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Retrospective Study

Does the intracoronary pressure differ according to two types (diffuse or focal) of coronary spasm?

Hiroki Teragawa, Chikage Oshita, Yuko Uchimura

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Abstract

BACKGROUND

Several reports show that two types of coronary vasospasm (diffuse and focal spasm) are associated with the severity or prognosis of coronary spasm in patients with vasospastic angina (VSA). It is unclear whether intracoronary pressure differs between the two spasm types.

AIM

To investigate such relationships using a pressure wire during the spasm provocation test (SPT) in patients with VSA.

METHODS

Eighty-seven patients with VSA (average age: 67 years; 50 men, 37 women) underwent SPT. During the SPT, a pressure wire was advanced into the distal portion of the right coronary artery and left anterior descending coronary artery, and the ratio of the intracoronary pressure to the aortic pressure (Pd/Pa) was continuously monitored. An SPT was performed using acetylcholine (ACh), and the presence of coronary spasm was defined as the presence of > 90% arterial narrowing in response to an ACh infusion, with the usual chest symptoms and/or ischemic ECG changes. Focal spasm was defined as total or subtotal spasm within one segment of the AHA classification, while diffuse spasm was defined as > 90% spasm with two or more segments.

RESULTS

Among 87 patients, the frequencies of metabolic syndrome and having coronary atherosclerosis were higher in the focal group ($n = 33$) than in the diffuse spasm group ($n = 54$, $P < 0.05$). In the vessel analyses, in these 134 spastic segments, diffuse and focal spasms were detected in 100 and 34 vessels, respectively. The Pd/Pa at baseline was similar in both groups (diffuse: 0.96 ± 0.05 , focal: 0.95 ± 0.05 , $P = 0.35$); however, the Pd/Pa during coronary spasm was lower in focal spastic vessels (0.66 ± 0.20) than in diffuse spastic vessels (0.76 ± 0.11 , $P < 0.01$),

and the reduction in Pd/Pa during an SPT was also lower in focal spastic vessels (-0.29 ± 0.20) than in diffuse spastic vessels (-0.18 ± 0.11 , $P < 0.01$). The presence of focal spasm was a significant factor responsible for reduction in Pd/Pa during SPT.

CONCLUSION

These findings suggest that focal spasm may be more severe than diffuse spasm, judging from the intracoronary pressure during coronary spasm.

Key Words: Acetylcholine; Intracoronary pressure; Diffuse or focal spasm; Vasospastic angina

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Core Tip: Coronary spasm is classified into diffuse spasm and focal spasm based on its morphology; it is noted that focal spasm may have a worse prognosis. We compared the clinical backgrounds of patients with focal spasms. We also evaluated the intracoronary pressure in diffuse and focal spasms using a pressure wire. Patients in the focal spasm group were more likely to have metabolic syndrome and coronary atherosclerosis. The reduction in intracoronary pressure during coronary spasms was greater in focal spasms than in diffuse spasms. These findings suggest that the degree of ischemia may be greater in patients with focal spasms.

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INTRODUCTION

Coronary spasm is the transient vasoconstriction of epicardial coronary arteries that leads to the occurrence of myocardial ischemia[1] and is considered the cause of not only rest angina and effort angina but also acute coronary syndrome or ischemic cardiac arrest[1,2]. Guidelines and expert consensus documents on coronary spasms and vasospastic angina (VSA) have already been published, and more interest has been focused on coronary spasms since they have been identified as a cause of ischemia with nonobstructive coronary artery disease (INOCA) or myocardial infarction with nonobstructive coronary artery disease (MINOCA)[3].

However, several issues regarding coronary spasm are not fully understood or solved, including the protocol for the spasm provocation test (SPT), the sequence of SPT during comprehensive coronary angiography, the treatment of medically refractory coronary spasm, and the need for implantable cardioverter defibrillators in the event of cardiac arrest[2-6]. The endotype of coronary spasm as focal and diffuse spasm is one such unsolved problem regarding coronary spasm[5]. The clinical characteristics of these two types of coronary spasm have been reported to be different: focal spasm occurs more frequently in men than in women[7,8] and is more frequently recognized in atherosclerotic lesions than diffuse spasm[9]. Regarding prognosis, it has been demonstrated that the prognosis is worse in patients with VSA and focal spasm than in those with diffuse spasm[7,10,11]. The cause of the worse prognosis in focal spasm than in diffuse spasm may, in part, be the progression of atherosclerosis or destabilization of the atherosclerotic lesion with focal spasm[9,12-15]. The severity of myocardial ischemia due to focal or diffuse coronary spasm may be one of the possible mechanisms responsible for the difference in prognosis between the two types of coronary spasm; however, the method of assessing the severity of myocardial ischemia due to focal or diffuse spasm has been unclear.

