*[36], 2020	2	1	1	4
Bolinder *et al*[33], 2014	2	2	1	5
Rosenstock *et al*[37], 2015	2	1	1	4
Rosenstock *et al*[38], 2014	2	1	1	4
Kohan *et al*[28], 2016	1	1	1	3
Zinman *et al*[5], 2015	2	1	1	3
Brown *et al*[35], 2020	1	1	1	3
Qin *et al*[32], 2019	1	U	U	1
Gause-Nilsson 2014[1]	1	U	U	1
List *et al*[39], 2009	1	1	1	3
McMurray *et al*[31], 2019	2	2	1	5

[1]No baseline data reported for Gause-Nilsson 2014.
U: Unclear.

MATERIALS AND METHODS

Data sources and searches

Two authors independently searched the electronic library database in Medline, Scopus and the Cochrane central from inception to December 9, 2021, using the following keywords: SGLT2-I, metabolic, cardiometabolic, TGL, FPG, BP, HDL, waist, abdominal, circumference, lipids, waist-to-height ratio, hypertriglyceridemia, HTN, MetS, RCT, random allocation, randomly allocated, random, and allocated randomly. Additionally, different combinations of these keywords were applied in each database search. The search was extended to ClinicalTrials.gov. An independent search was also conducted by a qualified librarian using similar search terms.

Study selection

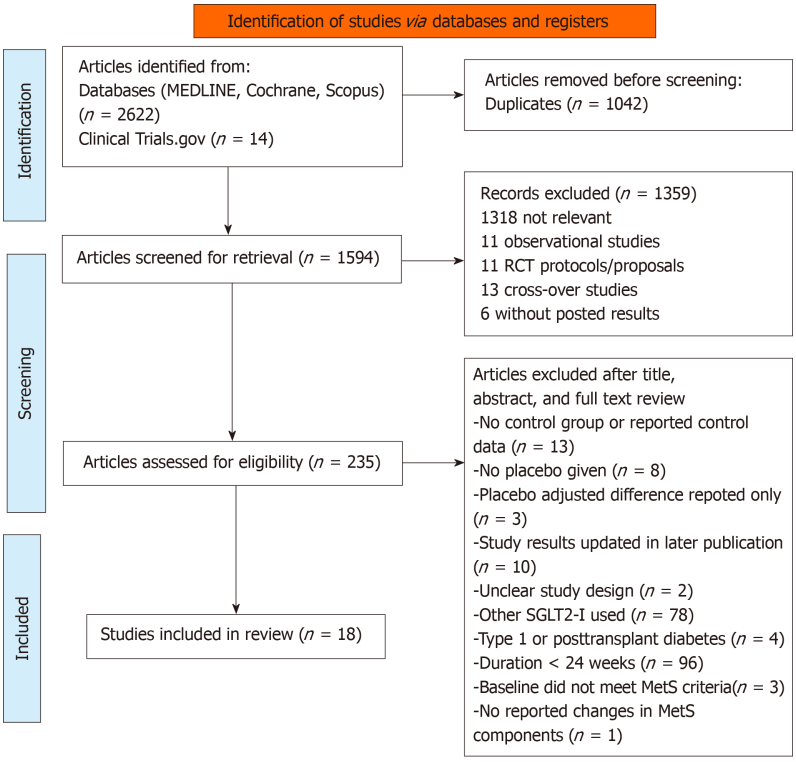
The eligible studies were RCTs, allocated patients to an SGLT2-I group (that received either Dapagliflozin or Empagliflozin) or a placebo group, reported baseline and post-treatment values ≥ 1 component of MetS, had a treatment duration 6 mo and were published in the English language. Studies not meeting these criteria were excluded. Disagreements on study selection were either resolved by consensus or by Farouk Mookadam. The study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guideline[22] (PRISMA checklist).

Data extraction

Extracted data included duration of follow-up, sample size and dose of dapagliflozin and empagliflozin studied. Demographic and biomarker characteristics extracted at baseline and follow up included mean age, gender, race, DM, mean WC, FPG, TGL, HDL, systolic BP (SBP), diastolic BP (DBP), HbA1C, BW and UA.

Quality assessment

The methodologic quality of the RCTs was assessed using the Jadad score. Points were allocated for randomization, blinding and accountability of the study participants, with a total score range from 0 to 5 [23] (Table 1).



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Figure 1 PRISMA flow diagram showing outcomes of databases and registers search. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; Mets: Metabolic syndrome.

Outcomes

The primary outcomes of this study are post-treatment changes in WC, FPG, TGL, HDL, and BP. The secondary outcomes are post-treatment changes in BW, HbA1C and UA.

Statistical analysis

All outcome data were reported as mean with standard deviation and were converted to conventional units. Data analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). The forest plots of the above outcomes were visually represented after pooling the mean differences using the random-effects model. Heterogeneity was assessed with the I^2 test. Post-hoc subgroup analyses including doses and/or SGLT2-I type were performed if there was significant heterogeneity.

RESULTS

Search results and study inclusion

The initial literature search identified a total of 2636 potentially relevant studies, 14 of which were gathered from ClinicalTrials.gov. After excluding 1042 duplicates, a total of 1594 studies were screened. Of these, 235 studies were selected for abstract and/or full text review. An additional 217 studies were excluded either because they did not meet the above inclusion criteria, precursors of long-term studies, had a cross-over design or had no published results. A total of 18 studies[5,15,24-39] were eligible for meta-analysis (Figure 1). Of these, 3 studies reported WC[30,33,36], 9 reported FPG[24-27,29,30,34-36,39], 4 reported TGL[5,30,35,38], 3 reported HDL[34,37,38], 7 reported SBP[12,15,28,29,33,35,36] and 6 reported DBP[24,26,28,33,35,39] (Table 2 and 3).

Participant characteristics

A total of 26427 patients were included in the analysis. The SGLT2-I group comprised a total of 15914 patients. Of these, 7355 patients received dapagliflozin and 8559 received empagliflozin. The placebo group comprised a total of 10513 patients (Table 2 and 3). 59.4% were men. Among studies with reported data, 75% were White, 19.9% were Asian and 4.8% were Black. The mean treatment duration was 79 wk. The mean age in the SGLT2-I group was 53.4 years, and 54.8 years in the placebo group. The vast majority (78.6%) were DM patients. The baseline and post-treatment values of MetS components and the cardiometabolic variables are presented in Tables 3 and 4.

Table 2 Characteristics of included studies

				Treatment group		Placebo group	Participants (*n*)		Mean age (yr)		Race (*n*)		
Ref.	Duration (*wk*)	%male	%DM	SGLT2-I	Other therapy	Other therapy	SGLT2-I	Placebo	SGLT2-I	Placebo	White	Asian	Black
Bailey *et al*[25], 2013	102		100%	DAPA (2.5)	Metformin	Metformin	137	137	55.0 (9.3)	53.7 (10.3)			
				DAPA (5)	Metformin		137		54.3 (9.4)				
				DAPA (10)	Metformin		135		52.7 (9.9)				
Bailey *et al*[24], 2015	102		100%	DAPA (2.5)	Metformin	Metformin	65	75	53.0 (11.7)	52.7 (10.3)			
				DAPA (5)	Metformin		64		52.6 (10.9)				
				DAPA (10)	Metformin		70		50.6 (10.0)				
Bolinder *et al*[33], 2014	102	55.6%	100%	DAPA (10)		Placebo only	69	71	60.6 (8.2)	60.8 (6.9)	140	NR	NR
Brown *et al*[35], 2020	52	57.6%	100%	DAPA (10)		Placebo only	32	34	64.25 (7.01)	66.74 (6.62)			
Gause-Nilsson 2014[1]	104		100%	DAPA (10)	Insulin	Insulin	480	482					
Jabbour *et al*[30], 2014	48	54.8%	100%	DAPA (10)	Sitagliptin, metformin	Sitagliptin, metformin	223	224	54.8 (10.4)	55.0 (10.2)	332	4	17
Zinman *et al*[5], 2015	102			DAPA (2.5)		Placebo only	625	785	57.5 (9.9)	56.9 (10.2)			
				DAPA (5)			767		56.5 (10.1)				
				DAPA (10)			859		56.0 (9.9)				
List *et al*[39], 2009	12		100%	DAPA (2.5)		Placebo only	59	54	55 (11)	53 (11)			
				DAPA (5)		Metformin	58	56	55 (12)	54 (9)			
				DAPA (10)			47		54 (9)				
				DAPA (20)			59		55 (10)				
				DAPA (50)			56		53 (10)				
Matthaei *et al*[34], 2015	52	49.2%	100%	DAPA (10)		Placebo only	108	108	61.1 (9.7)	60.9 (9.2)	206	NR	NR
McMurray *et al*[31], 2019	72	77%	45%	DAPA (10)		Placebo only	2373	2371	66.2 (11.0)	66.5 (10.8)	3333	1116	226
Qin *et al*[32], 2019	16		100%	DAPA (10)		Placebo only	22	12					
				DAPA (10)	Saxagliptin		22						
Rosenstock *et al*[26], 2012	48		100%	DAPA (5)	Pioglitazone	Pioglitazone	141	139	53.2 (10.9)	53.5 (11.4)			
				DAPA (10)	Pioglitazone		140		53.8 (10.4)				

Wilding *et al*[27], 2014	104		100%	DAPA (2.5)	Insulin, existing OAD	Insulin, existing OAD	202	193	59.8 (7.6)	58.8 (8.6)			
				DAPA (5/10)[2]	Insulin, existing OAD		211		59.3 (7.9)				
				DAPA (10)	Insulin, existing OAD		194		59.3 (8.8)				
Anker *et al*[15], 2021	112	55%	49%	EMPA (10)		Placebo only	2997	2991	71.8 (9.3)	71.9 (9.6)	4542	824	258
Sone *et al*[36], 2020	52	72.6%	100%	EMPA (10)		Placebo only	86	90	58.3 (10.0)	59.1 (10.7)	NR	266	NR
				EMPA (25)			90		58.6 (9.5)				
Rosenstock *et al*[37], 2015	78	56%	100%	EMPA (10)		Placebo only	169	170	58.6 (9.8)	58.1 (9.4)	343	98	48
				EMPA (25)			155		59.9 (10.5)				
Rosenstock *et al*[38], 2014	52	45%	100%	EMPA (10)		Placebo only	186	188	56.7 (8.7)	55.3 (10.1)	531	NR	19
				EMPA (25)			189		58.0 (9.4)				
Zinman *et al*[5], 2015	220	71.5%	100%	EMPA (10)		Placebo only	2345	2333	63.0 (8.6)	63.2 (8.8)	5081	1517	357
				EMPA (25)			2342		63.2 (8.6)				

Data reported as mean (SD).

[1]No baseline data reported for Gause-Nilsson 2014.

[2]5 for 48 wk, 10 for 56 wk.

NR: Not reported; OAD: Oral antidiabetic drugs; SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; DM: Diabetes mellitus.

SGLT2-Is and FPG: Nine RCTs in which a total of 1474 patients received SGLT2-Is were analyzed. The random effect model demonstrated a mean reduction in FPG of –18.07 mg/dL (95%CI: -25.32 to –10.82; I^2 = 99%) (Figure 2A). The significant heterogeneity persisted after a subgroup analysis based on dose of SGLT2-Is (2.5 mg *vs* 10 mg). 463 participants received the 2.5 mg dose which had a similar impact as placebo on FPG: -1.45 mg/dL (95%CI: -8.73 to 5.82; I^2 = 71%) (Figure 2B). The 10 mg dose resulted in a higher reduction in mean FPG of –30.02 mg/dL (95%CI: -38.97 to –21.08; I^2 = 87%) (Figure 2B).

SGLT2-Is and BP: The analysis for SBP included a total of 6662 participants from seven RCTs. There was a modest mean reduction in SBP of –1.37 mmHg (95%CI: -2.08 to –0.65, I^2 = 85%) (Figure 3A). A subsequent post-hoc analysis based on SGLT2-I type demonstrated the empagliflozin RCTs were responsible for the high heterogeneity. The mean reduction noted with empagliflozin was not statistically significant: -0.70 mmHg (95%CI: 1.72 to 0.32; I^2 = 97%). Dapagliflozin use was associated with a higher mean SBP reduction of -2.03 mmHg (95%CI: -2.83 to –1.24; I^2 = 8%) (Figure 3B). The analysis of 6 RCTs that comprised 1018 total patients demonstrated no reduction in DBP with SGLT2-I use compared to placebo: -0.50 mmHg (-1.76 to 0.75; I^2 = 97%) (Figure 4).

SGLT2-Is and WC: A total of 378 patients from 3 RCTs received an SGLT2-I. The random effect model highlighted a mean reduction in WC of –1.28 cm (95%CI: -1.39 to –1.18; I^2 = 0%) (Figure 5).

Table 3 Baseline values for the MetS components

		Waist circumference (cm)		Triglyceride (mg/dL)		HDL (mg/dL)		SBP (mmHg)		DBP (mmHg)		Fasting plasma glucose	
Ref.	SGLT2-I (daily dose, mg)	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo
Bailey *et al*[25], 2013	DAPA (2.5)							126.6 (14.5)	127.7 (14.6)	79.5 (8.7)	80.9 (9.0)	161.3 ± 43	165.42 (46.44)
	DAPA (5)							126.9 (14.3)		80.8 (8.5)		169.0 ± 49	
	DAPA (10)							126.0 (15.9)		79.0 (10.2)		155.9 ± 38.7	
Bailey *et al*[24], 2015	DAPA (2.5)	105.6 (14.9)	103.2 (13.8)					129.3 (16.1)	124.7 (16.3)	79.1 (7.9)	81.0 (9.5)	163.8 ± 48.6	160.2 (41.4)
	DAPA (5)	104.3 (11.7)						124.7 (15.3)		81.6 (8.9)		162 ± 45	
	DAPA (10)	108.1 (13.2)						125.1 (16.4)		80.2 (8.6)		167.4 ± 41.4	
Bolinder *et al*[33], 2014	DAPA (10)	105.6 ± 10.1	104.5 ± 12.3					136.1 ± 13.8	133.3 ± 13.7	80.6 ± 8.0	80.4 ± 8.3	147.6 ± 25.2	149.4 ± 25.2
Brown *et al*[35], 2020	DAPA (10)							137.25 ± 7.5	136.15 ± 9.11	79.16 ± 8.63	77.79 ± 8.25	140.4 ± 63	144.9 ± 54.0
Jabbour *et al*[30], 2014	DAPA (10)											162.2 (36.8)	163.0 (34.5)
Kohan *et al*[28], 2016	DAPA (2.5)							133.1 (17.2)	130.8 (15.8)	79.8 (9.3)	79.6 (9.0)		
	DAPA (5)							130.5 (16.2)		79.5 (8.9)			
	DAPA (10)							131.1 (16.3)		79.1 (9.3)			
List *et al*[39], 2009	DAPA (2.5)							127 ± 14	126 ± 16	78 ± 8	77 ± 8	145 ± 34	150 ± 46
	DAPA (5)							126 ± 13	126 ± 13	76 ± 8	78 ± 8	153 ± 48	143 ± 33
	DAPA (10)							127 ± 16		77 ± 8		148 ± 38	
	DAPA (20)							127 ± 15		77 ± 8		149 ± 41	
	DAPA (50)							126 ± 16		77 ± 9		153 ± 42	
Matthaei *et al*[34], 2015	DAPA (10)			185.9 ± 123.9	177.1 ± 79.7	46.44 ± 11.6	46.4 ± 11.6	134.5 ± 12.6	136.4 ± 14.2	80.4 ± 9.2	81.6 ± 7.9	167.4 ± 43.3	180.2 ± 43.1
McMurray *et al*[31], 2019	DAPA (10)									72.5 ± 13.2			
Rosenstock *et al*[26], 2012	DAPA (5)											168.6 +/-52.1	160.7 +/-47.0
	DAPA (10)											164.9 +/-46.3	
Wilding *et al*[27], 2014	DAPA (2.5)	109.7 (13.4)	110.2 (14.5)									180 ± 59.4	171 (57.6)
	DAPA (5/10)[1]	109.3 (13.4)										185.4 ± 59.4	
	DAPA (10)	109.6 (12.5)										172.8 ± 54	
Anker *et al*[15], 2021	EMPA (10)							131.8 ± 15.6	131.9 ± 15.7	78			

Rosenstock *et al*[37], 2015	EMPA (10)			175.23 ± 14.2	158.5 ± 7.97	46.1 ± 0.77	46 ± 0.77	132.4 ± 15.5	133.9 ± 16.3	78.4 ± 9.2	78.6 ± 10.9	138.6 ± 52.2	142.2 ± 46.8
	EMPA (25)			162.8 ± 0.8		46.1 ± 0.78		132.8 ± 15.1		77.9 ± 10.2		145.8 ± 25	
Rosenstock *et al*[38], 2014	EMPA (10)			171.7 ± 8.85	178.9 ± 12.4	46.1 ± 0.79	45.2 ± 0.77	134.2 ± 16.4	132.6 ± 15.8	79.5 ± 8.5	78.2 ± 8.8	158.9 ± 46.8	151.38 ± 45.72
	EMPA (25)			169.9 ± 7.08		46.4 ± 0.77		132.9 ± 14.2		78.7 ± 8.5		149.2 ± 48.6	
Sone *et al*[36], 2020	EMPA (10)	93.3 ± 8.8	93.8 ± 9.6					134.2 ± 14.6	135.7 ± 14.0	80.1 ± 10.2	79.6 ± 8.7	168.8 ± 43.1	159.1 ± 38.5
	EMPA (25)	93.1 ± 8.3						136.3 ± 14.3		80.0 ± 10.6		156.1 ± 37.7	
Zinman *et al*[5], 2015	EMPA (10)	104.9	105.1	168.4 ± 2.67	170.7 ± 2.53	44.7 ± 0.25	44.0 ± 0.24	134.9 ± 16.8	135.8 ± 17.2	76.6 ± 9.8	76.8 ± 10.1		
	EMPA (25)	104.9		172.6 ± 2.27		44.5 ± 0.25		135.6 ± 17.0		76.6 ± 9.7			

[1]5 mg for 48 wk, 10 for 56 wk.

HDL: High-density lipoprotein; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; SGLT2-I: Sodium-glucose cotransporter 2 inhibitor.

SGLT2-Is and HDL: A total of 1080 patients from 3 RCTs were analyzed for the impact of SGLT2-Is on HDL. There was no significant difference in post-treatment HDL between the SGLT2-I and placebo groups: 0.01 mg/dL (95%CI: -0.05 to 0.07; I^2 = 100%) (Figure 6).

SGLT2-Is and TGL: TGL levels pre or post treatment were not reported in all the trials. Hence this component of the MetS could not be analyzed in this meta-analysis.

SGLT2-Is and other cardiometabolic parameters: HbA1C, BW and UA.

SGLT2-Is resulted in a modest mean reduction in HbA1C: -0.68% (95%CI: -0.88 to –0.48; I^2 = 89%) (Figure 7A). A subgroup analysis based on doses (2.5 mg and 10 mg) demonstrated no change in heterogeneity and statistical significance. Both the 2.5 mg and 10 mg doses of SGLT2-I resulted in a statistically significant improvement in A1C (Figure 7B). There was a reduction in mean BW of –1.79 kg (95%CI: -2.07 to -1.51; I^2 = 97%) with SGLT2-I use (Figure 8A). This improvement in BW was noted regardless of SGLT2-I dose. The subgroup analysis based on dose and SGLT2-I type could not highlight the potential cause of the significant heterogeneity (Figures 8B and C). UA decreased with the use of SGLT2-I: -1.03 mg/dL (95%CI: -1.14 to –0.93; I^2 = 98%) (Figure 9A). This reduction was greater within the dapagliflozin subgroup: -4.52 mg/dL (95%CI: -8.96 to –0.08; I^2 = 100%) *vs* –0.20 mg/dL (95%CI: -0.51 to 0.12; I^2 = 88%) the empagliflozin subgroup. The impact on UA also appears to be dose-dependent: -1.05 mg/dL (95%CI: -1.98 to –0.12; I^2 = 99%) with 10 mg and –0.18 mg/dL (95%CI: -1.4 to 1.05; I^2 = 0%) (Figures 9B and C). Table 4 provides a summary of the placebo adjusted treatment effect of SGLT2-Is on metabolic parameters: HbA1C, BW and UA.

Table 4 Baseline data for HbA1C, BW, and UA

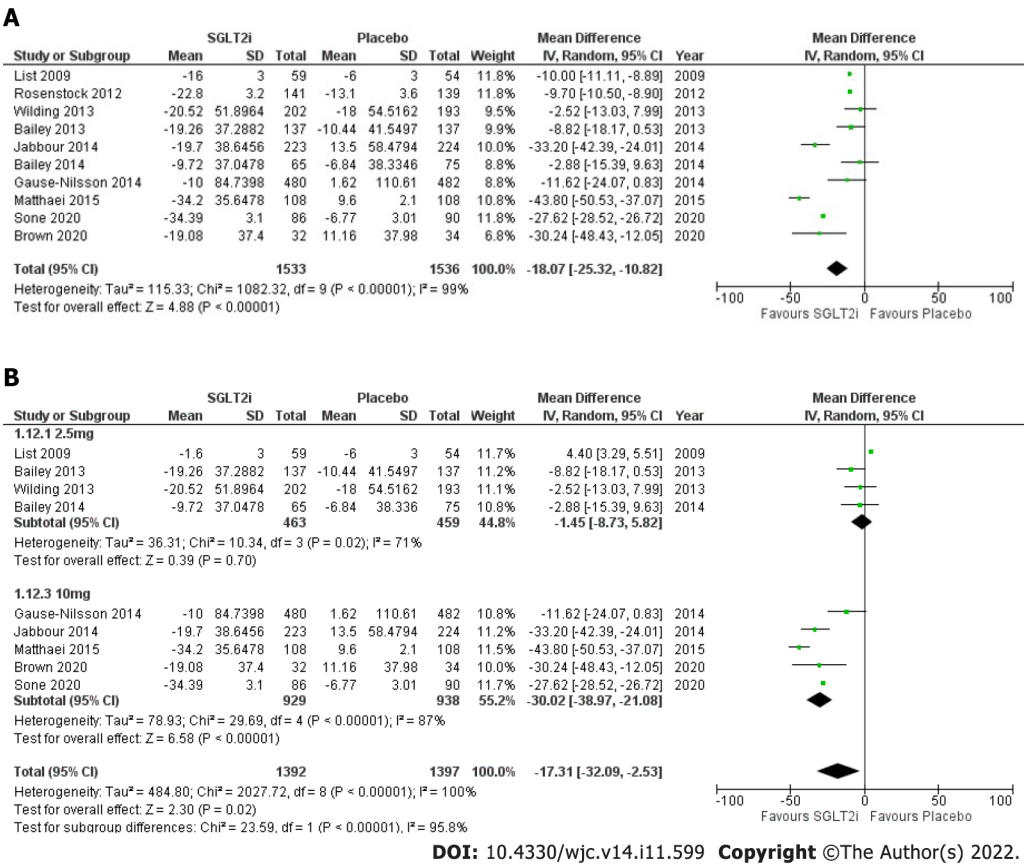
		Body weight (kg)		Hemoglobin A1c (%)		Uric acid (mg/dL)	
Ref.	**SGLT2-I (daily dose, mg)**	**SGLT2-I**	**Placebo**	**SGLT2-I**	**Placebo**	**SGLT2-I**	**Placebo**
Bailey *et al*[25], 2013	DAPA (2.5)	84.90 (17.77)	87.74 (19.24)	7.99 (0.90)	8.12 (0.96)		
	DAPA (5)	84.73 (16.26)		8.17 (0.96)			
	DAPA (10)	86.28 (17.53)		7.92 (0.82)			
Bailey *et al*[24], 2015	DAPA (2.5)	90.8 (22.8)	88.8 (19.0)	7.92 (0.90)	7.84 (0.87)	5.92 (1.42)	5.09 (1.32)
	DAPA (5)	87.6 (17.1)		7.86 (0.94)		5.55 (1.44)	
	DAPA (10)	94.2 (18.7)		8.01 (0.96)		5.67 (1.44)	
Bolinder *et al*[33], 2014	DAPA (10)	92.1 (14.1)	90.9 (13.7)	7.19 (0.44)	7.16 (0.53)		
Brown *et al*[35], 2020	DAPA (10)	91.58 (14.62)	91.48 (14.13)	7.8 (3.17)	7.66 (3.08)		
Jabbour *et al*[30], 2014	DAPA (10)	91.0 (21.6)	89.2 (20.9)	7.9 (0.8)	8.0 (0.8)		
Kohan *et al*[28], 2016	DAPA (2.5)			8.17 (0.86)	8.12 (0.92)		
	DAPA (5)			8.27 (0.95)			
	DAPA (10)			8.11 (0.93)			
List *et al*[39], 2009	DAPA (2.5)	90 (20)	89 (18)	7.6 (0.7)	7.9 (0.9)	5.5 (1.2)	5.5 (1.4)
	DAPA (5)	89 (17)		8.0 (0.9)		5.2 (1.3)	
	DAPA (10)	86 (17)		8.0 (0.8)		5.5 (1.2)	
	DAPA (20)	88 (18)		7.7 (0.9)		5.3 (1.3)	
	DAPA (50)	92 (19)		7.8 (1.0)		5.6 (1.4)	
Matthaei *et al*[34], 2015	DAPA (10)	88.6 (17.6)	90.1 (16.2)	8.08 (0.91)	8.24 (0.87)		
Rosenstock *et al*[26], 2012	DAPA (5)	87.8 (20.7)	86.4 (21.3)	8.40 (1.03)	8.34 (1.00)		
	DAPA (10)	84.8 (22.2)		8.37 (0.96)			
Wilding *et al*[27], 2014	DAPA (2.5)	93.0 (16.7)	94.5 (19.8)	8.46 (0.78)	8.47 (0.77)		
	DAPA (5/10)[1]	93.3 (17.4)		8.62 (0.89)			
	DAPA (10)	94.5 (16.8)		8.57 (0.82)			
Anker *et al*[15], 2021	EMPA (10)						
Sone *et al*[36], 2020	EMPA (10)	73.3 (11.5)	74.0 (11.3)	8.8 (0.7)	8.7 (0.7)		
	EMPA (25)	72.2 (11.4)		8.7 (0.7)			
Rosenstock *et al*[37], 2015	EMPA (10)	91.6 (20.1)	90.5 (22.5)	8.3 (0.8)	8.2 (0.8)	5.26 (1.71)	5.5 (2.1)
	EMPA (25)	94.7 (20.7)		8.3 (0.8)		5.63 (2)	
Rosenstock *et al*[38], 2014	EMPA (10)	96.7 (17.9)	95.5 (17.5)	8.39 (0.74)	8.33 (0.72)	5.48 (2.13)	5.5 (2.0)
	EMPA (25)	95.9 (17.3)		8.29 (0.72)		5.56 (2.07)	
Zinman *et al*[5], 2015	EMPA (10)	85.9 (18.8)	86.6 (19.1)	8.07 (0.86)	8.08 (0.84)	5.9	6
	EMPA (25)	86.5 (19.0)		8.06 (0.84)		5.98	

[1]5 for 48 wk, 10 for 56 wk.

SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; BW: Body weight; UA: Uric acid.

DISCUSSION

This meta-analysis of 18 placebo controlled RCTs was designed to primarily evaluate the impact of SGLT2-Is on the components of the MetS as defined by the NCEP ATP III criteria. In addition, it evaluated their impact on other cardiometabolic parameters including HbA1c, BW and UA. The major findings include: (1) An improvement in MetS components (FPG, WC and BP) in the SGLT2-I group compared to the placebo group, and (2) an improvement in HbA1c, BW and UA in the SGLT2-I group compared to the placebo group.

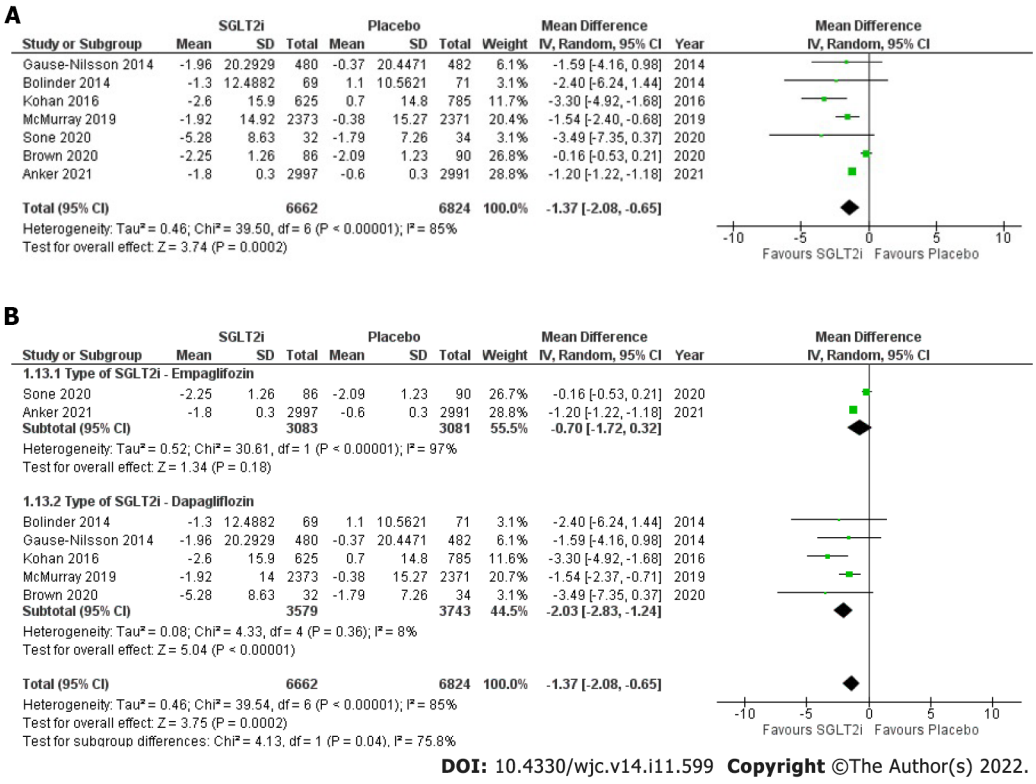


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Figure 2 Forest plot. A: Highlighting impact of SGLT2-I on FPG compared to placebo; B: SGLT2-I dose subgroup analysis performed for FPG. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; FPG: Fasting plasma glucose.

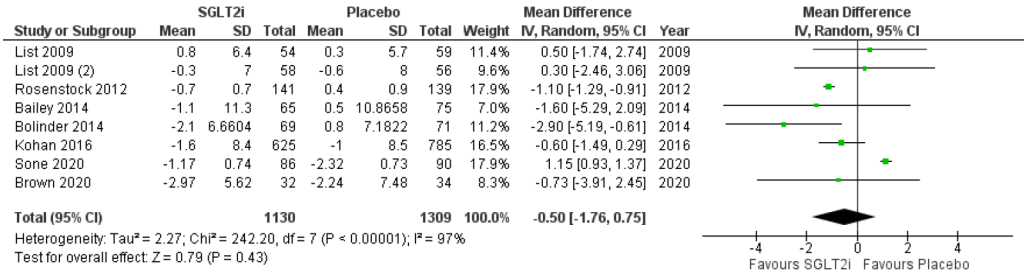
Previous meta-analyses[40-50] that evaluated the cardiometabolic effects of SGLT2-Is have only included at most four of the five components of MetS. Teo *et al*[40] evaluated WC, BP, FPG; Cho *et al*[49] analyzed WC, BP, HDL and Zaccardi *et al*[47] evaluated FPG, BP, HDL and TGL. In addition, the results of these studies have been inconsistent. While our study aimed to evaluate all components, we only had enough data for four components (FPG, BP, WC and HDL) owing to our inclusion criteria. In contrast to these studies[42,43,50], our study did not highlight a significant improvement in HDL with the use of SGLT2-Is. The reason behind this might be an inadequate statistical power; this study analyzed only 3 RCTs owing to the inclusion criteria compared to 47, 5 & 15 RCTs by Sánchez-García *et al*[41], Chen *et al*[42], and Shi *et al*[50] respectively. This study also evaluated the effect of low-dose SGLT2-Is on HDL, however it is unlikely this played a role in the outcome as the analysis by Chen *et al*[45] demonstrated a dose-independent impact. While this study has a higher mean treatment duration of 79 wk compared to prior meta-analyses which have a mean duration of 29 wk[40-50], the magnitude of the improvement in FPG, WC and BP appear similar between this study and its counterparts. This might suggest that SGLT2-Is have a ceiling effect on the components of MetS.

A high heterogeneity is noticed across all outcomes except for WC. This could be related to the differences in baseline diabetic medications taken by the patients, different doses, inclusion of more than one type of SGLT2-I and differences in the severity of hyperglycemia among the patients. However, the subgroup analysis for FPG based on dose revealed a significantly elevated heterogeneity with all doses evaluated. This study could not adjust for the differences in baseline diabetic medications and severity of hyperglycemia because these were universally different across the included RCTs, and a patient level meta-analysis would be needed for this. The heterogeneity associated with the SBP outcome in the empagliflozin subgroup may be due to the significant difference in sample size between the analyzed RCTs. A further sub-analysis based on the sample size was not completed because there were only 2 studies in the empagliflozin subgroup for SBP. The difference in efficacy between both SGLT2-Is on SBP appears to be largely due to the significant difference in the number of RCTs that constitute both SGLT2-I subgroup (2 RCTs in the empagliflozin subgroup *vs* 5 RCTs in the dapagliflozin subgroup). The small number of RCTs in the empagliflozin subgroup is due to this study's inclusion criteria. The differences between the patients' baseline antihypertensives could also be contributory to the high heterogeneity in the empagliflozin subgroup for SBP. The significant difference in treatment duration between the studies that evaluated DBP might explain the significant heterogeneity associated with the 10 mg dose of dapagliflozin. Inadequate power might explain the lack of statistical significance



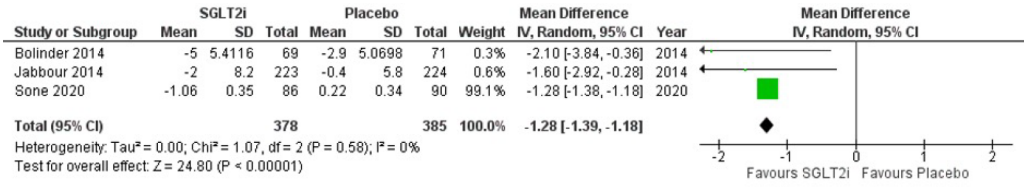
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Figure 3 Forest plot. A: Highlighting impact of SGLT2-I on SBP compared to placebo; B: SGLT2-I Type subgroup analysis performed for SBP. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; SBP: Systolic blood pressure.



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Figure 4 Forest plot highlighting impact of SGLT2-I on DBP compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; DBP: Diastolic blood pressure.

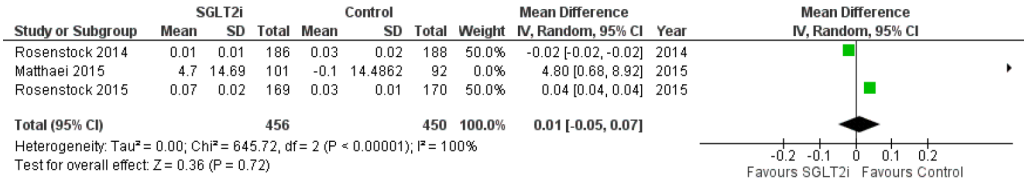


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Figure 5 Forest plot highlighting impact of SGLT2-I on WC compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; WC: Waist circumference.

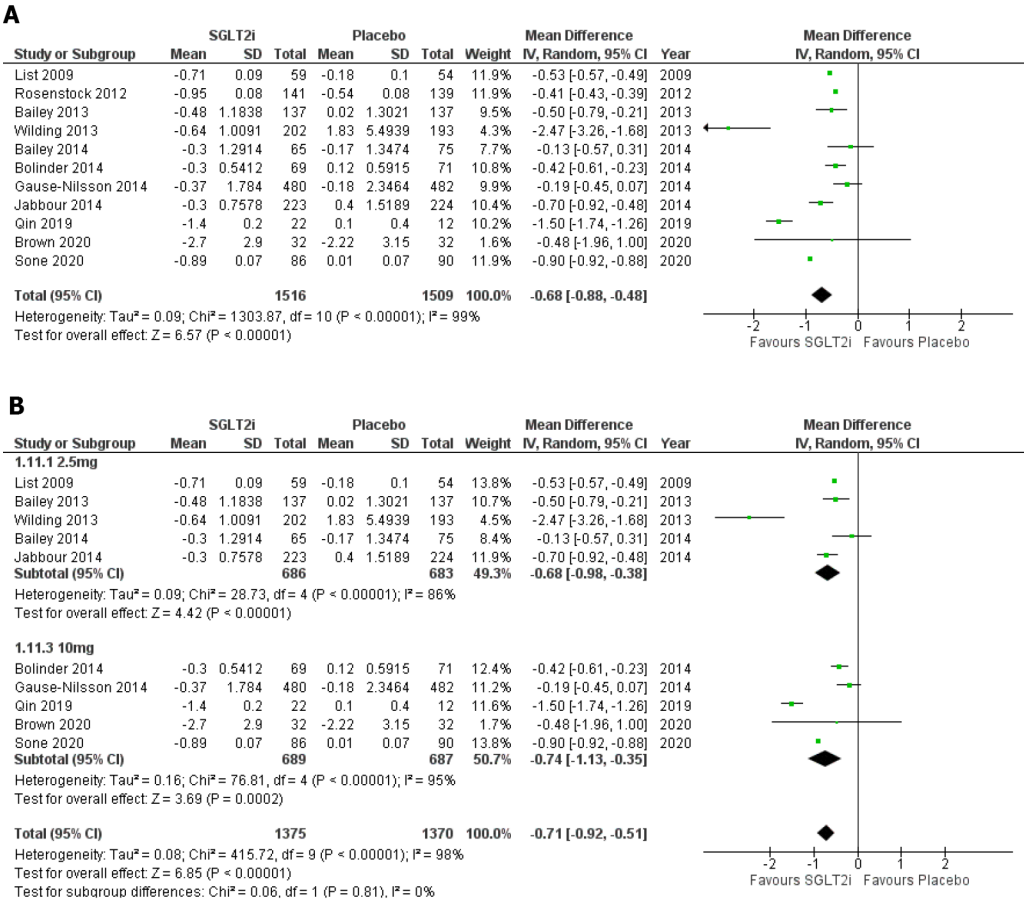
in the reduction of DBP.

The mechanism by which SGLT2-Is lead to improvement in the components of MetS and other cardiometabolic parameters have been partially elucidated[1,51-55]. The glucosuria, osmotic diuresis and natriuresis induced by the inhibition of SGLT-2 and the sodium hydrogen exchanger appears to play an important role in the improvement of FPG, HTN and HbA1c[51,52]. Their impact on HTN also



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Figure 6 Forest plot highlighting the absence of significant impact of SGLT2-I on HDL compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; HDL: High-density lipoprotein.

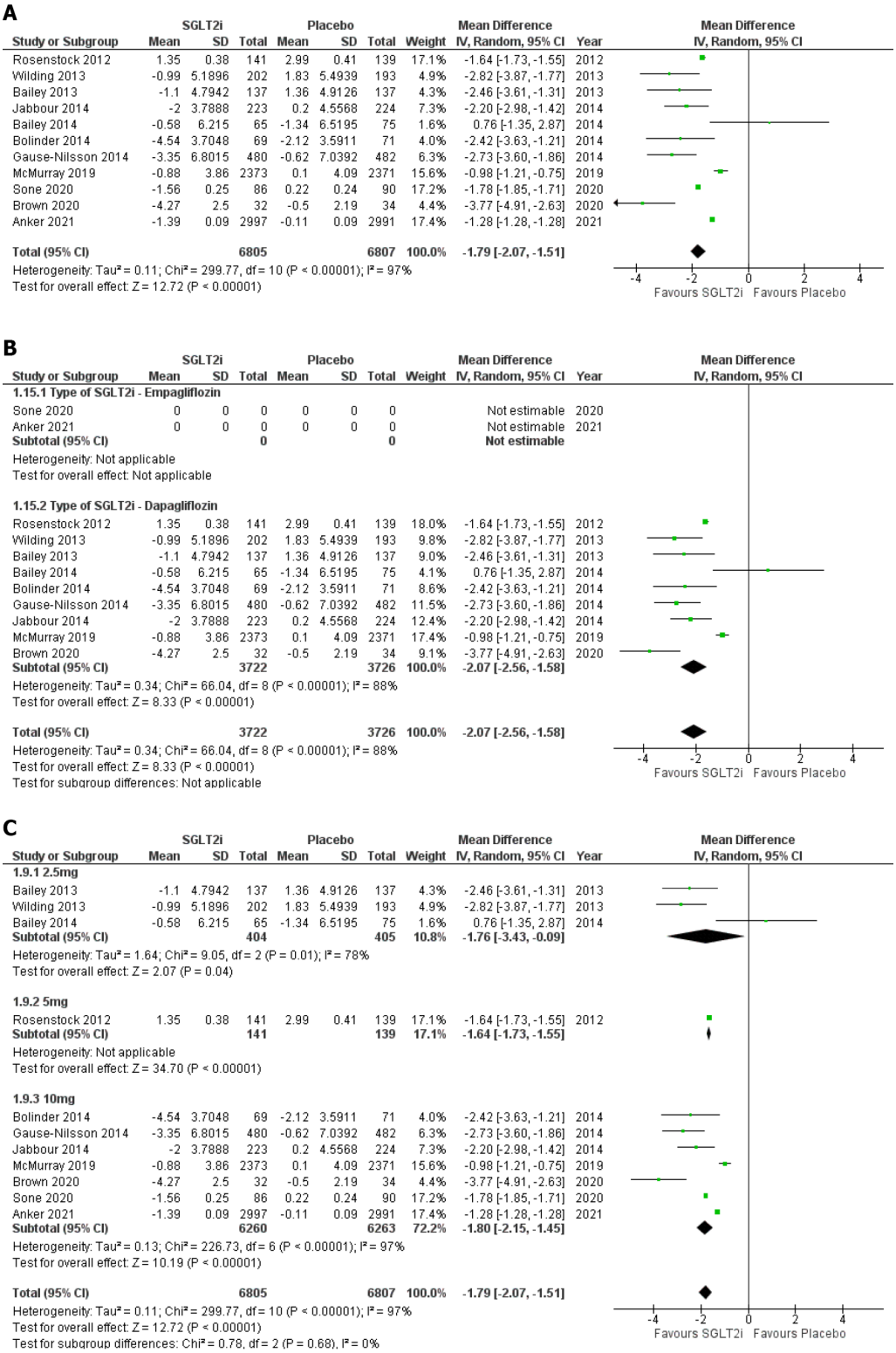


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Figure 7 Forest plot. A: Highlighting impact of SGLT2-I on HgbA1C compared to placebo; B: SGLT2-I Dose subgroup analysis performed for HgbA1C. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor.

stems from their ability to reduce arterial stiffness and endothelial dysfunction[51-53]. Furthermore, the improvement in UA noted with SGLT2-Is has been associated with the upregulation of the glucose transporter 9, a major urate transporter that secretes UA in the proximal kidney[1,53]. Interestingly, SGLT2-Is' cardiometabolic benefits have been linked to modification of certain genes involved in homeostasis[51,55]. These include a potential upregulation of Angiotensin 1-7 which leads to improvement in HTN and arterial stiffness[51]. The upregulation of genes involved in lipid metabolism including peroxisome proliferator-activated receptor alpha, acetyl-CoA carboxylase, fibroblast growth factor 21 and adenosine monophosphate-activated protein kinase have been associated with the improvement in TGL, HDL and BW[50]. SGLT2-Is have also been associated with increased levels of glucagon-like peptide 1, which is known to slow gastric emptying and reduce weight gain[54].