Intracoronary pressure assessment was originally adopted in the clinical setting to assess the immediate coronary stenosis[16], and the distal pressure (Pd) divided by the aortic pressure (Pa) during hyperemia, which has been recognized as the fractional flow reserve (FFR), decreases according to myocardial ischemia[17]. Intracoronary pressure assessments during SPT have recently been used[18,19]. Furthermore, recently, in European countries and the United States, SPT has been performed after an assessment of coronary microvascular function using a pressure wire or Doppler wire[3], which means that there may be more opportunities to perform SPT using a pressure wire[20]. Thus, in the present study, we clarified the clinical characteristics of patients with VSA who manifested focal spasm during the SPT compared with those of patients with VSA who manifested diffuse spasm during the SPT and investigated whether the severity of myocardial ischemia (shown by the Pd/Pa during SPT) differed according to the type of spasm (focal or diffuse spasm).

MATERIALS AND METHODS

Study patients

This observational retrospective study included patients with VSA diagnosed with SPT using a pressure wire who visited our institution between January 2012 and March 2017 ($n = 98$). The exclusion criteria were as follows: Significant coronary stenosis (%stenosis $> 50\%$, $n = 7$) or a previous medical history of percutaneous coronary intervention ($n = 4$). Ultimately, 87 patients were enrolled in the present study. The study protocol was approved by the ethics committee of our institution. Written informed consent was obtained from all participants.

Coronary angiography and SPT using a pressure wire

SPT was performed as previously described[21]. During this period, SPT were performed on the right coronary artery (RCA) at our institution. After the initial Coronary angiography (CAG), a 0.014-inch pressure wire (PrimeWire Prestige Plus Guide Wire or Verrata Pressure Guide Wire; Phillips Volcano, Amsterdam, Holland) was advanced through a 5-Fr catheter into the distal segments of the RCA. Before this, we calibrated the pressure between the tips of the catheters and the pressure wire at the ostium of the coronary arteries. The ratios of distal intracoronary pressure (Pd), derived from the pressure wire, to Pa, derived from the catheter tips (Pd/Pa index), were continuously monitored. Subsequently, 20 μ g and 50 μ g doses of acetylcholine (ACh) were injected into the RCA. When coronary spasm was not induced by 50 μ g ACh, a maximum dose of 80 μ g ACh was infused into the RCA. The minimal Pd/Pa index in response to each ACh dose was recorded, and when the Pd/Pa index was reduced during the coronary spasm, the values just before the angiograms were adopted. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion was completed. If coronary spasm was induced but improved spontaneously, SPT of the left coronary artery (LCA) was performed without intracoronary injection of NTG into the RCA. In such cases, once the SPT for the LCA was completed, CAG was repeated following an NTG injection into the RCA. If the coronary spasm provoked by ACh infusion into the RCA was prolonged or severe enough to induce hemodynamic instability, an intracoronary injection of 0.3 mg) was administered to relieve spasms. Subsequently, SPT of the LCA was performed. In the LCA SPT, a pressure wire was advanced into the distal segments of the left anterior descending coronary artery (LAD) immediately after the second pressure calibration at the LCA ostium. SPT was performed by infusing 50 and 100 μ g doses of ACh into the LCA using a similar method. If coronary spasm was not induced by 100 μ g ACh, a maximum of 200 μ g ACh was infused into the LCA. CAG was performed just after a coronary spasm was provoked or the maximum ACh infusion was completed. An intracoronary injection of 0.3 mg NTG was administered, followed by the final CAG for the LCA. In this study, low, moderate, and high doses of ACh were considered to be 20, 50, and 80 μ g for RCA, respectively, and 50, 100, and 200 μ g for LCA, respectively.

The minimal Pd/Pa index in response to each ACh dose was recorded, and when the Pd/Pa index was reduced during the coronary spasm, the values just before the angiograms were adopted. The difference in Pd/Pa (Δ Pd/Pa) during the SPT was defined as the minimal Pd/Pa minus the baseline Pd/Pa. During the period when a PrimeWire Prestige Plus Guide Wire was available, the instantaneous free-wave ratio (iFR) was measured immediately before ACh administration in some patients. In addition, FFR was also measured in patients with coronary atherosclerosis using the conventional method of intravenous administration of adenosine triphosphate[22].