Perhaps through the improvement in MetS components, the combination of the above mechanisms might explain the improvement in CV mortality and heart failure hospitalization associated with SGLT2-Is in landmark trials[1-4,6,7,9-13]. In addition to its role in CVD, MetS is an independent risk factor in the development of DM[55,56]. Patients with MetS are approximately three to five times more likely to develop type 2 DM[55,56]. This highlights the complex yet incompletely understood connection between MetS, type 2 DM and CVD. Although the improvement in MetS components in this study



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Figure 8 Forest plot. A: Highlighting impact of SGLT2-I on BW compared to placebo; B: SGLT2-I Type subgroup analysis performed for BW; C: SGLT2-I Dose subgroup analysis performed for BW. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; BW: Body weight.

appears to be modest, our findings anticipate a possible role for SGLT2-Is in the management of MetS. Hence, it highlights the need for RCTs to evaluate the impact of SGLT2-Is on MetS compared with current management modalities including lifestyle modification.

Limitations

The findings of this study should be interpreted cautiously bearing several limitations. First, the mean baseline HDL and DBP of included RCTs did not meet threshold values for MetS. This is likely because

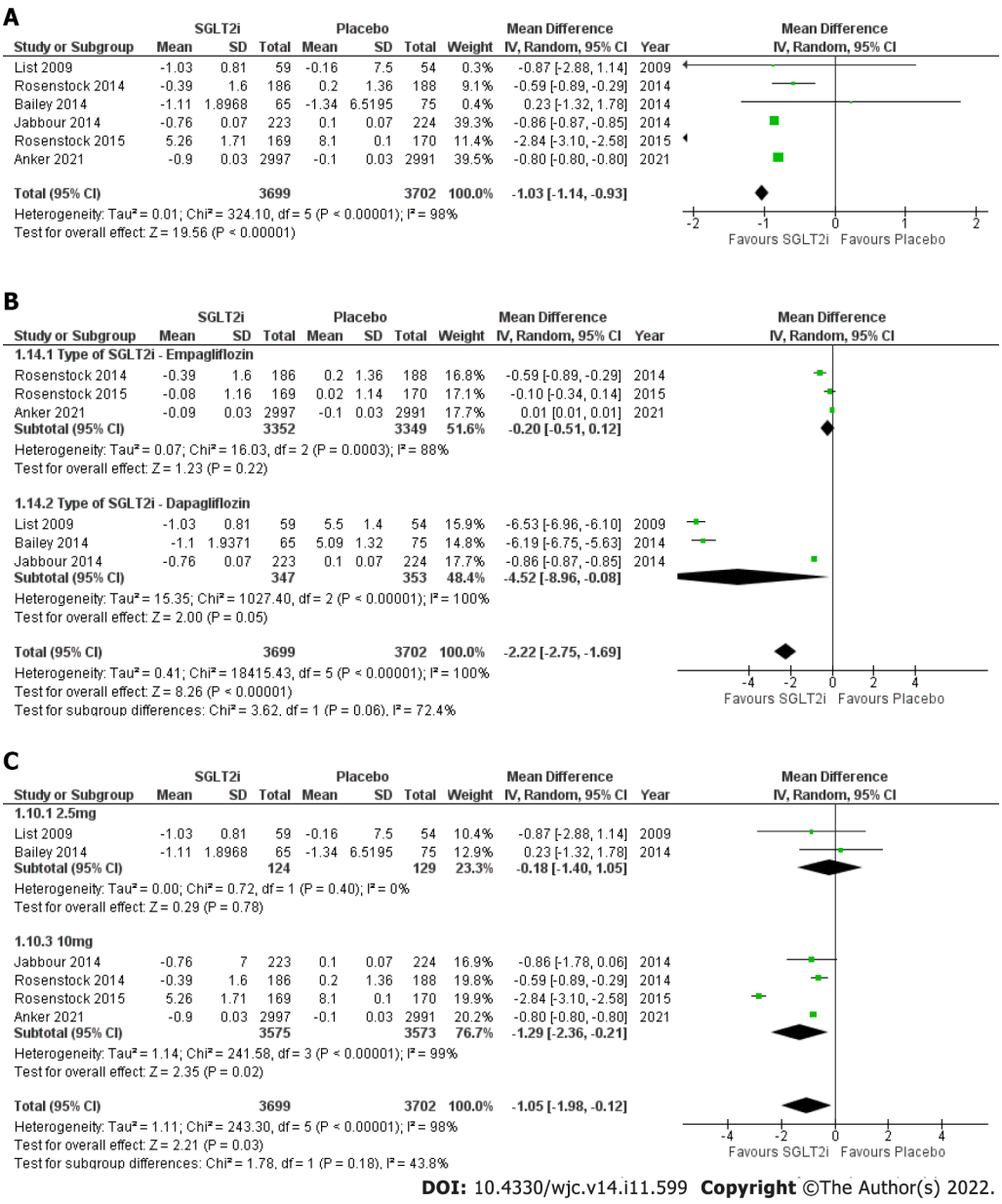


Figure 9 Forest plot. A: Highlighting impact of SGLT2-I on UA compared to placebo; B: SGLT2-I Type subgroup analysis performed for UA; C: SGLT2-I Dose subgroup analysis performed for UA. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; UA: Uric acid.

our primary objective was mostly a derivative of the secondary outcomes of the included RCTs. Second, owing to our inclusion criteria, only two of the included RCTs recruited patients without DM which limits the external validity of our study. Furthermore, we did not conduct a patient level analysis in those without DM. Third, this study limited its analysis to only dapagliflozin or empagliflozin and did not thoroughly compare the efficacy of both. Fourth, the improvement in MetS components noted by our analysis might be confounded by other medications taken by the RCTs' participants. Therefore, our analysis could not quantify the absolute effect of SGLT2-Is. This might imply the need for the evaluation of SGLT2-Is as a first line pharmacotherapy in treatment of MetS components. Additionally, MetS has multiple causes besides sedentary lifestyle, and unhealthy eating; it is usually heterogenous in its presentation due to the different possible combinations of its components; this study did not address these in its analysis. Lastly, not all included RCTs are open labelled and hence the risk of bias could not be reliably assessed by the Cochrane risk of bias tool.

CONCLUSION

SGLT2-Is were associated with an improvement in all components of MetS. There appears to be a role for their use in the management of patients with MetS regardless of the presence of DM and HF.

Prospective studies are needed to further evaluate the role of SGLT2-Is in patients with MetS either as first-line agents and/or add-on pharmacotherapy. This study, to the best of our knowledge, is the first to fully explore a possible role for SGLT2-Is in the management of MetS.

ARTICLE HIGHLIGHTS

Research background

According to the National Cholesterol Education Program Adult Treatment Panel III, metabolic syndrome is defined by the presence of three of five of the following: (1) Waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in females; (2) Serum triglycerides ≥ 150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) ≥ 130/85 mmHg or on drug treatment for hypertension; and (5) Fasting plasma glucose (FPG) ≥ 100 mg/dL or on drug treatment for elevated blood glucose.

Research motivation

The growing prevalence of metabolic syndrome (MetS), its association with the development of cardiovascular diseases (CVD) and the need to complement the therapeutic effect of lifestyle modification were the reasons behind conducting this study.

Research objectives

To evaluate the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) on metabolic syndrome (MetS) using data derived from randomized, placebo-controlled trials.

Research methods

A search of Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify randomized controlled trials (RCTs) that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.

Research results

SGLT2-Is resulted in a decrease in FPG, systolic BP and WC.

Research conclusions

Further studies are needed to evaluate the use of SGLT2-Is as the first-line phamacotherapy in the management of MetS.

Research perspectives

This meta-analysis has highlighted the impact of SGLT2-Is on MetS using data from RCTs that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components. In an attempt to improve the management of MetS, we hope this study will be a precursor for future prospective studies that will establish the use of SGLT2-Is in the treatment of MetS.

FOOTNOTES

Author contributions: Olagunju A, Mookadam M and Mookadam F designed the research; Olagunju A, Kenny D, Yamani N performed the research; Olagunju A, Kenny D, Yamani N, Mookadam M, Mookadam F and Unzek S analysed the data; Olagunju A, Kenny D, Yamani N and Mookadam F wrote the paper.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Observational Study

Conduction system disorders and electro-cardiographic findings in COVID-19 deceased patients in 2021, Shiraz, Iran

Mohammad Hossein Nikoo, Alireza Sadeghi, Alireza Estedlal, Reza Fereidooni, Niloofar Dehdari Ebrahimi, Amirhossein Maktabi, Mahtab Kamgar, Fatemeh Mehran, Omid Mehdibeygi, Haleh Esfandiari, Mohammadamir Taherinezhad Tayebi, Seyed Taghi Heydari

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Abstract

BACKGROUND

Cardiac conduction disorders and electrocardiographic (ECG) changes may occur as a manifestation of coronavirus disease 2019 (COVID-19), especially in severe cases.

AIM

To describe conduction system disorders and their association with other electro-cardiographic parameters in patients who died of COVID-19.

METHODS

In this cross-sectional study, electrocardiographic and clinical data of 432 patients who expired from COVID-19 between August 1st, 2021, and December 1st, 2021, in a tertiary hospital were reviewed.

RESULTS

Among 432 patients who died from COVID-19, atrioventricular block (AVB) was found in 40 (9.3%). Among these 40 patients, 28 (6.5%) suffered from 1st degree AVB, and 12 (2.8%) suffered from complete heart block (CHB). Changes in ST-T wave, compatible with myocardial infarction or localized myocarditis, appeared in 189 (59.0%). Findings compatible with myocardial injury, such as fragmented QRS and prolonged QTc, were found in 91 patients (21.1%) and 28 patients (6.5%),

respectively. In patients who died of COVID-19, conduction disorder was unrelated to any underlying medical condition. Fragmented QRS, axis deviation, and ST-T changes were significantly related to conduction system disorder in patients who died of COVID-19 (P value < 0.05).

CONCLUSION

Conduction system disorders are associated with several other ECG abnormalities, especially those indicative of myocardial ischemia or inflammation. Most patients (73.14%) who died of COVID-19 demonstrated at least one ECG abnormality parameter. Since a COVID-19 patient's ECG gives important information regarding their cardiac health, our findings can help develop a risk stratification method for at-risk COVID-19 patients in future studies.

Key Words: COVID-19; Conduction system disorder; Electrocardiography; Atrioventricular block

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Core Tip: No study has yet transpired to assess the correlation of conduction system disorders with other electrocardiographic findings in the setting of coronavirus disease 2019 (COVID-19). This paper can shed light on different conduction disorders seen in COVID-19.

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INTRODUCTION

In December 2019, a cluster of pneumonia cases was reported in Wuhan, Hubei Province, China, caused by a novel coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered the respiratory infection coronavirus disease 2019 (COVID-19). Due to the rapid transmission of COVID-19, WHO declared a pandemic on March 11th, 2020[1].

The initial studies of COVID-19 considered it to be predominantly a respiratory disease. However, recent evidence highlights multiple organ system involvements in COVID-19, including coagulation system disorder, acute kidney injury, hepatocellular injury, and cardiac and central nervous system complications[2]. The cardiac complications include thromboembolic events, heart failure, heart block, acute coronary syndrome, myocarditis, arrhythmias, and sudden cardiac death[3,4].

More recently, a growing body of literature on COVID-19 has investigated the electrophysiological changes that arise as a clinical manifestation of COVID-19 and highlighted the variety of arrhythmias observed in patients with COVID-19[5]. Moreover, multiple case reports introduce atrioventricular block as a potential manifestation of COVID-19[6-14]. In a retrospective study about the prognostic significance of electrocardiographic (ECG) findings in 319 patients with COVID-19, T-wave change (31.7%), QTc interval prolongation (30.1%), and arrhythmias (16.3%) were three most common found ECG abnormalities and atrioventricular block was presented in 3.9% of the patients[15]. First-degree atrioventricular block (AVB) was seen in 10 patients (3.3%), and second-degree AVB Mobitz type I was found in 2 patients (0.7%). In-hospital mortality risk increased with increasing abnormal ECG parameters[15]. In another study investigating the association between electrocardiographic features and mortality in COVID-19 patients, the overall prevalence of AVB was 11.8%, with deceased patients showing higher incidence than recovered patients (25% *vs* 9%)[16]. Another study conducted a rigorous patient-level analysis to determine the association of acute malignant cardiac arrhythmias, such as tachy- or bradyarrhythmias, and mortality in 140 hospitalized patients with COVID-19 and AVB was found in 5 patients, 2 of whom were associated with myocardial infarction (MI), and another 2 had metabolic abnormalities, suggesting that refractory shock was primarily responsible for conduction block, and the remaining patient had AVB in the setting of non–ST-segment–elevation myocardial infarction and newly diminished left ventricular ejection fraction[17]. However, no association between the presence of AVB and mortality was reported in these studies. Finally, it is evident that the knowledge of electrophysiological abnormalities, conduction system disorder, and particularly atrioventricular blocks is largely based on very limited data.

We designed the present study to investigate whether disruption of the conduction system can herald other ECG abnormalities in the setting of COVID-19, and whether it is associated with underlying diseases.

MATERIALS AND METHODS

This is a cross-sectional descriptive study that retrospectively reviewed demised COVID-19 patients who were admitted to Faghihi Hospital of Shiraz University of Medical Sciences from August 1st until December 1st, 2021. The inclusion criteria were all the admitted patients aged 18 or older who died with the diagnosis of COVID-19. Faghihi Hospital, located in Shiraz, Fars Province, Southern Iran, is one of the major tertiary teaching hospitals responsible for treating COVID-19 patients.

Data collection

Electronic demographic and on-paper medical records were evaluated. The data was gathered into a planned-out questionnaire. The questionnaire included demographic data, underlying diseases, and ECG factors. The data were collected by six independent practitioners. ECGs were interpreted by two cardiologists blinded to the patients' information and confirmed by an electrophysiologist.

Basic ECG parameters (rhythm, rate, axis, and ventricular hypertrophy), new findings attributable to COVID-19 (ST elevation and atrioventricular conductance disturbances), repolarization variants (J elevation, early repolarization, Brugada pattern, U wave, QTc prolongation, QT dispersion (QTd), the slope of terminal part of T wave (T-slope), depolarization abnormalities BBBs, low voltage QRS, poor R wave progression, and fragmented QRS (fQRS), QRS duration prolongation), and ECG pulmonary patterns such as S1Q3T3 were evaluated and recorded. Conduction system disorders were defined as BBBs and AVBs, and their coincidence with other ECG abnormalities was evaluated.

All ECGs were taken by the hospital's employed and trained technicians who were blinded to the purpose of the study and the patient's medical information using "Electrocardiogram Dena650" produced by SAADAT Company, Tehran, Iran.

COVID-19 was confirmed in these patients by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA detection with nasal and pharyngeal swabs, performed at admission or during hospitalization.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM corp.) for windows. Categorical variables were shown as frequency and percentages, and continuous variables as mean ± SD. Chi-square test was performed to assess the relationships between ECG parameters and patients' medical conditions with conduction system disease. The presence of conduction system disorders was considered the outcome variable, and ECG parameters were regarded as dependent variables. Then, the association of conduction system disorders and ECG parameters was calculated using logistic regression, and adjusted odds ratios were reported for univariate analysis and multivariate analysis after adjustment for the presence of other ECG parameters, sex, age, and underlying diseases. A two-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

Among the 432 deceased patients, 261 (60.4%) were male, with a mean age of 67.02 (± 14.44) years and age range of 28 - 96. The most prevalent comorbid diseases were hypertension (47.9%/207 cases), diabetes mellitus (36.3%/157 cases) and cardiac diseases (35.2%/158 cases). The prevalence of other co-morbidities in order of frequency is as follows: coronary disease (18.5%/80 cases), hyperlipidemia (12.5%/54 cases), pulmonary disease (8.6%/37 cases), and chronic kidney disease (6.3/27 cases). Evaluating the association between patients' past medical conditions and conduction system disorders in patients who died of COVID-19 revealed that conduction disorders were not related to any underlying medical condition. A summary of demographic and comorbid diseases is shown in Table 1.

Regarding heart rate and rhythm, sinus tachycardia (HR > 100) and bradycardia (HR < 60) were noticed in 100 (23.1%) and 9 (2.3%) patients, respectively. Abnormal rhythms were noted in 66 (15.2%) patients. The most prevalent arrhythmia was atrial fibrillation (12.5%). Reviewing electrocardiographic findings, AVB was found in 40 (9.3%) patients. 28 (6.5%) of the patients suffered from 1st degree AVB, and 12 (2.8%) suffered from CHB. Changes in ST-T wave compatible with myocardial infarction or localized myocarditis appeared in 189 (59.0%) patients. Other abnormal conduction system findings were bundle branch blocks. Left bundle branch block was seen in 25 (5.8%) patients, and right bundle branch block was seen in 50 (11.6%) patients. Moreover, the prevalence of findings compatible with pulmonary diseases such as S1Q3T3, poor R progression, axis deviations, and low voltage ECG was 14.4% (62 patients), 41.0% (177 patients), 21.7% (94 patients), and 11.3 (49 patients), respectively.

Table 1 Association of patients' past medical conditions and conduction system disorder in coronavirus disease 2019 deceased patients

Medical condition		Patients without conduction system disorder (*n* = 317)	Patients with conduction system disorder (*n* = 108)	*P* value
Sex	Female	125 (73.1)	46 (26.9)	0.654
	Male	196 (75.1)	65 (24.9)	
Age, yr	≤ 50	46 (79.3)	12 (20.7)	0.147
	51-60	65 (81.3)	15 (18.8)	
	61-70	82 (75.2)	27 (24.8)	
	> 70	128 (69.2)	57 (30.8)	
IHD	Yes	57 (71.3)	23 (28.8)	0.477
	No	260 (75.4)	85 (24.6)	
DM	Yes	113 (72.0)	44 (28.0)	0.357
	No	204 (76.1)	64 (23.9)	
Renal disease	Yes	42 (79.2)	11 (20.8)	0.501
	No	275 (73.9)	97 (26.1)	
Pulmonary disease	Yes	23 (62.2)	14 (37.8)	0.078
	No	292 (75.6)	94 (24.4)	
Hyperlipidemia	Yes	38 (70.4)	16 (29.6)	0.503
	No	279 (75.2)	92 (24.8)	
CKD	Yes	19 (70.4)	8 (29.6)	0.648
	No	298 (74.9)	100 (25.1)	
HTN	Yes	151 (72.9)	56 (27.1)	0.504
	No	165 (76.0)	52 (24.0)	

IHD: Ischemic heart disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; HTN: Hypertension.

Findings compatible with myocardial injury, such as fragmented QRS, and prolonged QTc, were assessed, with a prevalence of 21.1% (91 patients), and 6.5% (28 patients). Primary electrical cardiac diseases such as prominent J wave, Brugada pattern, and early repolarization were observed in 4.4% (19 patients), 1.2% (5 patients), and 4.2% (18 patients), respectively.

Regarding ECG parameters in patients who died of COVID-19, in univariate analysis, ST-T changes, fragmented QRS, axis deviation, presence of S1Q3T3, and poor R wave progression were significantly related to conduction system disorders in patients who died of COVID-19 (P value < 0.05, Table 2). However, when adjusted for age, sex, underlying diseases, and other ECG parameters, only fragmented QRS, ST-T changes, and axis deviation were significantly associated with conduction system disorders.

DISCUSSION

This is a single-center study conducted retrospectively. The small sample size of a single-center could result in less generalizability. Unfortunately, assessing the presence of myocarditis was not possible due to the absence of data on serum markers and echocardiographic examination for most of our enrolled patients. This descriptive study aims only to report the incidence of ECG abnormalities and their relationship with conduction system disorders in patients who died of COVID-19. To determine which conduction disorders are independently associated with mortality, case-control or cohort studies are recommended.

By reviewing previous literature, mounting evidence supports the association between influenza pneumonia and heart diseases, and it has been reported that influenza have been associated with a six-fold increased risk of acute MI[18,19]. COVID-19 also directly and indirectly affects the cardiovascular system and the heart in particular[3]. Previous studies have proved that COVID-19 augments the risk of cardiovascular complications, including dysrhythmias, both in the short and long term, and given that

Table 2 Electrocardiographic parameters in conduction system disease in COVID-19 deceased patients

ECG parameters		Patients without conduction system disorder (*n* = 317)	Patients with conduction system disorder (*n* = 108)	Univariate OR (95%CI for OR)	*P* value	Adjusted[1] odds ratio (95%CI for OR)	*P* value
Fragmented QRS	Yes	53 (58.2)	38 (41.8)	2.63 (1.61-4.30)	< 0.001	2.27 (1.23, 4.16)	0.008
	No	268 (78.6)	73 (21.4)	1	-	1	-
ST-T change	Yes	125 (66.1)	64 (33.9)	2.14 (1.38-3.31)	0.001	1.81 (1.07, 3.08)	0.030
	No	196 (80.7)	47 (19.3)	1	-	1	-
Rhythm	Sinus rhythm	279 (76.2)	87 (23.8)	1	-	1	-
	AF	34 (63.0)	20 (37.0)	1.89 (1.03-3.45)	0.039	1.70 (0.78-3.71)	0.179
	Others	8 (66.7)	4 (33.3)	1.60 (0.47-5.45)	0.450	0.75 (0.15, 3.62)	0.700
Rate	Bradycardia (HR < 60)	5 (55.6)	4 (44.4)	2.10 (0.55-8.01)	0.279	1.67 (0.31-9.06)	0.554
	Normal (60 < HR < 100)	234 (72.4)	89 (27.6)	1	-	1	-
	Tachycardia (HR > 100)	82 (82.0)	18 (18.0)	0.58 (0.33-1.02)	0.057	0.55 (0.27, 1.09)	0.086
Axis deviation	Normal	283 (83.7)	55 (16.3)	1	-	1	-
	Left	14 (48.3)	15 (51.7)	5.51 (2.52-12.07)	< 0.001	3.74 (1.50-9.33)	0.005
	Right	24 (36.9)	41 (63.1)	8.79 (4.92-15.71)	< 0.001	7.67 (3.95-14.88)	< 0.001
QTc 1	< 500	211 (75.1)	70 (24.9)	1	-	1	-
	> 500	110 (73.3)	40 (26.7)	1.10 (0.70-1.72)	0.691	0.94 (0.53, 1.66)	0.819
QTc 2	Male ≤ 440 and female ≤ 460	300 (74.4)	103 (25.6)	1	-	Not included due to collinearity with the above variable	
	Male > 440 and female > 460	21 (75.0)	9 (25.0)	0.97 (0.40-2.35)	0.948		
QTd	< 40	45 (81.8)	10 (18.2)	1	-	1	-
	≥ 40	276 (73.2)	101 (26.8)	1.65 (0.80-3.39)	0.176	1.42 (0.58-3.47)	0.446
J wave	Yes	13 (68.4)	6 (31.6)	1.35 (0.50-3.65)	0.550	0.98 (0.28-3.49)	0.978
	No	308 (74.6)	105 (25.4)	1	-	1	-
U wave	Yes	32 (71.1)	13 (28.9)	1.20 (0.60-2.38)	0.605	1.10 (0.47, 2.63)	0.815
	No	289 (74.7)	98 (25.3)	1	-	1	-
Early repolarization	Yes	15 (83.3)	108 (26.1)	0.57 (0.16-2.00)	0.377	1.00 (0.26-3.93)	0.998
	No	306 (73.9)	108 (26.1)	1	-	1	-
T slope	< 30	12 (75.0)	4 (25.0)	1	-	1	-
	30-60	302 (74.6)	103 (25.4)	1.02 (0.32-3.24)	0.969	0.79 (0.21, 2.98)	0.728
	> 60	7 (63.6)	4 (36.4)	1.71 (0.32-9.11)	0.527	1.87 (0.249-14.01)	0.551
S1Q3T3	Yes	38 (61.3)	24 (38.7)	2.05 (1.17-3.61)	0.012	1.83 (0.92-3.64)	0.086
	No	283 (76.5)	87 (23.5)	1	-	1	-
Low voltage QRS	Yes	42 (85.7)	7 (14.3)	0.45 (0.20-1.03)	0.058	0.38 (0.14-1.05)	0.063
	No	279 (72.8)	104 (27.2)	1	-	1	-
PRP	Yes	121 (68.4)	56 (31.6)	1.68 (1.09-2.60)	0.019	1.32 (0.77-2.26)	0.317
	No	200 (78.4)	55 (21.6)	1	-	1	-

[1]Adjusted for age, sex, underlying diseases, and other electrocardiography findings.
AF: Atrial fibrillation; HR: Heart rate; QTc: Corrected Q-T interval; QTd: Q-T interval dispersion; T slope: T-wave terminal slope; PRP: Poor R wave progression.

they are the most prevalent viral pneumonia at the time of writing this article, their complications impose a considerable burden on healthcare[20]. This study discusses the prevalence of arrhythmias and conduction system disorders in patients with COVID-19.

The mechanism underlying the development of arrhythmias in COVID-19 has not been specified. However, potential triggers are as follows[21]. First, electrolyte imbalance caused by COVID-19 symptoms such as diarrhea and complications such as acute kidney injury or severe sepsis is a notable cause[22]. Second, SARS-CoV-2-induced myocardial injury due to the upregulation of angiotensin-converting enzyme 2 (ACE2) receptor during viral invasion and severe hypoxia-induced myocyte necrosis are other potential causes of arrhythmias[23]. In addition, acute myocardial infarction due to demand/supply imbalance and arterial thrombotic events secondary to hypercoagulable state can cause acute arrhythmias[24,25]. Stress and cytokine storm in relation to sepsis and high inflammatory state is another potential mechanism[21]. Moreover, prolonged QTc-induced malignant ventricular arrhythmias and channelopathies induced by off-label medical therapy and antiviral therapy could be introduced as direct triggers of arrhythmias[26].

The most remarkable result acquired from the data was the prevalence of advanced AVB in patients who died of COVID-19. This prevalence was not yet assessed in deceased COVID-19 patients; however, the reported prevalence of AVB in COVID-19 patients ranged from 3 to 12% in different studies[14,15]. All types of AVBs were seen in 40 (9.3%) cases in our study. Among those with AVB, 12 (2.8%) cases suffered from 3rd degree complete heart block (CHB). CHB has been assumed to be a rare ECG feature of COVID-19, and this novel finding has only been reported in a few case studies[6,8,10].

Another interesting result was the high prevalence of fragmented QRS, prominent J wave, and ST-T wave change. These parameters can be directly related to myocardial injury induced by SARS-CoV-2 infection. In addition, the high incidence of S1Q3T3 and LBBB in this study could indicate pulmonary involvement in deceased COVID-19 cases. S1Q3T3 is a relatively specific pattern for pulmonary thromboembolism and a potential cause of death[27].

Moreover, ST-T changes, fragmented QRS, and axis deviation were significantly related to conduction disorders in our patients, suggestive of new-onset myocardial infarctions during the infection and increased mortality risk. Our study provides further evidence for the observed ST-T wave changes in COVID-19 patients, suggestive of myocardial infarction or localized myocarditis[28]. This indicates that disturbances in the conduction system are associated with COVID-19-related myocardial injury, either ischemic or inflammatory.

Compatible with previous studies, atrial fibrillation was the most prevalent arrhythmia[29]. It is notable that we witnessed these findings in patients who had no evidence of arrhythmia before their admission. Therefore, we suggest future studies to focus on the mechanism of arrhythmogenicity of COVID-19 and discover the proper screening and therapeutic strategies mitigating the adverse outcomes of COVID-19-induced arrhythmias.

CONCLUSION

To the best of our knowledge, this is the first study that exclusively assessed expired COVID-19 patients and illuminated the AVB and BBB prevalence among them. The myocardial injury appears to be closely associated with conduction system disorders and has a role in COVID-19 morbidity and mortality. Our findings can help develop a risk stratification method for susceptible COVID-19 patients in future studies. Consequently, we recommend that health policymakers should consider separate catheterization laboratories that provide service only to COVID-19 patients.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) is associated with a wide range of cardiovascular compilations, especially in severe cases. Electrocardiogram is a cheap, useful and readily available tool to investigate these complications.

Research motivation

We designed this study to better understand the conduction system disturbances in the setting of severe COVID-19.

Research objectives

To discover the prevalence and types of conduction system disorders in COVID-19 deceased patients as a population representing severe COVID-19.

Research methods

All electrocardiograms of patients who died of COVID-19 in our center were analyzed, and any abnormalities were reported.

Research results

Changes in ST-T were the most common (59%), which indicate myocardial infarction or localized myocarditis. Also, 21.1% showed fragmented QRS and prolonged QTc indicative of myocardial injury. Atrioventricular block (AVB) was found in 9.3% of patients.

Research conclusions

Among patients who expired from COVID-19, ST-T changes are the most common which heralds myocardial damage. Conduction disturbances like AVBs are also important findings and are associated with myocardial damage.

Research perspectives

ECG findings in COVID-19 are variable but mostly involve two pathologies, myocardial damage and conduction system disturbances. Clinicians should be aware of these two complications in the setting of COVID-19 and future research should focus on devising preventive measures to mitigate the cardiovascular complications of COVID-19.

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FOOTNOTES

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ORIGINAL ARTICLE

Randomized Clinical Trial

Impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and practice of hypertension management during the COVID-19 pandemic

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Abstract

BACKGROUND

One of the efforts to reduce hypertension rates in the community is through an educational campaign that refers to the NIH's National Heart, Lung, and Blood Institute curricula or abbreviated as NHLBI. However, during the coronavirus disease 2019 (COVID-19) pandemic, one of the hardest hit areas is health promotion, and there is a significant obstacle regarding the most effective way to transfer knowledge, attitude and practice towards society without transmitting the virus.

AIM

To evaluate the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

METHODS

An online action research with a randomized crossover-controlled trial using a pretest-posttest control group design. The study was conducted in October 2020-April 2021. The population in this study were patients with hypertension who were treated in the Mojo primary health care setting. A purposive sampling technique was done to receive 110 participants using an online questionnaire and invitation letter.

RESULTS

A total of 110 participants were included in the analysis, 55 in the intervention group and 55 in the control group. Following the Virtual Anti-Hypertensive Educational Campaign implementation, the only parameter that showed significant improvement was knowledge and attitude ($P < 0.001$). There is no significant change in the practice parameters ($P = 0.131$).

CONCLUSION

The Virtual Anti-Hypertensive Educational Campaign implementation in our study population seems to be effective to improve knowledge and attitude of participants, nevertheless, this program seems to be ineffective to improve the practice of hypertension management aspect in participants. Future study with longer durations and more comprehensive programs need to be done to scrutinize the clinical impact of this program nationwide.

Key Words: Hypertension; Awareness; Knowledge; Attitude; Practice; Public health

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Core Tip: In the unprecedented times of the coronavirus disease 2019 (COVID-19) pandemic, many offices shut down across the world. Onsite classes and events were postponed and as a result, the educational health campaign has changed dramatically. With the distinctive rise of e-learning, health campaigns can be undertaken remotely by digital platforms. With this sudden shift away from the conventional campaign, in many parts of the globe, some are wondering whether the adoption of virtual learning will continue to persist post-pandemic and how such a shift would impact the perception and transfer of knowledge towards hypertensive patients. To keep the community safe, but still well-informed about the dangers of hypertension and how to build a healthy lifestyle, we decided to create a Virtual Anti-Hypertensive Educational Campaign. The importance of this paper is to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

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INTRODUCTION

From early 2020, the world has been living in a state of public health disruption due to the novel coronavirus disease 2019 (COVID-19) pandemic[1]. COVID-19 has added various challenges and changes to human life worldwide, causing an unprecedented impact on human health, lifestyle, and social life, and has affected the local and international economy[2]. In Indonesia, schools and offices have been suspended during the pandemic and many people have been staying at home[3]. Amid the confinement due to the COVID-19 pandemic, offline activities involving large numbers of people were nearly interrupted[4]. Educators are scrambling to adapt to social distancing (self-quarantine) and the durations of quarantine and social isolation are unpredictable[5].

The COVID-19 pandemic also highlights the fact that the lack of health literacy is an underestimated public health problem in Indonesia[6]. The lack of health literacy is linked to the spread of communicable disease and also gives an opportunity to the increased burden of several non-communicable diseases such as hypertension and cardiovascular diseases[7]. There is no doubt that during times of quarantine and social isolation, food accessibility and availability may be affected, which in turn affects diet quality[8]. Levels of physical activity were also negatively affected during self-isolation and quarantine, due to closure of sport facilities and parks, overall movement restrictions have reduced the ability to engage in physical activity[9]. This was accompanied with an increase of sedentary behaviors related to self-isolation and quarantine, including distance learning and telework [10].

Hypertension can be prevented or delayed through mitigation of modifiable risk factors, such as healthier eating, weight loss, and increased physical activity[11]. Efforts to improve population health literacy can bring spectacular benefits in terms of building the populations' resilience to health threats, promoting healthy lifestyle changes, and empowering individuals to make a well- informed health decision[12]. One of the effective non-pharmacologic strategies to combat hypertension is a dietary

campaign[13]. One of the examples of effective diet to combat hypertension is Dietary Approaches to Stop Hypertension (DASH) Diet. DASH diet is one of the flexible and balanced dietary plans that is proven to reduce blood pressure[14]. The DASH eating plan requires no special foods and instead provides daily and weekly nutritional goals. Current evidence showed that a DASH diet could reduce blood pressure within 2 to 4 wk (by 6 mmHg systolic and 3 mmHg diastolic)[15-17]. Unfortunately, the COVID-19 pandemic which locked down policy in Indonesia have disrupted the opportunity for the conventional health education process and has increased the necessity to find alternative health campaign strategies[18].

Therefore, we try to build the anti-hypertensive educational campaign based on the DASH diet. Since the pandemic will undeniably continue to disrupt the conventional health campaign activity, some virtual alternatives are being used to continue health education activities. As we face the prospect of many urban people who have easy access to the internet and social media, we try to assess their feasibility and determine whether they are adequate in getting health education virtually.

Objective

Our teams designed a virtual anti-hypertensive educational campaign curriculum for community health care advocates in the community health care of the Mojo District, Surabaya, Indonesia to identify and prevent health risks of hypertension. The first goal is to conduct research on the risks of hypertension and identify an educational model for community health advocates. The second goal is to educate people to improve health literacy in the field of hypertensive healthy plans. The virtual anti-hypertensive educational campaign aims to help dispel misinformation while promoting healthy lifestyle recommendations and medical guidelines set by the Ministry of Health of the Indonesian Government and Indonesian Cardiologist Association. Therefore, the purpose of this paper is to highlight the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management during the COVID-19 pandemic.

MATERIALS AND METHODS

Ethical approval

In order to conduct the study, approval was obtained on July 1st, 2020 with a decision of the Bioethics Committee at the Faculty of Medicine Universitas Airlangga (Ref. number 532/UN3/2020) under the name of Andrianto as the principal investigator. All participants provided virtual informed consent prior to participating in the study, without identifiable data. The schedule of enrollment, intervention and measurements according to Standard Protocol Items: Recommendations for Intervention Trials requirements. The study's data were collected in accordance with the Helsinki Declaration. The consent form documented the aims, nature, and procedure of the study. Anonymity and confidentially were strictly maintained.

Study design and study setting

The trial was a randomized double-blind, placebo controlled, crossover design. The study was completed over a 6 mo duration (1 October 2020-30 April 2021) of the virtual anti-hypertensive educational campaign with randomization (1 mo); treatment period one (2 mo); washout (1 mo); and finally, treatment period two (2 mo). Subjects were randomly assigned among patients with established hypertension using a pre-test, post-test, controlled group design. This study was conducted in October-December 2020 in the Mojo District, Surabaya City. We conducted an online survey from October to December, 2020. The survey involved an online questionnaire that was distributed virtually, either by email or by WhatsApp and social media, to more than 500 hypertensive patients in the Mojo district of Surabaya, Indonesia, of which, 110 participants actively replied. The questionnaire was self-administered without intervention by the authors or any specific person, and it did not contain any identifying data of the participants to ensure confidentiality. Questionnaires with incomplete information or missing data were excluded from the analysis. Completed paper questionnaires were collected anonymously to ensure confidentiality and to prevent any response bias. Unreturned or uncompleted questionnaires were recorded as missing. Participants were not aware of the study aim or outcomes to reduce the risk of any possible bias. The survey included only hypertensive patients who were living in the Mojo district of Surabaya city.

Study tool and study protocol

In accordance with the aim of the study, a questionnaire consisting of "knowledge, attitudes, and practices" was prepared using the literature. The questionnaire covered participants' basic demographic data, such as their sex, age, and marital status, as well as general questions about their financial status, occupation, level of education, internal displacement, history of health problems, psychological illness, and learning disabilities, if present. The questionnaire also addressed their experience with telemedicine, including questions related to sphygmomanometer usage proficiency, type and quality of

sphygmomanometer used, daily antihypertensive drugs, and daily diets. We improved the previous questionnaire by conducting it virtually and adapting local wisdom for our hypertensive patients. Items in the questionnaire were then modified and new items were added based on the qualitative data collected in these interviews. We developed the questionnaire in Bahasa and tested its internal consistency in a pilot study comprising 40 subjects. We revised the questionnaire several times to ensure high internal consistency, which was determined by Cronbach's alpha. The sample from the pilot study was not included in the final analysis. We provided the questionnaire in Bahasa to accommodate respondents' native language. After designing the Bahasa version, three independent translators translated the questionnaire separately and compared the three versions to reach a consensus after consultation with a linguistic expert and three authors to ensure the same intended meaning. The "knowledge, attitudes, and practices" questionnaire had a high internal consistency, as evidenced by Cronbach's alpha values of 0.88 and 0.86 for the Bahasa versions.

Participants

The population in this study were all patients with hypertension who were treated in the Mojo primary health care setting or referred by general practitioners in the Mojo district of Surabaya city. Participants included in this study were adults, aged 18 years and older, with a grade I hypertension according to the ESC/ESH 2018 guideline (SBP of 140 to 159 mmHg and DBP of 90 to 99 mmHg) based on the average BP across three screening visits. Persons with a prior diagnosis of coronary heart disease, renal insufficiency, poorly controlled dyslipidemia, diabetes mellitus or heart failure were excluded from participation. Participants who have already taken more than 1 antihypertensive agent or insulin, education level higher than graduate school, subjects with cognitive impairment, and subjects who were unable to join or complete 7 virtual sessions had been excluded. Invitation letters to the study were sent to all subjects who met eligibility criteria.

Sample size

To detect a blood pressure difference of 10 mmHg (clinically relevant) with 90% power and $\alpha = 0.05$, 40 patients are needed in crossover design[19]. Silagy *et al*[20] detected a difference of 10 mmHg with less than 50 patients per group in a parallel trial. We have carried out a pilot cross-over virtual educational campaign study that detected a difference of 10 mmHg units with 40 patients, confirming that cross-over design substantially reduced the sample size required (unpublished results). To account for drop-out or non-compliance, this trial included 55 participants in the intervention group and 55 participants in the control group. Sample size calculation was performed with nQuery 7.0. Purposive sampling techniques were done to receive 110 participants.

Intervention

After the Indonesian government called for cooperation of its residents to practice social distancing measures, the Department of Cardiology and Vascular Medicine Universitas Airlangga created an approachable Virtual Anti-Hypertensive Educational Campaign using social media and a webinar-based platform to educate hypertensive patients in the Mojo District of Surabaya. The virtual campaign consisted of 7 sessions, between 1 October, 2020 and 30 April, 2021. The virtual campaign was held once a week and the duration of each session was approximately 2 h. The virtual anti-hypertensive educational campaign had been focusing on hypertensive prevention strategy towards society. The curriculum of our virtual anti-hypertensive educational campaign was based on NIH's National Heart, Lung, and Blood Institute curricula, with several improvisations in the usage of Bahasa and virtual content based on local wisdom. The schedule and subjects for the Virtual Anti-Hypertensive Educational Campaign can be seen in (Table 1).

The intervention and control periods were 2 mo, designed to coincide with the length of the virtual anti-hypertensive educational campaign curricula. The control arm was given a standard medical check and medical treatment without any anti-hypertensive education. Subjects were assigned to the group by random allocation based on block to assign sample numbers equally to each group and assign the block.

Outcomes

The knowledge concerning high blood pressure was measured using a 22-item Hypertension Knowledge Level Scale (HK-LS), from a previous study regarding patient knowledge of hypertension translated into Bahasa Indonesia[21,22].

The attitude towards hypertension was assessed with a 28-item instrument called Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH), using a 4-point Likert-type scale (alpha-reliability = 0.74) in the Bahasa version[23].

Practice was assessed by the 8-item Morisky Medication Adherence Scale (MMAS-8) translated into Bahasa[24].

Data analysis

We used descriptive statistics to examine respondents' characteristics and responses using frequencies and percentages. We described categorical variables as frequencies and percentages, and continuous

Table 1 Schedule for virtual anti-hypertensive educational campaign

No.	Sessions	Subjects	Duration
1	Session 1	Hypertension awareness campaign, definition and how to measure home blood pressure monitoring, understanding the silent killer of hypertension: dangerous effect towards cardiovascular diseases	2 h
2	Session 2	Healthy lifestyle: focusing on health diet, physical activity, and avoiding stress. Health benefits of the DASH eating plan and why DASH eating plan works	2 h
3	Session 3	Dietary recommendation for hypertension: getting started on DASH (live demo)	2 h + 2 h of live demo
4	Session 4	Tips to reduce salt and sodium intake (live demo: weigh salt before cooking)	2 h + 2 h of live demo
5	Session 5	Meal plans, measure each ingredients and oil products for cooking (live demo)	2 h + 2 h of live demo
6	Session 6	Living with the DASH eating plans. How to choose grains, fruits, vegetables, low fat and non-daily product (live demo)	2 h + 2 h of live demo
7	Session 7	How to educate others about dispelling misinformation in the healthy diet	2 h

variables as mean (SD) or median (lower-upper) values, as appropriate. The Kolmogorov-Smirnov test revealed that several variables did not follow a normal distribution. We conducted independent sample *t*-tests, paired sample *t*-tests, Wilcoxon signed rank tests and the Mann-Whitney *U*-test to identify differences between two groups of continuous variables. The Pearson's and Spearman's rank correlation coefficient was used to explore the relationship between knowledge, attitudes, and practice scores in respect to the virtual health education program and the studied variables. We performed all statistical analyses using SPSS version 25.0 (IBM Corp., Armonk, NY, United States).

Study validity and bias

Selection bias was reduced by ensuring high participation rates and reducing the subject's loss to follow-up. Interviewer bias was reduced by using standardized questionnaires. The "knowledge, attitudes, and practices" questionnaire had a high internal consistency, as evidenced by Cronbach's alpha values of 0.88 and 0.86 for the Bahasa versions. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.78. Bartlett's test of sphericity was significant ($\chi^2 = 3300.796$, df = 231, $P < 0.001$). The stability of our instrument over time was tested by the test-retest reliability methods. In instances, where clinic records were available, they were utilized for triangulation and to reduce information bias.

RESULTS

Flow diagram

All participants ($n = 110$) were recruited from the Mojo District, Surabaya City. A total of 110 study participants included in the cross-over study, 55 in the intervention group and 55 in the control group (Figure 1).

Demographic characteristics of participants

The demographic characteristics of participants in (Table 2) are outlined by sex, occupation, age and education level. Patients with hypertension who follow a virtual anti-hypertensive educational campaign at Mojo District, Surabaya City amounted to 41 males (37.27%) and 69 females (62.72%). The number of participants with hypertension who follow the virtual anti-hypertensive educational campaign at Mojo District, Surabaya City with the status of employed (civil servants/police, laborers, traders/entrepreneurs and private employees) was fewer, *i.e.*, 38 people (34.54%) compared with unemployed (unemployed, retired and housewife), *i.e.*, 72 people (65.45%). The average age of hypertensive patients who follow a virtual anti-hypertensive educational campaign at Mojo District, Surabaya City is 54.26 years, with the lowest age being 19 years and the highest age is 77 years. Among them, participants with the lowest level of education were 0 years (not attending school) and the highest level of education was 19 years (magister student). All patients completed the double-blind protocol. Of the 55 participants in the control group who started combined intervention, one interrupted and declined further participation. The age of the 109 remaining participants averaged 45 ± 5 years. Baseline sitting BP was 152 ± 15/93 ± 13 mmHg and the 24-h ambulatory pressure was 149 ± 12/87 ± 10 mmHg.