We used an autoinjector, as shown previously[21]. The coronary artery diameter was measured as previously described[21]. Lesions with $> 20\%$ stenosis were defined as atherosclerotic. We also investigated the possibility of myocardial bridging (MB), which is the presence of a $> 20\%$ systolic reduction in coronary artery diameter[23]. Complications of CAG and SPT include common severe complications, such as myocardial infarction, cerebral infarction, vascular trauma requiring surgery associated with CAG, induction of coronary spasm or coronary perforation associated with a pressure wire insertion, ventricular fibrillation (Vf), pulseless ventricular tachycardia (pVT) or hemodynamic compromise requiring catecholamine administration, and atrial fibrillation associated with SPT.

Definitions of VSA-related parameters

The activity of angina pectoris, when it occurs, was classified into three patterns: resting, exertion, and both resting and exertion. In addition, cold sweats and loss of consciousness were identified as serious signs of coronary spasms. VSA was defined as $> 90\%$ narrowing of coronary arteries on angiograms when provoked, accompanied by the presence of usual chest pain and/or the presence of an ST-segment deviation on ECG[2]. Focal spasm was defined as transient vessel narrowing of $> 90\%$ within the borders of one isolated coronary segment, as defined by the American Heart Association. Diffuse spasm was defined as a 90% diffuse vasoconstriction observed in ≥ 2 adjacent coronary segments of the coronary arteries[7]. In the present study, this assessment could be applied to each coronary artery; thus, in the assessment of each patient, the endotype of coronary spasm may differ between the RCA and LCA. In the present study, Group D consisted of patients with VSA and diffuse spasm that occurred in only one or both coronary arteries, and Group F consisted of patients with VSA and focal spasm that occurred in one coronary artery, both coronary arteries, or one of the coronary arteries. Multivessel

spasms were defined as coronary spasms that occurred in ≥ 2 major coronary arteries. For multivessel spasms, we could not assess when the subsequent SPT was negative after the avoidable use of NTG[24].

In lesion analyses, for the site of coronary spasm, each coronary artery was divided into three parts (proximal, mid, and distal), and the central part of the coronary spasm was described as diffuse.

Regarding the medications taken before SPT, although coronary vasodilators were discontinued 48 h before SPT, we investigated the number of vasodilators.

Other clinical characteristics measured in the present study

Patients were asked about their current smoking status and any family history of coronary artery disease (FH-CAD) was recorded. Hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome (MtS), and chronic kidney disease were defined based on the standard definitions and are described in previous papers[25,26]. The left ventricular ejection fraction was measured using cardiac ultrasonography. In the majority of study participants ($n = 80$), flow-mediated dilation (FMD), as an endothelium-dependent function, and NTG-induced dilation (NID), as an endothelium-independent function, were measured as previously described[27].

Statistical analyses

Data are presented as mean $\pm$ SD or median with interquartile ranges for non-normally distributed data and non-continuous variables. Baseline characteristics of the groups were compared using Student's unpaired *t*-tests, Wilcoxon signed-rank tests, or χ^2 analysis, as appropriate. Multivariate regression analysis was performed to determine the factors responsible for Δ Pd/Pa during the SPT. Statistical analyses were performed using the JMP version 16 (SAS Institute Inc., United States). A *P* value of < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

There were 54 patients (62%) in Group D and 33 (38%) in Group F. In Group D, diffuse spasm occurred in both the RCA and LAD in 32 patients, only in the LCA in 14 patients, and only in the RCA (the LCA was not assessed due to the unavoidable use of NTG) in eight patients. In Group F, focal spasm occurred both in the RCA and LCA in four patients, only in the LCA in 13 patients, in the LCA despite diffuse spasm in the RCA in seven patients, in the RCA despite diffuse spasm in the LCA in eight patients, and in the RCA (the LCA was not assessed due to an unavoidable use of NTG) in one patient. Patient characteristics are shown in Table 1. The frequency of MtS was higher in Group F than in Group D ($P = 0.04$). The frequency of hypertension tended to be higher in Group F than in Group D ($P = 0.06$). There were no significant differences in the blood chemical parameters displayed in Table 2. The NID tended to be lower in Group F than in Group D, but there was no significant difference in FMD between the two groups. Regarding the medications taken before admission, the frequency of calcium-channel blocker (CCB) consumption was significantly higher in Group F than in Group D ($P = 0.01$), and the frequency of long-acting nitrate consumption tended to be higher in Group F than in Group D ($P = 0.05$, Table 3). On CAG and SPT, the frequencies of coronary atherosclerosis ($P = 0.03$) and MB ($P = 0.047$, Table 3, $P = 0.05$) were significantly higher in Group F than in Group D, whereas the frequency of occurrence of multivessel spasm did not differ significantly between the two groups (Table 3). No serious complications occurred with CAG, and no coronary spasm was induced with pressure wire insertion or coronary perforation. In the SPT, no Vf or pVT occurred, but hemodynamic instability requiring catecholamine was observed in two patients (6%) in Group F and one patient (2%, $P = 0.30$) in Group D. Atrial fibrillation during SPT was observed in four patients (12%) in Group F and two patients (4%, $P = 0.13$) in Group D, but the difference was not statistically significant.