Knowledge

For each question of knowledge, the distribution of responses from participants is presented in (Table 3). The HK-LS was generated based on content, face, and construct validity, internal consistency,

Table 2 Distribution of characteristics in hypertensive subjects following a virtual anti-hypertensive educational campaign

Characteristics	Intervention, *n* = 55	Control, *n* = 55	*P* value
Sex			
Male	22 (40.0)	19 (34.5)	0.23
Female	33 (60.0)	36 (65.5)	
Age group, yr			
< 20	0	1 (1.8)	0.33
20-29	3 (5.4)	4 (7.2)	
30-39	12 (21.8)	10 (18.2)	
40-49	19 (34.5)	20 (36.4)	
50-59	16 (29.1)	16 (29.1)	
60-69	4 (7.2)	2 (3.6)	
> 70	1 (1.8)	2 (3.6)	
Marital status			
Single	2 (3.6)	1 (1.8)	0.35
Married	30 (54.5)	29 (52.7)	
Widowed	23 (41.8)	25 (45.4)	
Religion			
Muslim	42 (76.4)	47 (85.5)	0.28
Christianity	9 (16.4)	5 (9.1)	
Others	4 (7.2)	3 (5.4)	
Educational degree			
Not attending	4 (7.2)	4 (7.2)	0.41
Elementary school	16 (29.1)	18 (32.7)	
Junior high school	8 (14.5)	5 (9.1)	
Senior high school	20 (36.4)	19 (34.5)	
Diploma	5 (9.1)	4 (7.2)	
Undergraduate	2 (3.6)	4 (7.2)	
Graduate (magister)	0	1 (1.8)	
Occupation			
Civil servants	2 (3.6)	3 (5.4)	0.38
Police	1 (1.8)	0	
Laborers	7 (12.7)	4 (7.2)	
Entrepreneurs	5 (9.1)	7 (12.7)	
Private workers	5 (9.1)	4 (7.2)	
Housewives	25 (45.5)	29 (52.7)	
Retired	10 (18.2)	8 (14.5)	
Antihypertensive drugs			
ACE-inhibitor	17 (30.9)	15 (27.3)	0.27
ARBs	2 (3.6)	1 (1.8)	
Beta blocker	3 (5.4)	2 (3.6)	
CCBs	31 (56.4)	29 (52.7)	
Diuretics	2 (3.6)	8 (14.5)	

Baseline systolic BP	153 ± 15 mmHg	151 ± 15 mmHg	0.49
Baseline diastolic BP	96 ± 13 mm Hg	91 ± 13 mm Hg	0.42

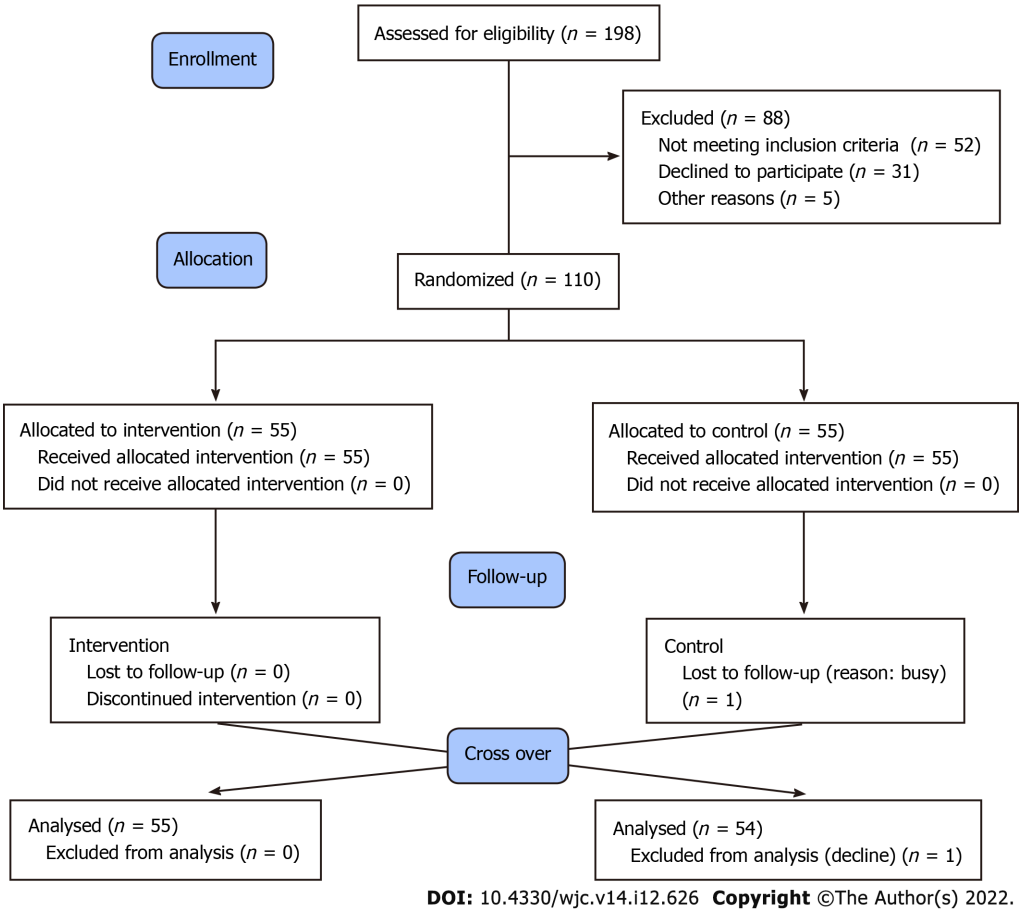
Data are presented as *n* (%) or mean ± SD. Comparative study used independent *t*-test for normally distribution data and Mann-Whitney *U* test for data that did not follow normal distribution. ACE: Angiotensin-converting enzyme; ARBs: Angiotensin II receptor blockers; CCBs: Calcium channel blockers; BP: Blood pressure.

Table 3 Results of the knowledge section evaluated with a 22-item Hypertension Knowledge Level Scale before and after virtual anti-hypertensive educational campaign

No.	Item	Subjects answered true		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Increased diastolic blood pressure also indicates increased blood pressure	65 (59.1)	81 (74.3)	< 0.001
2	High diastolic or systolic blood pressure indicates increased blood pressure	71 (64.5)	84 (77.1)	< 0.001
3	Drugs for increased blood pressure must be taken every day	76 (69.1)	99 (90.8)	< 0.001
4	Individuals with increased blood pressure must take their medication only when they feel ill	44 (40.0)	77 (70.6)	< 0.001
5	Individuals with increased blood pressure must take their medication throughout their life	43 (39.1)	75 (68.8)	< 0.001
6	Individuals with increased blood pressure must take their medication in a manner that makes them feel good	83 (75.5)	89 (81.6)	0.042
7	If the medication for increased blood pressure can control blood pressure, there is no need to change lifestyles	99 (90.0)	103 (94.5)	0.120
8	Increased blood pressure is the result of aging, so treatment is unnecessary	96 (87.3)	103 (94.5)	0.042
9	If individuals with increased blood pressure change their lifestyles, there is no need for treatment	17 (15.5)	59 (54.1)	< 0.001
10	Individuals with increased blood pressure can eat salty foods as long as they take their drugs regularly	78 (70.9)	96 (88.1)	< 0.001
11	Individuals with increased blood pressure can drink alcoholic beverages	107 (97.3)	107 (98.2)	0.420
12	Individuals with increased blood pressure must not smoke	103 (93.6)	105 (96.3)	0.270
13	Individuals with increased blood pressure must eat fruits and vegetables frequently	108 (98.2)	108 (99.1)	0.440
14	For individuals with increased blood pressure, the best cooking method is frying	107 (97.3)	106 (97.2)	0.490
15	For individuals with increased blood pressure, the best cooking method is boiling or grilling	98 (89.1)	101 (92.7)	0.120
16	The best type of meat for individuals with increased blood pressure is white meat	31 (28.2)	99 (80.7)	< 0.001
17	The best type of meat for individuals with increased blood pressure is red meat	103 (93.6)	105 (96.3)	0.270
18	Increased blood pressure can cause premature death if left untreated	46 (41.8)	91 (83.5)	< 0.001
19	Increased blood pressure can cause heart diseases, such as heart attack, if left untreated	87 (79.1)	108 (99.1)	< 0.001
20	Increased blood pressure can cause strokes, if left untreated	61 (55.5)	106 (97.2)	< 0.001
21	Increased blood pressure can cause kidney failure, if left untreated	57 (51.8)	91 (83.5)	< 0.001
22	Increased blood pressure can cause visual disturbances, if left untreated	39 (35.5)	59 (54.1)	< 0.001

Data are presented as *n* (%). Comparative study used paired sample *t*-test and Wilcoxon signed rank test.

test re-test reliability, and discriminative validity procedures. The final scale had 22 items with six sub-dimensions. The 22-item HK-LS scale was applied to all participants, before and 2 mo after the intervention ended. Following the Virtual Anti-Hypertensive Educational Campaign implementation, there was a significant improvement in the knowledge aspects ($P < 0.001$) in the intervention group[22].



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Figure 1 Flow chart diagram of this study.

Attitude

For each question that focused on attitude, the distribution of responses from participants is presented in (Table 4). We used the adapted 28-Likert items instrument of TAQPH instrument, to measure adherence to pharmacological and non-pharmacological treatment (lifestyle), in patients with primary hypertension, before and after the intervention. The adapted TAQPH version had modifications without affecting the instrument's original structure to maintain the semantic equivalence, a fact validated by its author. An average of a 4-point Likert-type scale were being used to determine the attitude of the subject participants (1 = strongly disagree; 2 = disagree; 3 = agree; 4 = strongly agree). Following the Virtual Anti-Hypertensive Educational Campaign implementation, there was a significant improvement in the knowledge aspects ($P < 0.001$) in the intervention group.

Practice

For each question of practice, the distribution of responses from participants is presented in (Table 5). Medication adherence was tested using the Bahasa version of the validated MMAS-8. The MMAS-8 is a structured self-report measure of medication-taking behavior that has been widely used in various cultures. Following the virtual anti-hypertensive educational health campaign, no significant change had been observed in the overall practice parameters ($P = 0.131$).

DISCUSSION

This study was conducted and aimed at measuring the baseline level of knowledge, attitude, and practice of hypertension management and perceptions regarding the disease among Indonesian people. The findings reveal the effects of planning virtual health education programs for non-communicable diseases and regarding the change of knowledge, attitude, and practice of hypertension management. Since the outbreak of the COVID-19 pandemic in Surabaya City which started in March 2020, this pandemic led to substantial socioeconomic damages in the whole town. Vigorous measurements have been enforced and implemented including lockdown of Surabaya City and a community quarantine by Surabaya local governments since the outbreak to mitigate the disease effectively. In addition, public health education has been recognized as an effective measure to prevent and control non-communicable

Table 4 Results of the attitude section evaluated with principal components of the items of the questionnaire to measure adherence in patients with primary hypertension

No.	Likert item	Average Likert scale		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Have you taken the medications according to the frequency indicated in the formula provided by the physician?	38 (34.5)	61 (55.9)	< 0.001
2	Have you taken the medications according to the dosage indicated by the physician?	82 (74.5)	87 (79.8)	0.035
3	Have you taken the medications according to the schedule indicated by the physician?	45 (40.9)	64 (58.7)	< 0.001
4	Have you taken the medications for a long period without interruptions, according to indications provided by the physician?	32 (29.1)	35 (32.1)	0.032
5	Have you taken the medications according to indications by the physician, without increasing or diminishing the dosage?	82 (74.5)	87 (79.8)	0.035
6	Have you continued taking the medications even if you don't have symptoms of hypertension?	38 (34.5)	61 (55.9)	< 0.001
7	Have you forgotten to take your medications?	72 (65.5)	49 (44.9)	< 0.001
8	Have you suspended the medications when you have felt that symptoms have improved?	73 (66.4)	59 (54.1)	< 0.001
9	Have kept using the medications in spite of feeling that the symptoms have worsened?	37 (33.6)	60 (55.0)	< 0.001
10	Have you complied with a low-salt diet?	32 (29.1)	81 (74.3)	< 0.001
11	Have you complied with a low-fat diet? Reducing consumption of fried preparations, sauces, dressings, sausages (cold cuts - Mortadella - fast foods in general)	28 (25.5)	67 (61.5)	< 0.001
12	Have you complied with a low-cholesterol diet? Reducing consumption of red meats, chicken skin, eggs, sauces (mayonnaise - tomato sauce - industrial vinaigrettes), oil, lard and butter)	45 (40.9)	71 (65.1)	< 0.001
13	Have you diminished consumption of sugar and sweets?	18 (16.4)	31 (28.4)	< 0.001
14	Have you increased consumption of fiber? Such as papaya, pineapple, soursop, peaches, pears, and apples; also cereals, like oats, quinoa and bran	29 (26.4)	47 (43.1)	< 0.001
15	Have you increased consumption of fresh vegetables?	71 (64.5)	89 (81.6)	0.006
16	Have you increased consumption of fresh fruits?	36 (32.7)	70 (64.2)	< 0.001
17	Have you increased consumption of grains? Including beans, chickpeas, lentils, peas. Besides dry nuts, like peanuts and almonds?	28 (25.5)	47 (43.1)	< 0.001
18	Have you increased consumption of low-fat dairy products?	28 (25.5)	67 (61.5)	< 0.001
19	Have you diminished the consumption of coffee?	63 (57.3)	70 (64.2)	0.028
20	Have you limited consumption of alcoholic beverages?	106 (96.4)	107 (98.2)	0.440
21	Have you stopped smoking?	13 (11.8)	28 (25.7)	< 0.001
22	Have you performed physical exercise at least five times per week?	17 (15.5)	32 (29.4)	< 0.001
23	When performing physical exercise, have you dedicated at least 30 min to it?	12 (10.9)	25 (22.9)	< 0.001
24	Have you been able to control the amount of food you consume?	63 (57.3)	68 (62.4)	0.032
25	Have you maintained your body weight under control?	59 (53.6)	61 (55.9)	0.280
26	Have you set aside daily time for relaxation for yourself?	14 (12.7)	26 (23.8)	< 0.001
27	Have you recurred to some forms to relieve stress or tension?	17 (15.5)	18 (16.5)	0.240
28	Have you controlled yourself emotionally in light of sudden events?	51 (46.4)	59 (54.1)	0.012

Data are presented as *n* (%).

diseases.

In managing non-communicable diseases such as hypertension and cardiovascular diseases, there are no better ways than prevention[25]. However, traditional diet campaign may not be the optimal educational strategy during this situation. In our study, the virtual anti-hypertensive educational

Table 5 Item structure of the 8-item Morisky Medication Adherence Scale rotation of the initial factor extraction using the principal component method

No.	Items	Subjects answered "yes"		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Do you sometimes forget to take your hypertensive pills?	47 (42.7)	39 (35.8)	0.160
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your hypertensive medicine?	70 (63.6)	65 (59.6)	0.310
3	Have you ever cut back or stopped taking your hypertensive medication without telling your doctor, because you felt worse when you took it?	23 (20.9)	19 (17.4)	0.180
4	When you travel or leave home, do you sometimes forget to bring along your hypertensive medication?	49 (44.5)	47 (43.1)	0.380
5	Did you take your hypertensive medicine yesterday?	96 (87.3)	97 (89.0)	0.430
6	When you feel like your hypertension is under control, do you sometimes stop taking your medicine?	81 (73.6)	65 (59.6)	< 0.001
7	Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your hypertensive treatment plan?	51 (46.4)	49 (44.9)	0.390
8	How often do you have difficulty remembering to take all your medications? (likert scale: 1 = never; 2 = seldom; 3 = sometime; 4 = frequently)	3.1 ± 0.8	2.3 ± 0.6	< 0.001

Data are presented as *n* (%). Response choices are "yes" or "no" for items, except Likert scale for item number 8.

campaign and various educational interventions augments the health literacy of individuals and found to moderately improve knowledge and attitude towards hypertension, medication and healthy lifestyle. While individuals with hypertension benefited from practical interventions, there is no beneficial effect on practical aspects with the virtual anti-hypertensive educational campaigns. Different from knowledge and attitude aspects, practice of our subjects did not change significantly. Therefore, an effective strategy to improve the practical aspects in hypertension management and to achieve blood pressure goal is mandatory.

Virtual anti-hypertensive educational campaigns alone are unable to increase the individual's practice towards healthy diets and lifestyles, and therefore there may be no tangible benefit to blood pressure reduction. Despite finding heterogeneity in the population of this study, there are a few reasons why practical aspects did not improve significantly following serial interventions. Firstly, conducting only one education session every week may diminish the importance in lifestyle changing. Secondly, in virtual education, subjects are more engaged in the home environment and healthcare professionals find it difficult to accurately assess each individuals lifestyle changes and get immediate feedback. Thirdly, conducting an education session virtually has greater physical and psychological barriers compared with face-to-face education. However, in the pandemic era, online education modalities should be encouraged as improvement was seen in the knowledge and attitude aspects in hypertensive patients who received the virtual anti-hypertensive educational campaigns where barriers to face-to-face education were assessed and addressed.

Dealing with hypertension is a behavior change process which demands serious learning efforts from patients, families and caregivers. Strong organized efforts by multiple stakeholders, including governments, non-government organizations, public and private partnership, and medical workers at all levels, will be key not only to improve health literacy, but also to achieve sustainable strengthening of health systems for a healthier future and well-being for all[26]. While the outbreak is ongoing, staying at home is safe. In many ways, social media and webinar platforms have transformed the practice of cardiovascular preventionists and have opened up new avenues for communicating food and nutrition information. Social media and webinar have also been an effective tool for virtual nutrition counselling, patient education, peer-to-peer support, and public health campaigns[27]. Virtual health education activities should enhance the overall goal of the health promotion and disease prevention program[28].

In a previous study by Oliveira-Filho *et al*[29], the diagnosis of non-adherent behavior through the use of the new MMAS-8 in patients treated with antihypertensive drugs was a risk factor of elevated systolic and diastolic blood pressure[29]. Considering that non-adherence is a major cause of uncontrolled blood pressure, the use of self-report scales related to BP is a simple and inexpensive measure to assist the clinical treatment of patients with hypertension.

Strength and limitation

The strengths of the present study include that our population is a crossover experimental study and that the study used strict quality control methods. Also, we have developed an interactive session of virtual education with the aid of a webinar-based platform. Several instructors were involved in observing participants' focus and concentration. Each session had a 2 h duration, with serial evaluation given at the end of each session. However, some limitations should be acknowledged. First, the nature of our data precludes establishing causal associations between education and CV health. Therefore, we may only discern association. Second, since our virtual anti-hypertensive educational campaign consisted of online self-assessment questionnaires and online education, we cannot guarantee that our population is characterized as real-practice patients, because subjects may not be sincere and may even over-evaluate their own performance. Compared with face-to-face interviews, a virtual self-report has limitations including multiple biases. Third, the study sample was drawn from one district in Surabaya; thus, the findings cannot be generalized to all subjects across the country. Fourth, virtual assessment from population surveys invariably poses the problem of social desirability, whereby study participants are reluctant to admit socially poor acceptable knowledge, attitude, and practice to avoid giving a negative impression.

Despite several limitations, our data clearly indicates a significant improvement of knowledge and attitude, but no significant change in the practice and blood pressure status in the setting of hypertensive patients. In our opinion, these data have important implications for policy making. The general recommendation would be to focus on creating the most effective way to transfer practice and health benefits throughout the virtual education series. Such a strategy should ensure that subjects with hypertension are not disadvantaged with respect to educational background or access to the internet or other opportunities. Accordingly, a virtual healthy educational campaign clearly has to be considered in the strategies of hypertension control and global cardiovascular risk reduction.

CONCLUSION

The COVID-19 pandemic has created many challenges for healthcare providers to deliver health education to the society, even during the new normal era. Remote and virtual options that align with the WHO's social distancing guidelines are essential for the continuation of health education. Creating a virtual health education program takes time and does not happen overnight. It requires sources, funding and precise guidelines. It is similar to telemedicine applied to society. The different background of subjects in the society poses a unique challenge to the maintenance of quality of information transmitted to the subjects in these pandemics. It should be remembered that conducting virtual health education programs may be better than doing nothing during this pandemic. This study relied on online questionnaires, suggesting that virtual anti-hypertensive educational campaigns may be effective in transforming knowledge and attitude, yet may not be effective to improve practice of hypertension management in the society. It is concluded that multiple experts from different fields are needed to work together addressing this issue and put their suggestions into practice.

ARTICLE HIGHLIGHTS

Research background

In the unprecedented times of the coronavirus disease 2019 (COVID-19) pandemic, many offices were shut down all across the world. Onsite classes and events were postponed. As a result, the educational health campaign has changed dramatically, with the distinctive rise of e-learning, whereby the health campaign is undertaken remotely by digital platforms. With this sudden shift away from the conventional campaign, in many parts of the globe, some are wondering whether the adoption of virtual learning will continue to persist post-pandemic, and how such a shift would impact the perception and transfer of knowledge towards hypertensive patients. To keep the community safe, but still well-informed about the dangers of hypertension and how to build a healthy lifestyle, we decided to create a Virtual Anti-Hypertensive Educational Campaign.

Research motivation

The importance of this paper is to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

Research objectives

Our teams designed a virtual anti-hypertensive educational campaign curriculum for community health care advocates in the community health care of the Mojo District, Surabaya, Indonesia to identify and

prevent health risks of hypertension. The first goal is to conduct research on the risks of hypertension and identify an educational model for community health advocates. The second goal is to educate people to improve health literacy in the field of hypertensive healthy plans. The virtual anti-hypertensive educational campaign aimed to help dispel misinformation while promoting healthy lifestyle recommendations and medical guidelines set by the Ministry of Health of the Indonesian Government and Indonesian Cardiologist Association. Therefore, the purpose of this paper is to highlight the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management during the COVID-19 pandemic.