Lesion characteristics in focal and diffuse spasms

In 87 study participants, because of a small RCA ($n = 6$) and inability to advance a guidewire into the distal coronary artery ($n = 1$ in the RCA, $n = 2$ in the LAD, total $n = 3$), 165 coronary arteries were assessed for intracoronary pressure using a pressure wire, including 80 RCAs and 85 LADs). Among the 165 coronary arteries, there were 100 diffuse spasms, 34 focal spasms, and 31 negatives, including the case with unavoidable use of NTG. The lesion characteristics of diffuse and focal spasms are shown in Table 4. Coronary atherosclerosis was more frequently observed during focal spasms than during diffuse spasms ($P = 0.01$). The baseline Pd/Pa and iFR did not differ significantly between the two groups; however, the minimal Pd/Pa during the SPT and Δ Pd/pa during the SPT were significantly lower in focal spasm than in diffuse spasm ($P < 0.01$, Figure 1). The ACh dose at spasm provocation differed significantly between the two groups ($P = 0.03$). The frequencies of subtotal/total occlusion on CAG and ST elevation on ECG were more frequently associated with focal spasms than with diffuse spasms. FFR after SPT did not differ significantly between the two groups, perhaps because the number of study participants was small. Multivariate regression analyses using the endotype of coronary spasm,

Table 1 Patients characteristics

	Group D	Group F	P value
No. (%)	54 (62)	33 (38)	
Age (yr)	65 ± 11	69 ± 10	0.06
Male/Female	28/26	22/11	0.18
BMI (kg/m ²)	24.4 ± 4.2	24.7 ± 3.4	0.77
Coronary risk factors (%)			
Current smoker	11 (20)	8 (24)	0.67
Hypertension	34 (63)	27 (82)	0.06
Dyslipidemia	36 (67)	19 (58)	0.39
Diabetes mellitus	10 (19)	9 (27)	0.34
Family history of CAD (%)	12 (22)	8 (24)	0.83
MTS (%)	12 (22)	14 (42)	0.04
CKD (%)	16 (30)	13 (39)	0.35

BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; D: Diffuse; F: Focal; MTS: Metabolic syndrome; No.: Number.

Table 2 The results of blood chemical and echographic parameters in the 2 groups

	Group D	Group F	P value
Blood chemical parameters			
Total cholesterol (mg/dL)	193 ± 33	202 ± 40	0.26
Triglyceride (mg/dL)	142 ± 76	143 ± 58	0.93
HDL-cholesterol (mg/dL)	57 ± 17	57 ± 17	0.99
LDL-cholesterol (mg/dL)	107 ± 25	116 ± 32	0.16
Fasting blood sugar (mg/dL)	103 ± 30	107 ± 15	0.53
Hemoglobin A1c (%)	5.8 ± 0.9	6.1 ± 0.8	0.18
C-reactive protein (mg/dL)	0.06 (0.04, 0.18)	0.07 (0.02, 0.17)	0.74
Brain natriuretic peptide (pg/mL)	16 (10, 35)	20 (10, 30)	0.92
eGFR (mL/min/1.73 m ²)	70.7 ± 14.5	67.8 ± 14.8	0.37
Echographic parameters			
LVEF on UCG (%)	66 ± 9	67 ± 6	0.61
FMD on brachial ultrasonography (%)	3.9 ± 2.8 (n = 47)	2.8 ± 3.3 (n = 33)	0.11
NID on brachial ultrasonography (%)	15.2 ± 7.5 (n = 47)	12.3 ± 5.2 (n = 33)	0.05

D: Diffuse; eGFR: Estimated glomerular filtration ratio; F: Focal; FMD: Flow-mediated dilation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; UCG: Cardiac ultrasonography.

presence of coronary atherosclerosis, and dose of ACh at spasm provocation showed that focal spasm was a significant factor responsible for the reduction of intracoronary pressure during ACh provocation ($P < 0.01$, Table 5).

The representative cases of focal and diffuse spasms with intracoronary pressure are shown in Figure 2.