Research methods

The trial was a randomized double-blind, placebo controlled, crossover design. The study was completed over 6 mo duration (1 October 2020-30 April 2021) of the virtual anti-hypertensive educational campaign with randomization (1 mo); treatment period one (2 mo); washout (1 mo); and finally, treatment period two (2 mo). Subjects were randomly assigned among patients with established hypertension using a pre-test post-test-controlled group design. This study was conducted in October-December 2020 in the Mojo District of Surabaya City. We conducted an online survey from October to December 2020. The survey involved an online questionnaire that was distributed virtually, by email or by WhatsApp and social media, to more than 500 hypertensive patients in the Mojo district of Surabaya, Indonesia, to which 110 participants actively replied. The questionnaire was self-administered without intervention by the authors or any specific person, and it did not contain any identifying data of the participants to ensure confidentiality. Questionnaires with incomplete information or missing data were excluded from the analysis. Completed paper questionnaires were collected anonymously to ensure confidentiality and to prevent any response bias. Unreturned or uncompleted questionnaires were recorded as missing. Participants were not aware of the study aim or outcomes to reduce the risk of any possible bias. The survey included only hypertensive patients who were living in the Mojo district of Surabaya city.

Research results

A total of 110 participants were included in the analysis, 55 in the intervention group and 55 in the control group. Following the Virtual Anti-Hypertensive Educational Campaign implementation, the only parameter that showed significant improvement were knowledge and attitude ($P < 0.001$). There is no significant change in the practice parameters ($P = 0.131$).

Research conclusions

The COVID-19 pandemic has created many challenges for healthcare providers to deliver health education to the society, even during the new normal era. Remote and virtual options that align with the WHO's social distancing guidelines are essential for the continuation of health education. Creating a virtual health education program takes time and does not happen overnight. It requires sources, funding, and precise guidelines. It is like telemedicine applied to society. The different background of subjects in the society poses a unique challenge to the maintenance of quality of information transmitted to the subjects in these pandemics. It should be remembered that conducting virtual health education programs may be better than doing nothing during this pandemic. This study relied on online questionnaires, suggesting that virtual anti-hypertensive educational campaigns may be effective in transforming knowledge and attitude, yet may not be effective to improve the practice of hypertension management in the society. It is concluded that multiple experts from different fields are needed to work together addressing this issue and put their suggestions into practice.

Research perspectives

The Department of Cardiology and Vascular Medicine created a virtual education series about healthy lifestyle and dietary guidelines that refers to Dietary Approaches to Stop Hypertension by adapting the local wisdom of the Surabaya community. We aimed to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

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FOOTNOTES

Author contributions: Andrianto A is the principal investigator, conceived the ideas and supervised the project; Ardiana M helped project administration, validation and funding; Nugraha RA initially wrote the manuscript and interpreted the data; Yutha A, Khrisna BPD and Nugraha RA highlighted the potential use of virtual health education for society during the coronavirus disease 2019 pandemic and drafted the manuscript; Putra TS and Shahab AR provided the materials and access to crucial research components; Andrianto H, Kikuko IH, Puspitasari AN and Hajjrin MR participated in the design of the study and the visualization of the software; All authors read and approved the final manuscript.

Institutional review board statement: In order to conduct the study, approval was obtained on July 1st, 2020, with a decision of the Bioethics Committee at the Faculty of Medicine Universitas Airlangga (Ref. number 532/UN3/2020) under the name of Andrianto as principal investigator.

Informed consent statement: All participants provided virtual informed consent prior to participating in the study, without identifiable data. The schedule of enrolment, intervention and measurements according to Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) requirements. The study's data were collected in accordance with the Helsinki Declaration. The consent form documented the aims, nature, and procedure of the study. Anonymity and confidentially were strictly maintained.

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SYSTEMATIC REVIEWS

Telemonitoring in heart failure patients: Systematic review and meta-analysis of randomized controlled trials

Chukwuemeka Anthony Umeh, Adrian Torbela, Shipra Saigal, Harpreet Kaur, Shadi Kazourra, Rahul Gupta, Shivang Shah

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Abstract

BACKGROUND

Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure. However, studies have produced conflicting outcomes over the years.

AIM

To determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients.

METHODS

We conducted a systematic review and meta-analysis of 38 home telemonitoring randomized controlled trials involving 14993 patients. We also conducted a sensitivity analysis to examine the effect of telemonitoring duration, recent heart failure hospitalization, and age on telemonitoring outcomes.

RESULTS

Our study demonstrated that home telemonitoring in heart failure patients was associated with reduced all-cause [relative risk (RR) = 0.83, 95% confidence interval (CI): 0.75-0.92, $P = 0.001$] and cardiovascular mortality (RR = 0.66, 95%CI: 0.54-0.81, $P < 0.001$). Additionally, telemonitoring decreased the all-cause hospitalization (RR = 0.87, 95%CI: 0.80-0.94, $P = 0.002$) but did not decrease heart failure-related hospitalization (RR = 0.88, 95%CI: 0.77-1.01, $P = 0.066$). However,

prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring.

CONCLUSION
Home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data reduces all-cause and cardiovascular mortality in heart failure patients. In addition, prolonged telemonitoring (≥ 12 mo) reduces all-cause and heart failure-related hospitalization. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

Key Words: Telemonitoring; Heart failure; Telehealth; Home monitoring; Remote monitoring

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Core Tip: Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure. However, studies have produced conflicting outcomes over the years. This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. This study found that home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data reduces all-cause and cardiovascular mortality in heart failure patients. Additionally, prolonged home telemonitoring (12 mo or more) led to both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

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INTRODUCTION

Heart failure is a clinical syndrome in which patients develop signs and symptoms, including dyspnea, fatigue, and/or fluid retention due to cardiac dysfunction or abnormality in cardiac structure[1]. Heart failure is classified as heart failure with reduced ejection fraction (EF) (< 40%), heart failure with mildly reduced EF (41% to 49%), or heart failure with preserved EF (> 50%)[1]. Heart failure has become the primary cause of hospitalization in the United States in the elderly[2,3]. The prevalence increases with increasing age, and affected individuals significantly consume healthcare resources. It has significant public health implications, with an estimated cost of about $30.7 billion in the United States in 2012, with the projected total rise in cost up to $69.7 billion by 2030[2,4]. Additionally, heart failure is associated with high morbidity and mortality, with a readmission rate during six months following discharge as high as 50%[5]. Heart failure is not just a problem in the United States but a global disease, with its prevalence increasing across the globe[1,2].

As the survival of patients with acute myocardial infarction improves and with a population that continues to age, we will continually see a rise in patients with heart failure and, thus, more rehospitalizations. Various modalities have been in the works to improve outcomes for patients with heart failure to prevent readmission. One of these modalities, termed home telemonitoring, involves tracking patients' health status using electronic devices at home[6-10]. Healthcare providers can obtain patients' vital signs, weight, and other parameters recorded and transmitted through communication technology and contact the patients if abnormalities are noted. In this way, deteriorations in patients' conditions are detected early, resulting in early interventions. A review of randomized controlled trials of noninvasive home telemonitoring compared to standard practice for people with heart failure has shown a reduced risk of all-cause mortality, heart failure-related hospitalizations, and improvement in quality of life and heart failure knowledge and self-care behaviors in some studies[6].

Though using home telemonitoring to monitor patients remotely has been going on for a while, further evaluation is needed as studies have reported inconsistent results over the years. While telemonitoring was beneficial in reducing hospital admission, all-cause mortality, and emergency room visits in some studies, others did not show such benefits[7-10]. These differences in outcomes from multiple

studies suggest that careful analysis of study outcomes is needed to determine its aggregate benefit to heart failure patients. This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. We also conducted sensitivity analysis to examine the effect of telemonitoring duration, recent heart failure hospitalization, and age on telemonitoring outcome.

MATERIALS AND METHODS

Study design

Our systematic review and meta-analysis was designed according to the guidelines included in the PRISMA statement[11].

Outcomes

Our primary outcomes were all-cause and heart failure-related mortality and all-cause and heart failure-related hospitalizations.

Eligibility criteria

We included only randomized controlled trials of home telemonitoring in heart failure patients that reported mortality or readmissions as the outcome measure. We defined home telemonitoring as patients self-measuring their vital signs (such as pulse, weight, blood pressure) at home and using a digital/broadband/satellite/wireless or blue-tooth device to transmit the data to healthcare professionals. The healthcare professionals reviewed the transmitted data and instructed the patient on the next steps if the values were abnormal, including medication adjustment. We excluded studies not written in English. Two authors independently reviewed the abstracts after our literature search to assess if they met the inclusion and exclusion criteria to be included in the study.

Literature search

Articles were obtained by searching the PubMed, Embase, Google scholar, Reference Citation Analysis and Cochrane databases with the term heart failure, combined with the following terms: "telemonitoring", "telehealth", "home monitoring", and "remote monitoring". In PubMed and Embase, we used a filter to limit our search to randomized controlled trials conducted between January 1, 2000, and September 2021. In the Google scholar search, we restricted the search to the article titles that contain the search terms.

Data extraction of primary studies

Information on study participants, methods, interventions, and outcomes, including hospitalization and death, was extracted onto a data-sheet in Excel (Microsoft Corporation, 2018). We reported only the result of the heart failure patients for articles that included heart failure patients and patients with other illnesses but reported separate results.

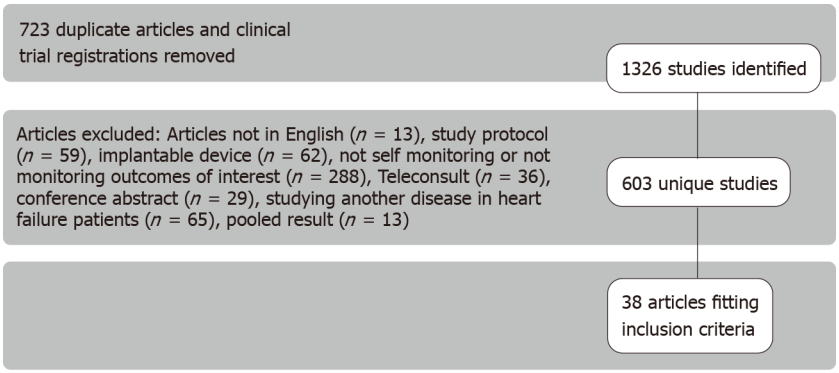
Methods for assessing the risk of bias

We assessed the risk of bias using the methods presented in the Cochrane handbook[12]. First, the risk of bias was evaluated independently by two authors. In case of disagreement between the two authors, the matter was discussed and decided by consensus. The presence of publication bias for each outcome was assessed using funnel plots.

Quantitative data synthesis

The study's primary endpoints are the effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. We calculated the relative risk (RR) and 95% confidence interval (CI) for each outcome in each study. We used the random effect model and tested the null hypothesis using Z-score. A P value of < 0.05 was interpreted as statistically significant. We tested heterogeneity in study outcomes using the χ^2 test and the I^2 statistic.

To assess the outcomes in different sub-groups, we performed a series of subgroup analyses: (1) Comparison of cumulative outcomes in the telemonitoring and usual care approach, according to the duration of follow-up (≤ 6 mo and ≥ 12 mo). The median and modal duration of follow-up in the studies was six months, and most of the studies that extended beyond six months lasted for at least 12 mo. Thus, we decided to compare studies with a duration of ≤ 6 mo with those ≥ 12 mo; (2) Comparison of cumulative outcomes in the telemonitoring and usual care approach, in studies of patients with recent heart failure hospitalization, which we defined as heart failure hospitalization within six weeks before the study, and those that did not; and (3) Comparison of cumulative outcomes in the telemonitoring and usual care approach, in studies that recruited patients ≥ 65 years. The analysis was done using Comprehensive Meta-Analysis Version 3.



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Figure 1 The literature search result.

RESULTS

Identification of relevant studies

Our search produced 1326 articles, of which 603 were unique articles after removing duplicate publications and clinical trial registrations. Two researchers independently reviewed the 603 abstracts to assess if they met the inclusion and exclusion criteria in the review. We excluded papers not in English (n = 13), papers that used implantable devices such as pacemakers (n = 62), papers on telemonitoring study protocol (n = 59), papers on teleconsulting (n = 36), conference abstracts (n = 29), papers that did not measure heart failure patients' hospitalization or mortality or did not include self-monitoring (n = 288), papers studying another disease in heart failure patients (n = 65), and papers that joined the results of patients with heart failure and patients with other illnesses (n = 13) (Figure 1).

Our study included 38 randomized controlled trials on telemonitoring in heart failure patients between January 1, 2000, and October 3, 2021[7-10,13-46] (Table 1). Fourteen thousand nine hundred and ninety-three patients were recruited in the 38 studies, with a mean of 394 and a range of 48 to 1653. The mean duration of the studies was 9.4 mo and a range of 1 to 32 mo in Table 1. Forty-seven percent of the studies were done in North America (the United States of America and Canada), and the majority of the remaining were done in Europe. All the studies involved patients measuring their vital signs and weight and using digital/broadband/satellite/wireless or blue-tooth to transmit the data to the healthcare providers. The patients transmitted their data daily in 92% of the studies and weekly in 8% of studies (Table 1). The nurses were the primary healthcare professionals that monitored the patients' data and informed the physicians of abnormal values in 79% of the studies. They also contacted the patient if there were abnormal values with instructions on what to do next. Physicians led the process in 6 studies (16%), where the physicians reviewed the transmitted patients' data and contacted them if values were abnormal with instructions on what to do next. A case manager led the process in one of the studies, and a non-clinician led one study (Table 1).

Risk of bias assessment

There was a low risk of bias in the randomization process, measurement of outcome data, or missing outcome data in the studies included in the meta-analysis. However, the intervention was not blinded in any of the primary studies because of the nature of the studies. Additionally, many of the studies did not provide information on whether outcome assessors were aware of the intervention received by study participants. Thus, it is unclear how these affected the study outcomes. Furthermore, many studies did not indicate if the data was analyzed per a pre-specified plan that was finalized before unblinded outcome data were available for analysis. Thus, we did not have information to assess the risk of bias in selecting the reported result. Table 2 shows the bias assessment in each of the primary studies. The heterogeneity within the studies ranged from low (for cardiovascular mortality, I^2 = 0%) to substantial (for all-cause hospitalizations, I^2 = 69%). The funnel plots did not show any major publication bias in the primary outcomes assessed (Supplementary Figures 1-3).

All-cause mortality

The pooled estimate of the effect of telemonitoring on all-cause death in comparison with standard care in 28 studies with 13188 patients showed that telemonitoring was associated with reduced all-cause mortality in heart failure patients (RR = 0.83, 95%CI: 0.75-0.92, P = 0.001) (Figure 2A). Our sensitivity analysis showed that the duration of telemonitoring did not influence all-cause mortality in heart failure patients. Analysis of 15 studies of six months or less duration showed reduced all-cause mortality (RR = 0.78, 95%CI: 0.65-0.94, P = 0.009). Similarly, analysis of 12 studies of 12 mo or more months duration also showed reduced all-cause mortality (RR = 0.86, 95%CI: 0.74-0.99, P = 0.032) (Table 3).

Table 1 Summary of studies included in the meta-analysis

Ref.	Number of patients	Duration of follow-up (mo)	Country	Person responsible for monitoring telemedicine data	Frequency of measuring and transmitting vital signs	Frequency of clinicians reviewing data	Included telemonitoring patients' education	Included control group patient education	Recruited patients ≥ 65 yr	Recruited recently discharged patients	Recruited frequently hospitalized patients
Nouryan *et al* [15], 2019	89	6	United States	Nurse	Daily	Daily	Yes	Yes	Yes	No	No
Seto *et al*[16], 2012	100	6	Canada	Physician	Daily	Daily	No	No	No	No	No
Weintraub *et al* [17], 2010	188	3	United States	Nurse	Daily	Daily	Yes	Yes	No	Yes	No
Blum and Gottlieb[18], 2014	156	27	United States	Nurse	Daily	Daily	No	No	No	No	No
Dansky *et al* [19], 2008	284	4	United States	Nurse	Daily	Daily	No	No	No	No	No
Kashem *et al* [20], 2008	48	12	United States	Nurse	Daily	Daily	No	No	No	No	No
Benatar *et al* [21], 2003	216	12	United States	Nurse	Daily	Daily	No	Yes	No	Yes	No
Pedone *et al* [22], 2015	96	6	Italy	Physician	Daily	Daily	No	No	Yes	No	No
Wade *et al*[23], 2011	316	6	United States	Case manager	Daily	Daily	Yes	Yes	Yes	No	No
Comín-Colet *et al*[24], 2016	178	6	Spain	Nurse	Daily	Daily	No	No	No	Yes	No
Olivari *et al* [25], 2018	339	12	Italy	Non-clinician	Daily	Daily	No	No	Yes	No	No
Lyngå *et al*[26], 2012	319	12	Sweden	Nurse	Daily	3 d a week	No	No	No	No	No
Scherr *et al*[27], 2009	120	6	Austria	Physician	Daily	Daily	No	No	No	Yes	No
Antonicelli *et al* [28], 2008	57	12	Italy	Nurse	Weekly	Weekly	Yes	No	Yes	No	No
Giordano *et al* [29], 2009	460	12	Italy	Nurse	Daily	Daily	Yes	No	No	No	No

Ong *et al*[30], 2016	1437	6	United States	Nurse	Daily	Daily	Yes	No	No	Yes	No
Kalter-Leibovici *et al*[10], 2017	1360	32	Isreal	Nurse	Daily	Daily	Yes	No	No	No	No
Mortara *et al* [31], 2009	461	12	United Kingdom, Poland, and Italy	Nurse	Weekly	Weekly	No	No	No	No	No
Dar *et al*[32], 2009	182	6	United Kingdom	Nurse	Daily	Daily	No	No	No	Yes	No
Vuorinen *et al* [33], 2014	94	6	Finland	Nurse	Weekly	Weekly	No	No	No	No	No
Goldberg *et al* [34], 2003	280	6	United States	Nurse	Daily	Daily	No	No	No	No	No
Soran *et al*[35], 2008	315	6	United States	Nurse	Daily	Daily	No	No	Yes	No	No
Chaudhry *et al* [36], 2010	1653	6	United States	Physician	Daily	Daily	No	No	No	Yes	No
Koehler *et al* [13], 2018	1571	12	Germany	Physician	Daily	Daily	Yes	No	No	No	No
Cleland *et al* [14], 2005	418	8	Germany, Netherlands, and United Kingdom	Nurse	Daily	Daily	Yes	No	No	Yes	No
Koehler *et al*[7], 2011	710	26	Germany	Physician	Daily	Daily	No	No	No	No	No
Kotooka *et al* [8], 2018	181	15	Japan	Nurse	Daily	Daily	No	No	No	Yes	No
Pekmezaris *et al* [9], 2019	104	3	United States	Nurse	Daily	Daily	Yes	No	No	Yes	No
Villani *et al*[37], 2014	80	12	Italy	Nurse	Daily	Daily	No	No	Yes	Yes	Yes
Dendale *et al* [38], 2012	160	6	Belgium	Nurse	Daily	Daily	No	No	No	Yes	No
Woodend *et al* [39], 2007	121	3	Canada	Nurse	Daily	Daily	Yes	No	No	Yes	No
Galinier *et al* [40], 2020	937	18	France	Nurse	Daily	Daily	Yes	No	No	No	No
Capomolla *et al* [41], 2004	133	12	Italy	Nurse	Daily	Daily	Yes	No	No	No	No

Kulshreshtha *et al*[42], 2010	150	6	United States	Nurse	Daily	Daily	No	No	No	Yes	Yes
Kenealy *et al* [43], 2015	98	6	New Zealand	Nurse	Daily	Daily	No	No	No	No	No
Dawson *et al* [44], 2021	1380	1	United States	Nurse	Daily	Daily	No	No	No	Yes	Yes
Delaney *et al* [45], 2013	100	3	United States	Nurse	Daily	Daily	No	No	No	No	No
Schwarz *et al* [46], 2008	102	3	United States	Nurse	Daily	Daily	No	No	Yes	Yes	No

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure, which we defined as heart failure hospitalization within six weeks before the study, did not affect the telemonitoring outcome. The analysis of 12 studies that recruited patients recently hospitalized for heart failure showed reduced all-cause mortality in telemonitoring patients (RR = 0.83, 95%CI: 0.71-0.97, P = 0.021). Similarly, an analysis of 16 studies that recruited patients who were not recently hospitalized showed reduced all-cause mortality in telemonitoring patients (RR = 0.81, 95%CI: 0.69-0.95, P = 0.01) (Table 3). Analysis of seven studies that recruited only patients 65 years or more showed that telemonitoring reduced all-cause mortality in this age group (RR = 0.66, 95%CI: 0.50-0.87, P = 0.004).

Cardiovascular mortality

The pooled estimate of the effect of telemonitoring on cardiovascular death in comparison with standard care in nine studies with 4043 patients showed that telemonitoring was associated with reduced cardiovascular mortality in heart failure patients (RR = 0.66, 95%CI: 0.54-0.81, P < 0.001) (Figure 2B). Two studies were excluded from the analysis because they reported no cardiovascular deaths in the telemonitoring and usual care groups.

Our sensitivity analysis showed that the duration of telemonitoring did not influence cardiovascular mortality in heart failure patients. Analysis of 3 studies of 6 mo or less duration showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.47, 95%CI: 0.28-0.79, P = 0.005). Similarly, our analysis of 5 studies of 12 mo or more duration showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.71, 95%CI: 0.56-0.90, P = 0.005) (Table 3).

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure, which we defined as heart failure hospitalization within six weeks before the study, did not affect the telemonitoring outcome. Analysis of 3 studies that recruited patients with recent hospitalization showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.57, 95%CI: 0.35-0.94, P = 0.026). Similarly, our analysis of 6 studies that recruited patients with no recent hospitalization showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.68, 95%CI: 0.54-0.85, P = 0.001) (Table 3).