DISCUSSION

This study investigated the clinical characteristics of patients with VSA and focal spasm, and compared

Table 3 The results of VSA-related parameters in the 2 groups

	Group D	Group F	P value
Medications taken before CAG			
Calcium-channel blocker (%)	11 (20)	16 (48)	0.01
Long-acting nitrate (%)	6 (11)	9 (27)	0.05
Statins (%)	26 (48)	9 (27)	0.05
Anti-platelet therapy (%)	14 (26)	9 (27)	0.89
VSA-related symptom			
Cold sweating or syncope (%)	5 (9)	4 (12)	0.67
CAG.SPT			
Coronary atherosclerosis (%)	28 (52)	25 (76)	0.03
MB (%)	7 (13)	10 (30)	0.05
Multi-vessel spasm (% , n)	32 (74, 43)	19 (66, 29)	0.42

CAG: Coronary angiography; D: Diffuse; F: Focal; MB: Myocardial bridging; SPT: Spasm provocation test; VSA: Vasospastic angina.

Table 4 Lesional characteristics in the diffuse and focal spasms

	Diffuse spasm	Focal spasm	P value
No.	100	34	
ST elevation on ECG during SPT	6 (6)	13 (35)	< 0.01
Total or subtotal occlusion on CAG	9 (9)	9 (26)	0.02
Spastic vessels: RCA/LAD	46/54	13/21	0.43
Spasm site			
Proximal/Mid/Distal	12/57/31	5/16/13	0.58
Dose of ACh at spasm provocation			
Low (%) / Moderate (%) / High (%)	32 (32) / 65 (65) / 3 (3)	13 (38) / 16 (47) / 5 (15)	0.03
Intracoronary pressure indexes			
Baseline Pd/Pa	0.96 ± 0.05	0.95 ± 0.05	0.35
Minimal Pd/Pa	0.77 ± 0.11	0.66 ± 0.20	< 0.01
Δ Pd/Pa	- 0.19 ± 0.11	- 0.29 ± 0.20	< 0.01
iFR (n)	0.96 ± 0.07 (n = 52)	0.95 ± 0.08 (n = 17)	0.83
FFR (n)	0.85 ± 0.08 (n = 26)	0.80 ± 0.10 (n = 8)	0.18

ACh: Acetylcholine; CAG: Coronary angiography; ECG: Electrocardiogram; FFR: Fractional flow reserve; iFR: Instantaneous free-wave ratio; LAD: Left anterior descending coronary artery; No.: Number; Pd: Distal pressure; Pa: Aortic pressure; RCA: Right coronary artery; SPT: Spasm provocation test.

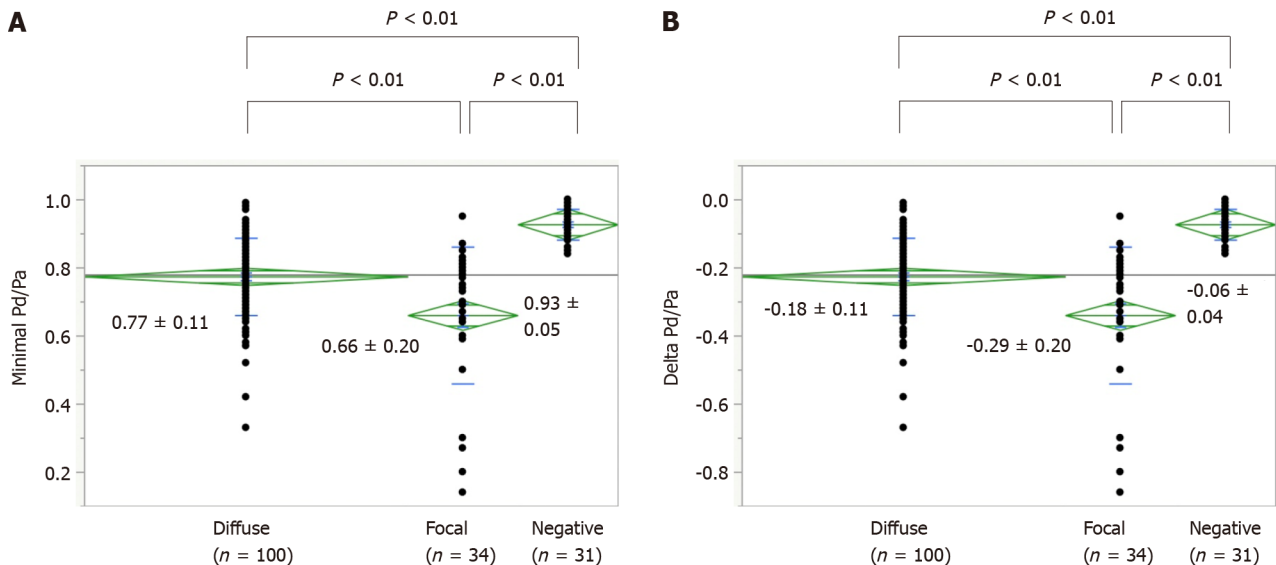
these characteristics with those of patients with diffuse spasm. Our data showed a higher frequency of Mts and coronary atherosclerosis in patients with VSA and focal spasms. Lesion analyses using a pressure wire showed that the reduction in Pd/Pa during SPT was significantly greater in focal spasm than in diffuse spasm, as well as a higher frequency of coronary atherosclerosis. These findings may indicate that focal spasm causes a greater degree of myocardial ischemia than diffuse spasm does.

According to several studies investigating the prognoses of focal and diffuse spasms[7,10,11], focal spasm has the worst prognosis. Sato *et al*[7] reported that the major cardiovascular events (MACE)-free rate over six years of follow-up was 92.5% in patients with focal spasm and 96.5% in those with diffuse spasm, showing that focal spasm is a factor indicating a worse prognosis. Kim *et al*[10] showed that the MACE-free rate over 2 years of follow-up was 91.8% in patients with focal spasm and 96.8% in those with diffuse spasm, and that the cause of MACE in patients with focal spasm was acute coronary syndrome, especially unstable angina (UAP). Nishimiya *et al*[11] demonstrated that the prognosis over 6

Table 5 Multivessel regression analysis for Δ distal pressure/aortic pressure during spasm provocation test

Factors	F value	P value
Focal spasm	14.14	< 0.01
Atherosclerosis	1.38	0.24
ACh dose at spasm provocation	1.08	0.34
$R^2 = 0.18$		

ACh: Acetylcholine.



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Figure 1 The minimal distal pressure (Pd)/aortic pressure (Pa) and reduction in Pd/Pa during spasm provocation test according to the types of coronary spasm. A: Shows the minimal Pd/Pa during the spasm provocation test (SPT); B: Shows the delta Pd/Pa during the SPT in the diffuse, focal spasm, and spasm-negative vessels. In both panels, each value was lower in vessels with diffuse and focal spasms than in spasm-negative vessels ($P < 0.01$). Furthermore, each value was lower in vessels with focal spasms than in those with diffuse spasms ($P < 0.01$). Pa: Aortic pressure; Pd: Distal pressure.

years of follow-up was worse in patients with focal spasm than in those with diffuse spasm, and that the causes of MACE included nonfatal myocardial infarction and readmission for UAP or heart failure.

Several studies have used intracoronary imaging modalities for the possible mechanisms of focal spasm-induced worse prognoses[9,12-15]. Several studies using intravascular ultrasonography have demonstrated the presence of atherosclerosis at focal spastic sites[12-14]. Using optical coherence tomography (OCT), Kitano *et al*[9] demonstrated that intima area, maximum intima thickness, and lipid content were higher in focal spasm sites than in diffuse spasm sites. In a recent study using OCT, intraplaque neovessels and macrophage infiltration were also more frequently observed in focal spastic segments than in diffuse spastic segments[11]. Using coronary angioscopy (CAS), Kitano *et al*[9] also showed that atherosclerotic yellow plaques and thrombi were more frequently observed in focal spastic sites than in diffuse spastic sites. Our previous report using CAS showed that intracoronary thrombi were recognized only in focal spastic sites[15]. Taken together, these findings suggest that unstable atherosclerotic lesions may be present at the focal spastic sites. Recently, it was reported that coronary microvascular dysfunction may contribute to INOCA[28], and such coronary microvascular dysfunction was more frequently observed in coronary arteries with focal spasm than in those with diffuse spasm [22]. Such coexistence of coronary microvascular dysfunction may, in part, contribute to readmission for UAP.

In the present study, we focused on the severity of myocardial ischemia caused by focal spasms. The possibility of higher severity of myocardial ischemia by focal spasm has been demonstrated not only by ECG findings (with ST elevation) but also by the reduction of intracoronary pressure during coronary spasm induced using a pressure wire, independent of the presence of atherosclerotic lesions, spasm vessels, and the spasm segment of the coronary artery. Recently, SPT has been recommended after the assessment of microvascular function using a pressure wire[20], which shows an increase in the opportunity for SPT using a pressure wire. We hope that further studies will confirm these findings.