All-cause hospitalization

The pooled estimate of the effect of telemonitoring on all-cause hospitalization in comparison with

Table 2 Showing the bias assessment of the primary studies

Ref.	The allocation sequence was random	The allocation sequence was adequately concealed	Participants aware of their assigned intervention	Interventions implementors were aware of participants' assigned groups	Outcome data were available for all, or nearly all, participants randomized	Outcome measurement could have differed between groups	Outcome assessors were aware of the intervention received by participants	Data analysis plan was finalized before data were available for analysis
Nouryan *et al* [15], 2019	Yes	Probably yes	Yes	Yes	Yes	No	No information	No information
Seto *et al*[16], 2012	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Weintraub *et al* [17], 2010	Probably yes	No information	Yes	Yes	Yes	No	No	Yes
Blum and Gottlieb[18], 2014	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Dansky *et al* [19], 2008	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Kashem *et al* [20], 2008	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Benatar *et al* [21], 2003	Probably yes	No information	Yes	Yes	Probably yes	No	No information	No information
Pedone *et al*[22], 2015	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Wade *et al*[23], 2011	Yes	No information	Yes	Yes	No	No	No information	No information
Comín-Colet *et al*[24], 2016	Yes	Yes	Yes	Yes	Yes	No	No	No information
Olivari *et al*[25], 2018	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Lyngå *et al*[26], 2012	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Scherr *et al*[27], 2009	Probably yes	No information	Yes	Yes	No	No	No information	No information
Antonicelli *et al* [28], 2008	Probably yes	No information	Yes	Yes	Probably yes	No	No information	No information
Giordano *et al* [29], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information

Ong *et al*[30], 2016	Yes	Yes	Yes	Yes	Probably yes	No	No	Yes
Kalter-Leibovici *et al*[10], 2017	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Mortara *et al* [31], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Dar *et al*[32], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Vuorinen *et al* [33], 2014	Yes	No information	Yes	Yes	Yes	No	No information	No information
Goldberg *et al* [34], 2003	Yes	No information	Yes	Yes	No	No	No information	No information
Soran *et al*[35], 2008	Yes	No information	Yes	Yes	Yes	No	No information	No information
Chaudhry *et al* [36], 2010	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Koehler *et al* [13], 2018	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Cleland *et al* [14], 2005	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Koehler *et al*[7], 2011	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Kotooka *et al*[8], 2018	Yes	Yes	Yes	Yes	No	No	No	Yes
Pekmezaris *et al* [9], 2019	Yes	No information	Yes	Yes	Yes	No	No information	No information
Villani *et al*[37], 2014	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Dendale *et al* [38], 2012	Yes	Yes	Yes	Yes	Yes	No	No	No information
Woodend *et al* [39], 2007	Yes	No information	Yes	Yes	Yes	No	No information	No information
Galinier *et al* [40], 2020	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Capomolla *et al* [41], 2004	Yes	No information	Yes	Yes	No	No	No information	No information
Kulshreshtha *et*	Yes	No	Yes	Yes	No	No	No information	No information

al[42], 2010								
Kenealy *et al* [43], 2015	Yes	Yes	Yes	Yes	Yes	No	No	No information
Dawson *et al* [44], 2021	Yes	Yes	Yes	Yes	No	No	No information	No information
Delaney *et al* [45], 2013	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Schwarz *et al* [46], 2008	Yes	No information	Yes	Yes	Yes	No	No information	No information

Table 3 Result of sensitivity analysis

	All-cause mortality			Cardiovascular mortality			All-cause hospitalization			Heart failure hospitalization		
	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect
Follow up ≤ 6 mo	15	6781	Reduced	3	773	Reduced	19	7442	No effect	8	2774	No effect
Follow up ≥ 12 mo	12	6159	Reduced	5	3022	Reduced	13	5360	Reduced	6	2962	Reduced
Recent hospitalization	12	5865	Reduced	3	607	Reduced	13	6057	Reduced	6	2486	No effect
No recent hospitalization	16	7417	Reduced	6	3436	Reduced	20	6993	Reduced	8	3250	Reduced
Patients ≥ 65 yr	7	1522	Reduced	-	-	-	8	1611	No effect	-	-	-

standard care in 33 studies with 13050 patients showed that telemonitoring was associated with reduced all-cause hospitalization in heart failure patients (RR = 0.87, 95%CI: 0.80-0.94, P = 0.002) (Figure 2C).

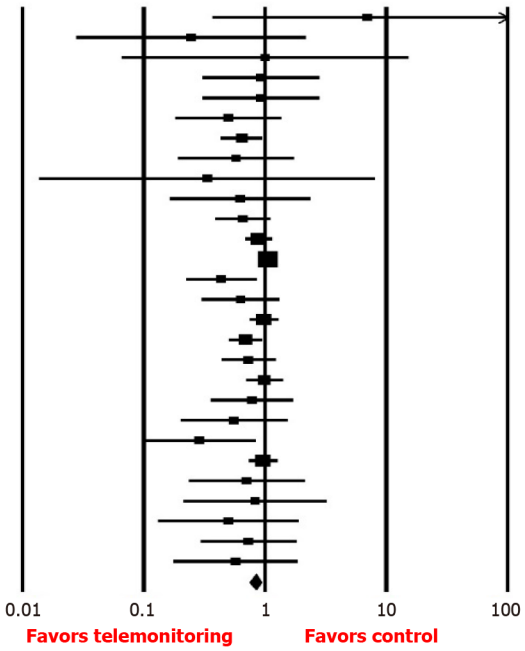
Our sensitivity analysis showed that the duration of telemonitoring influenced all-cause hospitalization in heart failure patients. Analysis of 19 studies with six months or less duration showed no effect of telemonitoring on all-cause hospitalization (RR = 0.93, 95%CI: 0.83-1.04, P = 0.21). Conversely, our analysis of 13 studies with 12 mo or more duration showed that telemonitoring reduced all-cause hospitalization (RR = 0.79, 95%CI: 0.68-0.92, P = 0.002) (Table 3).

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure did not affect the all-cause hospitalization. Analysis of 13 studies that recruited recently hospitalized heart failure patients showed that telemonitoring reduced all-cause hospitalization (RR = 0.85, 95%CI: 0.74-0.98, P = 0.03). Similarly, our analysis of 20 studies that recruited patients that were not recently hospitalized showed that telemonitoring also reduced all-cause hospitalization in this group (RR = 0.88, 95%CI: 0.78-0.98, P = 0.03) (Table 3). Analysis of eight studies that recruited only patients 65 years or older showed that telemonitoring did not affect all-cause hospitalization in this age group (RR = 0.77, 95%CI: 0.58-1.02, P = 0.071).

A

Effect of home telemonitoring on all-cause mortality in heart failure patients

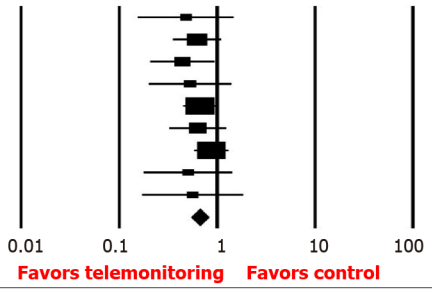
Study name	Risk ratio	Lower limit	Upper limit	*P* value
Seto *et al*[16], 2012	7.000	0.371	132.101	0.194
Weintraub *et al*[17], 2010	0.245	0.028	2.149	0.204
Kashem *et al*[20], 2008	1.000	0.066	15.081	1.000
Pedone *et al*[22], 2015	0.927	0.305	2.812	0.893
Wade *et al*[23], 2011	0.927	0.305	2.812	0.893
Comín-Colet *et al*[24], 2016	0.499	0.183	1.357	0.173
Olivari *et al*[25], 2018	0.643	0 .437	0.947	0.025
Lyngå *et al*[26], 2012	0.567	0.193	1.723	0.324
Scherr *et al*[27], 2009	0.333	0.014	8.005	0.498
Antonicelli *et al*[28], 2008	0.621	0.164	2.359	0.485
Giordano *et al*[29], 2009	0.656	0.390	1.103	0.112
Ong *et al*[30], 2016	0.886	0.691	1.135	0.337
Kalter-Leibovici *et al*[10], 2017	1.058	0.909	1.231	0.465
Goldberg *et al*[34], 2003	0.435	0.224	0.846	0.014
Soran *et al*[35], 2008	0.627	0.303	1.295	0.207
Chaudhry *et al*[36], 2010	0.980	0.747	1.285	0.883
Koehler *et al*[13], 2018	0.693	0.508	0.944	0.020
Cleland *et al*[14], 2005	0.730	0.438	1.216	0.227
Koehler *et al*[7], 2011	0.987	0.699	1.395	0.942
Kotooka *et al*[8], 2018	0.778	0.360	1.682	0.523
Villani *et al*[37], 2014	0.556	0.204	1.512	0.250
Dendale *et al*[38], 2012	0.286	0.098	0.831	0.021
Galinier *et al*[40], 2020	0.965	0.742	1.255	0.791
Capomolla *et al*[41], 2004	0.704	0.235	2.106	0.530
Kulshreshtha *et al*[42], 2010	0.829	0.215	3.193	0.785
Kenealy *et al*[43], 2015	0.500	0.132	1.887	0.306
Dawson *et al*[44], 2021	0.727	0.294	1.797	0.490
Schwarz *et al*[46], 2008	0.571	0.178	1.833	0.347
	0.829	0.745	0.923	0.001



B

Effect of home telemonitoring on cardiovascular mortality in heart failure patients

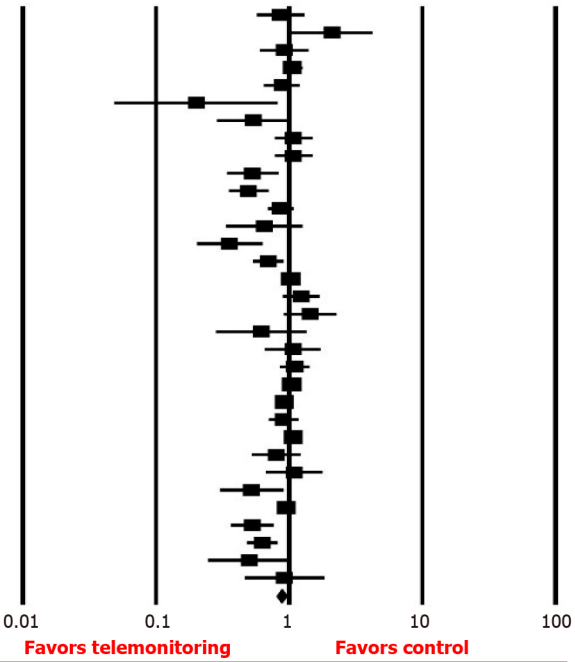
Study name	Risk ratio	Lower limit	Upper limit	*P* value
Comín-Colet *et al*[24], 2016	0.479	0.156	1.470	0.198
Giordano *et al*[29], 2009	0.621	0.355	1.086	0.094
Goldberg *et al*[34], 2003	0.441	0.209	0.929	0.031
Soran *et al*[35], 2008	0.528	0.200	1.394	0.197
Koehler *et al*[13], 2018	0.668	0.451	0.988	0.044
Cleland *et al*[14], 2005	0.633	0.328	1.221	0.173
Koehler *et al*[7], 2011	0.874	0.588	1.301	0.508
Kotooka *et al*[8], 2018	0.506	0.180	1.421	0.196
Capomolla *et al*[41], 2004	0.563	0.173	1.833	0.340
	0.660	0.537	0.810	0.000

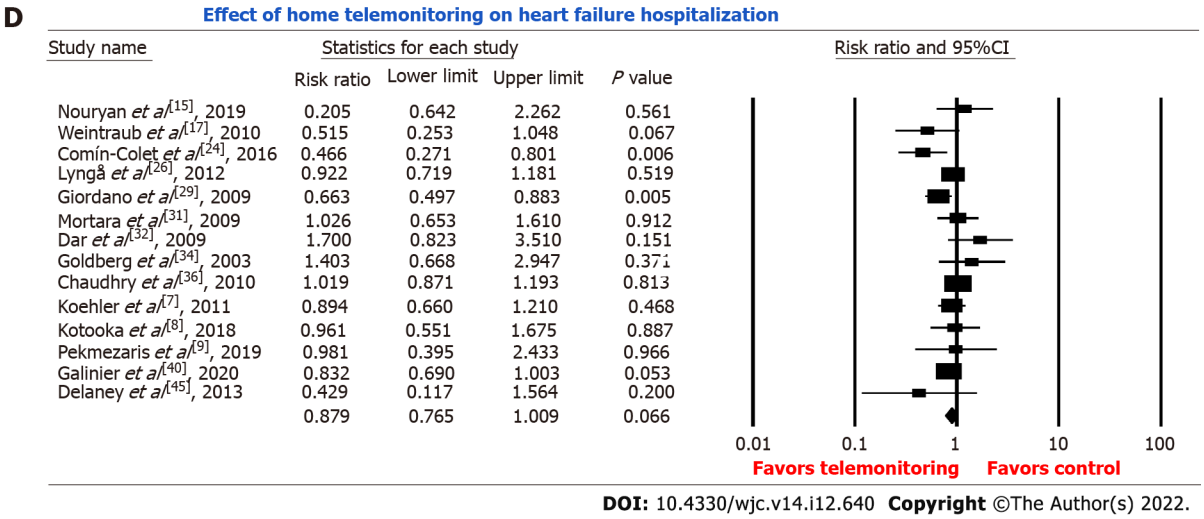


C

Effect of home telemonitoring on all-cause hospitalization in heart failure patients

Study name	Risk ratio	Lower limit	Upper limit	*P* value
Nouryan *et al*[15], 2019	0.861	0.572	1.295	0.472
Seto *et al*[16], 2012	2.111	1.059	4.207	0.034
Weintraub *et al*[17], 2010	0.916	0.603	1.391	0.680
Blum and Gottlieb[18], 2014	1.060	0.904	1.243	0.471
Dansky *et al*[19], 2008	0.883	0.652	1.195	0.419
Kashem *et al*[20], 2008	0.200	0.049	0.818	0.025
Benatar *et al*[21], 2003	0.542	0.291	1.007	0.053
Pedone *et al*[22], 2015	1.078	0.790	1.472	0.636
Wade *et al*[23], 2011	1.078	0.790	1.472	0.636
Comín-Colet *et al*[24], 2016	0.532	0.344	0.823	0.005
Olivari *et al*[25], 2018	0.496	0.355	0.692	0.000
Lyngå *et al*[26], 2012	0.867	0.699	1.074	0.192
Scherr *et al*[27], 2009	0.647	0.335	1.249	0.195
Antonicelli *et al*[28], 2008	0.359	0.206	0.623	0.000
Giordano *et al*[29], 2009	0.689	0.542	0.899	0.005
Ong *et al*[30], 2016	1.033	0.931	1.145	0.544
Mortara *et al*[31], 2009	1.231	0.904	1.676	0.188
Dar *et al*[32], 2009	1.435	0.918	2.241	0.113
Vuorinen *et al*[33], 2014	0.615	0.281	1.346	0.224
Goldberg *et al*[34], 2003	1.067	0.664	1.714	0.788
Soran *et al*[35], 2008	1.101	0.861	1.408	0.444
Chaudhry *et al*[36], 2010	1.040	0.941	1.149	0.446
Koehler *et al*[13], 2018	0.923	0.706	1.165	0.445
Cleland *et al*[14], 2005	0.803	0.531	1.213	0.297
Koehler *et al*[7], 2011	1.089	0.676	1.754	0.726
Kotooka *et al*[8], 2018	0.803	0.531	1.213	0.297
Pekmezaris *et al*[9], 2019	1.089	0.676	1.754	0.726
Villani *et al*[37], 2014	0.522	0.303	0.898	0.019
Galinier *et al*[40], 2020	0.948	0.837	1.073	0.398
Capomolla *et al*[41], 2004	0.525	0.366	0.753	0.000
Dawson *et al*[44], 2021	0.628	0.486	0.812	0.000
Delaney *et al*[45], 2013	0.500	0.249	1.004	0.051
Schwarz *et al*[46], 2008	0.923	0.467	1.825	0.818
	0.869	0.796	0.949	0.002





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Figure 2 Forest plot showing the effect of home telemonitoring. A: On all-cause mortality; B: On cardiovascular mortality; C: On all-cause hospitalization; D: On heart failure hospitalization. CI: Confidence interval.

Heart failure hospitalization

The pooled estimate of the effect of telemonitoring on heart failure hospitalization compared to standard care in 14 studies with 5736 patients showed that telemonitoring had no effect on heart failure hospitalization (RR = 0.88, 95%CI: 0.77-1.01, *P* = 0.066) (Figure 2D). Our sensitivity analysis showed that the duration of telemonitoring influenced heart failure hospitalization. Analysis of 8 studies of six months or less duration showed no effect of telemonitoring on heart failure hospitalization (RR = 0.90, 95%CI: 0.65-1.23, *P* = 0.50). Conversely, our analysis of 6 studies of 12 mo or more duration showed that telemonitoring reduced heart failure hospitalization (RR = 0.85, 95%CI: 0.75-0.95, *P* = 0.004) (Table 3).

Sensitivity analysis showed that telemonitoring had no effect on heart failure hospitalization in patients recently discharged from the hospital. Analysis of 6 studies showed no effect on heart failure hospitalization (RR = 0.85, 95%CI: 0.61-1.21, *P* = 0.37). Conversely, our analysis of 8 studies that recruited patients that were not recently hospitalized showed that telemonitoring reduced heart failure hospitalization (RR = 0.86, 95%CI: 0.76-0.98, *P* = 0.02) (Table 3).

DISCUSSION

Our study demonstrated that home telemonitoring in heart failure patients was associated with reduced all-cause and cardiovascular mortality. These findings are consistent with previous meta-analyses of heart failure patients but inconsistent with some others[6,47-49]. Our sensitivity analysis showed that all-cause and cardiovascular mortality reduction was seen with short (six months or less) and longer (one year or more) telemonitoring. The decrease in mortality was also seen in studies that recruited recently hospitalized heart failure patients, which we defined as heart failure hospitalization within six weeks before the study, and those that did not. The decrease in mortality seen in-home telemonitoring could be due to early detection of clinical deterioration and early intervention.

Our study found that telemonitoring marginally decreased the all-cause hospitalization but did not decrease heart failure-related hospitalization. Some prior meta-analysis did not show reduced all-cause hospitalization[49-52] or heart failure-related hospitalization[52] with telemonitoring in heart failure patients. It is reasonable to expect that telemonitoring and early intervention will reduce hospitalization by detecting clinical deterioration early and early intervention. Conversely, telemonitoring could lead to more frequent hospitalization. This is because telemonitoring patients have more frequent contact with the healthcare system, and severe episodes of decompensation requiring hospitalization will be detected early. In this case, it will be expected that such patients will come to the hospital at the early stage of severe decompensation and that duration of hospitalization will be shorter. Unfortunately, length of hospital stay was inconsistently reported in the studies, preventing meta-analysis of telemonitoring on this outcome. However, our sensitivity analysis showed that while short-duration telemonitoring (6 mo or less) did not affect both all-cause hospitalization and heart failure hospitalization, long-duration telemonitoring (12 mo or more) showed a reduction in both all-cause and heart failure hospitalization. This may explain why some earlier meta-analyses with fewer studies showed a decrease in heart failure hospitalization with telemonitoring[49,53]. In the long run, telemonitoring may lead to early detection of clinical deterioration and early interventions that reduce hospitalization.

Some studies included scheduled nurse-led patient interaction or education as part of the intervention in addition to measuring and transmitting vital signs. The scheduled patient-nurse interactions included counseling if there is an acute change in health status, providing patient self-care education, adjusting medications using designated protocols, monitoring disease signs and symptoms, monitoring medication adherence, and addressing technical and social issues[10,13,14]. Three studies had the scheduled patient-nurse education and interaction in both the control and telemonitoring groups, while seven had the education and interaction in only the telemonitoring group. Thus, we thought that the additional intervention might partially explain the decrease in all-cause mortality with telemonitoring in those studies. However, our sensitivity analysis in the seven studies that received further intervention showed that telemonitoring with additional patient education did not affect heart failure hospitalization or mortality. This points that telemonitoring and not the additional interventions were likely responsible for the improved mortality seen in these studies.

Additionally, we had thought that home telemonitoring might be more helpful in reducing hospitalization and death in recently hospitalized or newly diagnosed heart failure patients who need support and education. However, our sensitivity analysis showed that home telemonitoring reduced all-cause and cardiovascular mortality in both studies that recruited patients recently hospitalized for heart failure and those that did not. Similarly, telemonitoring reduced all-cause hospitalization in both studies that recruited patients who were recently hospitalized for heart failure and those who had not. However, contrary to our expectation, home telemonitoring did not affect heart failure hospitalization in studies that recruited patients recently hospitalized for heart failure. However, this might reflect the small number of trials and participants rather than an actual lack of effect.

Limitations of the study

There are certain limitations to this study. First, home telemonitoring organizations sponsored some of the studies included in this review. This may have introduced a conflict of interest and bias in the results that were published. Secondly, many of the studies had incomplete reporting of their study methodology, making it difficult to classify them as high or low bias studies. Thus, the risk of bias in some of the studies was unclear. Thirdly, some of the sensitivity analyses involved a combination of a few small-sized studies. The small number of studies and participants may make it difficult to detect an effect, even if one exists.

Implications of the results for practice, policy, and future research

Prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for. In addition, these hospitals or organizations will need to consider the cost of prolonged telemonitoring *viz-a-viz* the cost of rehospitalization. The opportunities for future research include a cost-benefit analysis of home telemonitoring in heart failure patients. There is also a need for more studies on the effect of telemonitoring on frequently hospitalized heart failure patients.

CONCLUSION

The results of this meta-analysis support the benefit of home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data in reducing all-cause and cardiovascular mortality in heart failure patients. In addition, this analysis also shows the benefit of prolonged telemonitoring (≥ 12 mo) in reducing all-cause and heart failure-related hospitalization.

ARTICLE HIGHLIGHTS

Research background

Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure.

Research motivation

However, while telemonitoring was beneficial in reducing hospital admission, all-cause mortality, and emergency room visits in some studies, others did not show such benefits. These differences in outcomes from multiple studies suggest that a careful analysis of study outcomes is needed to determine its aggregate benefit to heart failure patients.

Research objectives

This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients.

Research methods

We conducted a systematic review and meta-analysis of 38 home telemonitoring randomized controlled trials involving 14993 patients.

Research results

Home telemonitoring in heart failure patients was associated with reduced cardiovascular [relative risk (RR) = 0.66, 95% confidence interval (CI): 0.54-0.81, $P < 0.001$] and all-cause mortality (RR = 0.83, 95%CI: 0.75-0.92, $P = 0.001$). Furthermore, telemonitoring was associated with decreased all-cause hospitalization (RR = 0.87, 95%CI: 0.80-0.94, $P = 0.002$) but not heart failure-related hospitalization (RR = 0.88, 95%CI: 0.77-1.01, $P = 0.066$). Interestingly, prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring.

Research conclusions

Home telemonitoring reduces all-cause and cardiovascular mortality in heart failure patients. This study found that prolonged home telemonitoring (12 mo or more) led to both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

Research perspectives

The opportunities for future research include a cost-benefit analysis of home telemonitoring in heart failure patients. There is also a need for more studies on the effect of telemonitoring on frequently hospitalized heart failure patients.

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FOOTNOTES

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CASE REPORT

Early and aggressive presentation of wild-type transthyretin amyloid cardiomyopathy: A case report

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Abstract

BACKGROUND

Wild-type transthyretin amyloidosis (ATTRwt) is the most common form of transthyretin amyloid cardiomyopathy, occurring mostly over age of 60 years (mean age of 80 years). Mean survival without treatment is 3.6 years, making early detection imperative. We report an unusual case of a 58-year-old patient with ATTRwt cardiomyopathy requiring heart transplantation.

CASE SUMMARY

A 58-year-old male presented with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. Approximately ten months before this clinical presentation, the patient had first received a diagnosis of heart failure with reduced ejection fraction (EF) of 15% to 20%. The patient was started on appropriate guideline-directed medical therapy with only mild improvement in his EF. Upon further investigation, echocardiogram, technetium pyrophosphate scan (Tc PYP), and cardiac magnetic resonance imaging (cMRI) suggested a diagnosis of amyloidosis, and ATTRwt was subsequently confirmed with native heart tissue biopsy, congo red staining, liquid chromatography-tandem mass spectrometry, and genetic testing. The patient was successfully treated with heart transplantation and is doing well post-transplant.

CONCLUSION

Wild-type ATTR amyloidosis should be kept on differentials in all patients (even less than 60 years old) with non-ischemic cardiomyopathy, especially in the setting of increased ventricular wall thickness and other classic echocardiogram,

cMRI, and Tc PYP findings. Early diagnosis and management can be consequential in improving patient outcomes.

Key Words: Wild-type; Transthyretin; Amyloidosis; Young; Heart failure; Heart transplant; Case report

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Core Tip: Wild-type transthyretin amyloidosis (ATTRwt) continues to be an underdiagnosed condition. Although rare in patients under 60 years of age, physicians should include the condition in their differential as early diagnosis and early management can impact patient outcomes. Physicians should be aware of the findings on non-invasive testing that supports ATTRwt. Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, biatrial enlargement, apical sparing on longitudinal strain and signs of elevated filling pressures and restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities). Cardiac magnetic resonance imaging classically shows late gadolinium enhancement. A technetium pyrophosphate study shows an increased heart-to-contralateral ratio and increased Perugini visual grade.

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INTRODUCTION

Amyloid deposition is commonly found in aging populations. Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative, progressive, and potentially fatal cardiomyopathy that is caused by extracellular deposition of misfolded transthyretin-derived insoluble amyloid fibrils in the myocardium [1]. Wild-type transthyretin amyloidosis (ATTRwt) is the most common type of ATTR-CM[2]. ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old[2,3]. A retrospective review of 360 patients diagnosed with ATTRwt showed that 93% of the patients with an antemortem diagnosis were Caucasian males greater than 70 years old [4]. Another retrospective review showed only a handful of patients that were diagnosed with ATTRwt in their forties[2]. A recent case of ATTRwt was identified in a 34-year-old male in India[5]. Our case report highlights an unusual case of ATTRwt cardiomyopathy presenting in a relatively young, 58-year-old patient with end stage heart failure (HF) symptoms.

CASE PRESENTATION

Chief complaints

Progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea.

History of present illness

A 58-year-old Caucasian man presented to the heart failure clinic with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. On review of symptoms, the patient had no palpitations, carpal tunnel symptoms, neuropathy, or back pain.

History of past illness

Approximately ten months before this clinic presentation, the patient had first received a diagnosis of HF with reduced ejection fraction (EF) of 15% to 20%. At that time, he underwent left heart catheterization which showed no obstructive coronary artery disease. The patient was started on appropriate guideline-directed medical therapy (GDMT) with only mild improvement in his EF. The patient was followed in the heart failure clinic and had recurrences of acute on chronic heart failure episodes. Unfortunately, due to borderline hypotension, he was unable to reach maximum doses of GDMT which ultimately had to be stopped.

Personal and family history

His past medical history was significant for non-ischemic cardiomyopathy (EF 15%-20%), left ventricular hypertrophy, implantable cardioverter defibrillator in situ, atrial fibrillation, moderate to severe mitral regurgitation, prior left atrial thrombus, and prior tobacco use disorder. Other than atrial fibrillation, he had no significant history of other arrhythmias. He worked as a construction worker. His family history was notable only for his father who underwent a coronary artery bypass graft at age 59 years.

Physical examination

Physical exam was notable for the patient appearing well-nourished; however, jugular venous distension, a holosystolic murmur consistent with known mitral regurgitation, abdominal distention, and bilateral lower extremity edema were present. Vital signs depicted borderline systolic blood pressure of 95/70 mmHg with a mean of 78 mmHg, normal heart rate, normal respiratory rate and saturation on room air, and normal temperature.

Laboratory examinations

The patient's presentation to the clinic with progressively worsening heart failure symptoms prompted admission to the hospital.

Imaging examinations

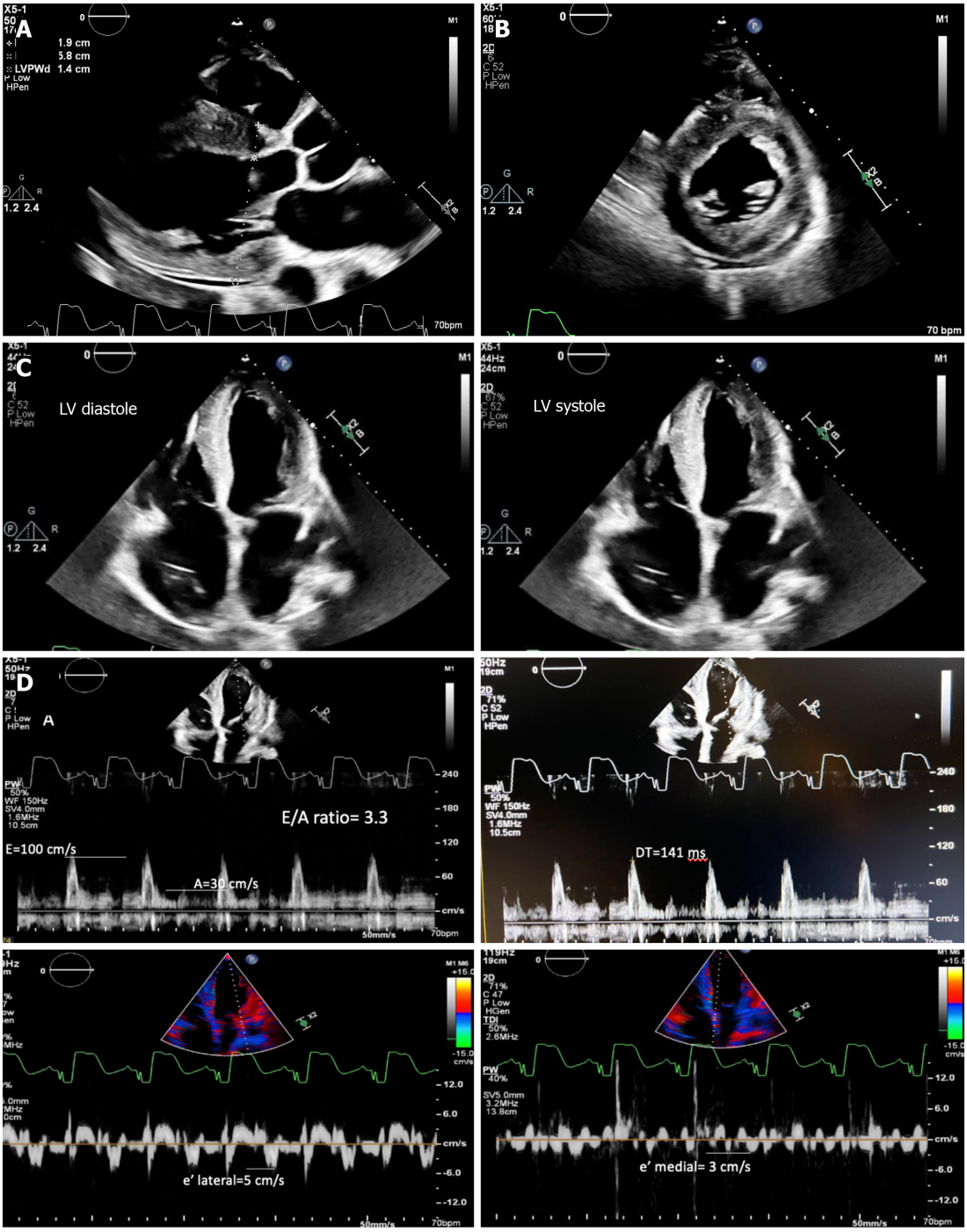
Electrocardiogram showed AV-paced complexes and low voltage in both limb and precordial leads. He underwent right heart catheterization which was consistent with cardiogenic shock with central venous pressure 18 mmHg, polymeraseacidicprotein 43/25 with mean of 32 mmHg, pulmonary capillary wedge pressure 23 mmHg, fick cardiac output of 4.6 L/min, and cardiac index of 2.1 L/min/m^2. Transthoracic echocardiogram demonstrated a reduced EF of 10%, concentric hypertrophy with interventricular septal thickness of 1.9 cm and posterior wall thickness of 1.4 cm, moderately reduced right ventricle (RV) function with a dilated RV, moderate mitral regurgitation, and trivial pericardial effusion (Figure 1A-C). Diastology additionally showed an E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time of 141 ms (Figure 1D). The increased myocardial wall thickness on echocardiogram as well as parameters consistent with restrictive pathology led to a detailed amyloidosis workup. A technetium pyrophosphate scan (Tc PYP) showed a heart/contralateral lung ratio of 1.77 and visual grade 3 as per the Perugini scale, highly suggestive of cardiac amyloidosis (Figure 2). Cardiac magnetic resonance imaging (cMRI) showed global myocardial delayed hyperenhancement and failure to null most likely due to cardiac amyloidosis (Figure 3). Amyloid light chain amyloidosis work-up including kappa and lambda light chains levels, serum protein electrophoresis, and urine protein electrophoresis was unremarkable. The native heart tissue pathology showed diffuse amyloid deposits between the myocardial fibrils, confirmed on Congo red staining (Figure 4). Liquid chromatography-tandem mass spectrometry was also performed on peptides extracted from the Congo red-positive areas of tissue and was consistent with ATTR-CM. The spectrometry did not detect an amino acid sequence abnormality in the transthyretin protein, suggesting ATTRwt as the diagnosis. Genetic testing was performed and was unremarkable, showing two variants of unknown significance, c.3262-3C>G in the LAMA4 gene and p.K963E in the RBM20 gene. Screening of the TTR gene was unremarkable ruling out hereditary TTR cardiomyopathy.

FINAL DIAGNOSIS

In conclusion, the history, exam, and workup, including genetic testing, confirmed ATTRwt as the final diagnosis.

TREATMENT

The patient was initially supported with inotropes; however, given the concern for end-stage cardiac amyloidosis and risk for progressive cardiogenic shock in the setting of biventricular failure, orthotopic heart transplant evaluation was initiated. He was deemed a suitable candidate for heart transplantation by our multidisciplinary transplant committee. The patient was maintained on milrinone and epinephrine for inotropic support until he underwent transplantation.

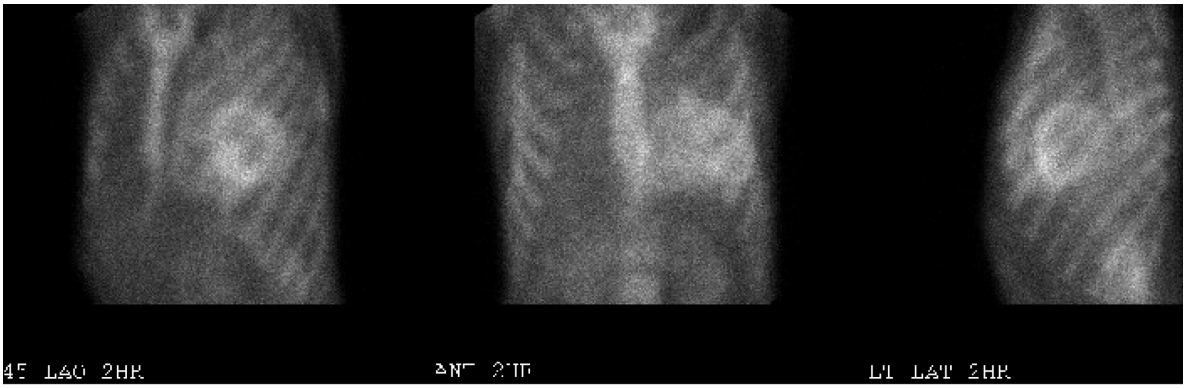


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Figure 1 Transthoracic echocardiography. A: Parasternal long axis of left ventricle shows concentric hypertrophy with an increased interventricular septum and posterior wall thickness and a trivial pericardial effusion; B: Parasternal short axis showing thickened walls of the left ventricular myocardium; C: Four-chamber view showing lehigh valley diastole and systole; D: E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time time of 141 ms, consistent with restrictive pathology. LV: Lehigh valley.

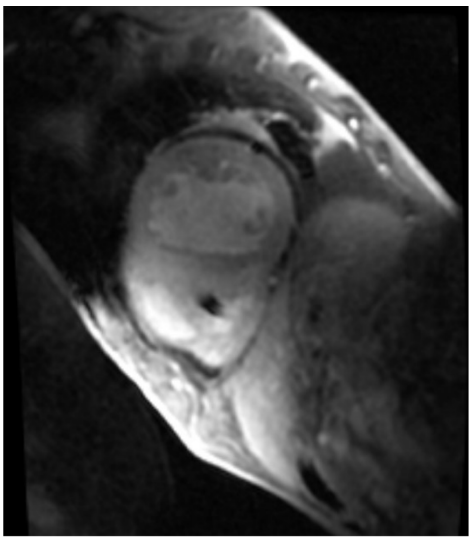
OUTCOME AND FOLLOW-UP

Unfortunately, a few days following the transplant, the patient had pericardial bleeding with tamponade followed by successful evacuation of blood. He had no other postoperative complications and was discharged home on postoperative day eight. The patient has followed closely in the heart failure clinic and is doing very well post-transplant.



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Figure 2 Technetium pyrophosphate scan showing increased myocardial uptake of tracer (visual grade 3) suggestive of transthyretin-mediated cardiac amyloidosis.



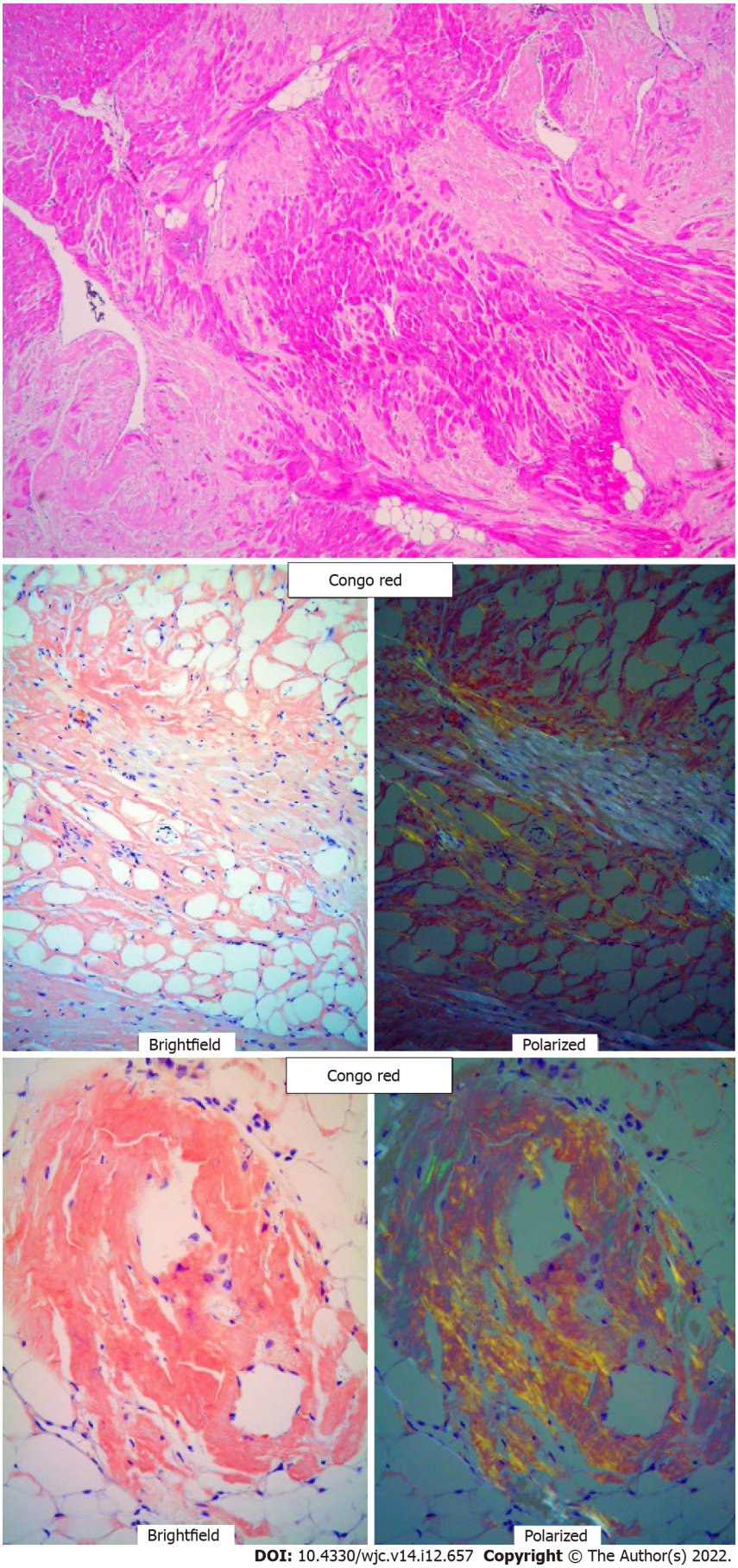
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Figure 3 Cardiac magnetic resonance imaging showing delayed global hyperenhancement and failure to null likely due to cardiac amyloidosis.

DISCUSSION

ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old. Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential. Our patient not only developed ATTRwt below the age of 60, but also within 1 year of the patient's HF diagnosis that rapidly progressed to end-stage cardiomyopathy. After review of the literature, it remains uncertain why some individuals may be predisposed to developing ATTRwt at an earlier age. However, early diagnosis can lead to improved management and outcomes as ATTRwt continues to be an underdiagnosed condition.

Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, valve thickening, atrial enlargement, apical sparing on strain and signs of elevated filling pressures, restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities)[6]. In patients with ATTR-CM amyloidosis, late gadolinium enhancement (LGE) is almost always present on cMRI. Studies have shown with LGE cMRI, an inability to suppress or "null" the myocardial signal or the presence of diffuse subendocardial or transmural enhancement patterns, which suggests amyloidosis with a sensitivity and specificity that approach 85%-90%[7,8]. cMRI also shows elevated native T1 values and increased extracellular volume[7]. Bone scans using Tc PYP scan show increased ^{99m}Tc-PYP uptake in the heart of patients with amyloid infiltration leading to increased heart-to-contralateral ratio and visual grading[3]. The non-biopsy diagnosis of ATTR-CM with TcPYP scan (first described by Gillmore *et al*[9]) is now widely accepted and has replaced the historical endocardial biopsy provided AL amyloidosis is ruled out.



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Figure 4 Native heart tissue pathology on H and E staining showing extracellular amyloid deposits, followed beneath by Congo red

staining showing apple green refringence of amyloid deposits (100× magnification).

In ATTR-CM, several new pharmaceutical therapies that target the disease at various levels have emerged, including TTR stabilizers (example: Tafamidis), and antisense oligonucleotides, RNA interference (example: Patisiran, Vutrisiran and Inotersen). Tafamidis is the only drug approved for ATTR cardiomyopathy so far, although trials with patisiran, vutrisiran, inotersen and eplontersen are underway. All of these are most effective when administered prior to significant cardiac dysfunction[3, 10]. There are rare and isolated case reports of amyloid cardiac deposition recurrence post-transplant [11]. Since there are very few cases of heart transplantation for ATTR-CM reported in the literature given that most patients have a median age of 80, it is unknown how to best prevent the deposition of amyloid again in the transplanted heart. Our patient remains on Tafamidis post-transplant with the hope of stabilizing TTR protein tetramer and preventing amyloid fibrils from depositing in the myocardium.

Hence, it is imperative to diagnose ATTR-CM at earlier stages with available non-invasive testing and FDA approved treatments. Heart transplantation can be considered in select patients with Stage D HF [12]. The current allocation system provides priority as Status 4 to these stage D ATTR-CM patients due to a lack of durable mechanical support options[10].

CONCLUSION

Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential, especially in non-ischemic cardiomyopathy patients with thickened interventricular septum, posterior wall thickness, and arrhythmias especially atrial fibrillation. Early diagnosis of ATTRwt combined with newer therapies can be consequential in increasing patients' quality of life and survival [3].

FOOTNOTES

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