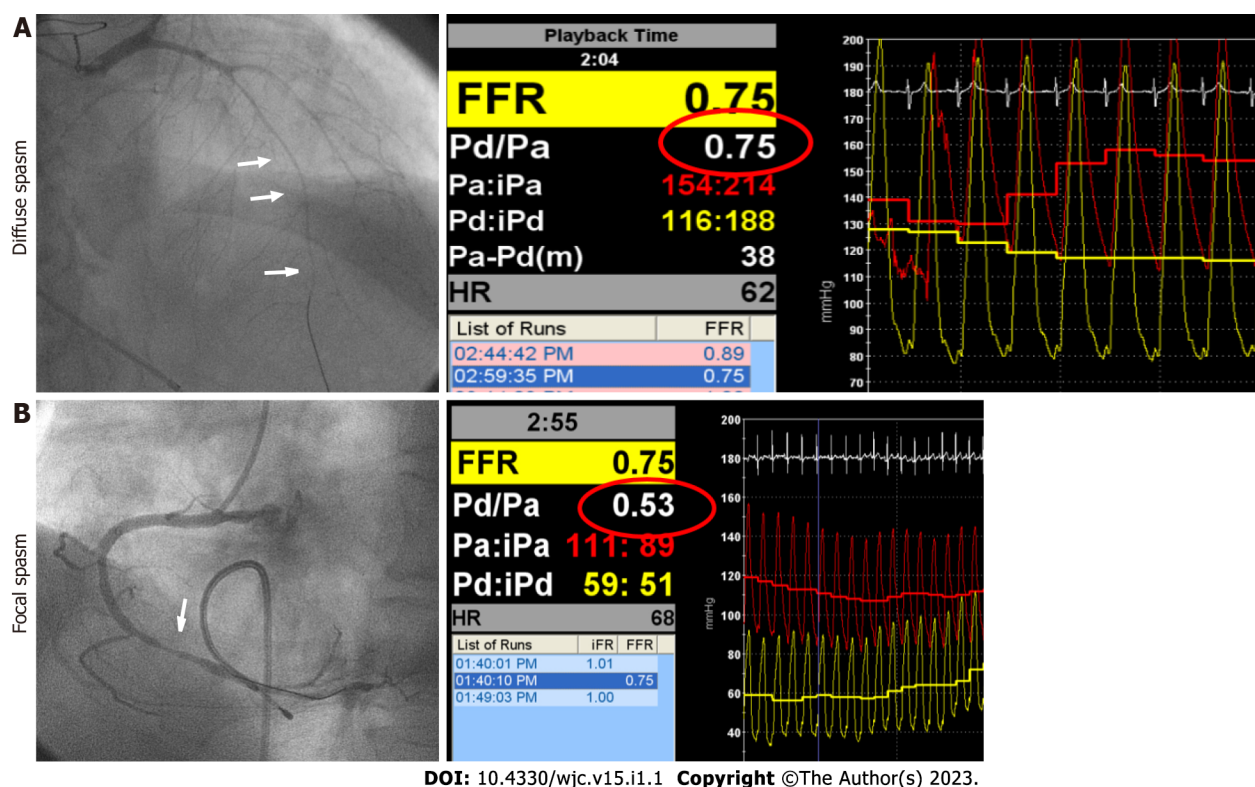


Figure 2 The representative cases. A: Shows the presence of diffuse spasm in the left anterior descending coronary artery, and the minimal distal pressure (Pd)/aortic pressure (Pa) was 0.75; B: Shows the presence of a focal spasm on the right coronary artery, with a minimal Pd/Pa of 0.53. LAD: Left anterior descending coronary artery; Pa: Aortic pressure; Pd: Distal pressure; FFR: Fractional flow reserve.

In the present study, the dose of ACh at spasm provocation was different for focal and diffuse spasm, and Sueda *et al*[29] reported that focal spasm tends to cause coronary spasm at lower loading doses of ACh, which may be consistent with the findings of the present study. In contrast, higher doses of ACh during spasm provocation appeared to be more frequently observed in focal spasms. In the present study, the frequency of coronary dilators, such as CCB or long-acting nitrates, was high in Group F. Although we could not evaluate chest symptoms on admission in the present study, the high frequency of coronary dilator medications on admission may be due to the aim of improving chest symptoms due to the high degree of myocardial ischemia caused by focal spasm. At our institution, as per the guidelines[2], coronary dilators were discontinued 48 h prior to the SPT, but the long-acting CCB may have remained effective, resulting in higher ACh doses in the SPT in Group F.

Regarding the clinical characteristics of patients with focal spasm, it has been reported that more men than women have focal spasm[7,8]; however, our study did not confirm that more men had focal spasm. The backgrounds of the study participants may have differed slightly. Moreover, the finding of more patients with MtS and hypertension may also support the finding that patients with focal spasms had more atherosclerotic lesions. We observed a different trend of endothelium-dependent vasodilatory response in vascular endothelial dysfunction; however, it is unclear whether this is a result or a cause, and we would like to investigate this in a future study with more participants. It is still possible that there may have been a slight residual effect of the oral medication.

The implication of this study is that focal spasm may mean that the degree of ischemia is so great that effective and sufficient doses of coronary dilators should be administered. This could improve the prognosis of patients with focal spasm; however, future prospective studies are needed.

This study had several limitations. First, it was a single-center study with a small number of patients, and the results of the present examination may not be applicable to all patients with coronary spasm. Second, in classifying patients, those with both focal and diffuse spasms were assigned to the focal spasm group; however, it is unclear whether this classification is correct. Third, in this study, a pressure wire was inserted to apply a load, and it was unclear whether the insertion of the pressure wire affected the morphology of the coronary spasm. The morphology of the coronary spasm may have been affected by the insertion of a pressure wire. We also encountered a case in which it was difficult to distinguish the distal portion of a coronary spasm because of the pressure wire. Fourth, noninvasive tests such as ergonovine stress echocardiography[30] and coronary computed tomography[31,32] have been used to evaluate coronary spasm, and their usefulness has been reported; however, these tests are not routinely performed in our hospital and have not been evaluated. Fifth, we have experienced that troponin, a myocardial enzyme, is positive during severe myocardial ischemia in some VSA patients. We believe

this is an important indicator for assessing the severity of myocardial ischemia, even in VSA patients. However, at our institution, it is not routinely measured in patients with worsening chest symptoms and a long duration of attacks. Finally, the doses of ACh that induced the focal/diffuse spasms were different. Although this factor was not significant in the multivariate analysis, it may have influenced the reduction in intracoronary pressure during ACh provocation.

CONCLUSION

In conclusion, patients with focal spasm may have more atherosclerotic lesions and a greater degree of myocardial ischemia than those with diffuse spasm. Since the prognosis of patients with focal spasm has been reported to be poor, it may be necessary to administer adequate doses of coronary dilators, especially in these patients. Further prospective studies and multicenter registries are needed to clarify the need for medication.

ARTICLE HIGHLIGHTS

Research background

Coronary spasm can be divided into two types: Focal spasm and diffuse spasm, but the prognosis for focal spasm is reported to be worse than that for diffuse spasm.

Research motivation

The cause of the worse prognosis in focal spasm is unclear, and although the degree of myocardial ischemia may be more severe in focal spasm, no method has been established to evaluate the severity of coronary spasm.

Research objectives

The objective of the present study was to investigate such relationships using a pressure wire during the spasm provocation test (SPT) in patients with vasospastic angina (VSA).

Research methods

Eighty-seven patients with VSA (average age: 67 years; 50 men, 37 women) underwent SPT. During SPT, a pressure wire was advanced into the distal portion of the right coronary artery and the left anterior descending coronary artery, and the ratio of intracoronary pressure to aortic pressure (Pd/Pa) was continuously monitored. An SPT was performed with acetylcholine (ACh), and the presence of coronary spasm was defined as the presence of > 90% arterial narrowing in response to an ACh infusion, with the usual chest symptoms and/or ischemic ECG changes. Focal spasm was defined as total or subtotal spasm within one segment of the AHA classification, while diffuse spasm was defined as > 90% spasm with two or more segments. The group with focal spasm in at least one major coronary artery was classified as the focal group, and the group without focal spasm as the diffuse group.

Research results

Among 87 patients, the frequencies of metabolic syndrome and coronary atherosclerosis were higher in the focal group ($n = 33$) than in the diffuse spasm group ($n = 54$, $P < 0.05$). In vessel analyzes, in these 134 spastic segments, diffuse and focal spasms were detected in 100 and 34 vessels, respectively. Pd/Pa at baseline was similar in both groups (diffuse: 0.96 ± 0.05 , focal: 0.95 ± 0.05 , $P = 0.35$); however, Pd/Pa during coronary spasm was lower in focal spastic vessels (0.66 ± 0.20) than in diffuse spastic vessels (0.76 ± 0.11 , $P < 0.01$), and the reduction in Pd/Pa during an SPT was also lower in focal spastic vessels (-0.29 ± 0.20) than in diffuse spastic vessels (-0.18 ± 0.11 , $P < 0.01$). The presence of focal spasm was a significant factor responsible for the reduction in Pd/Pa during SPT.

Research conclusions

These findings suggest that focal spasm may be more severe than diffuse spasm, judging by intracoronary pressure during coronary spasm. This mechanism may be involved in the poor prognosis of focal spasm, and careful measures, such as intensified drug therapy, should be taken when focal spasm is detected.

Research perspectives

In recent years, more patients have been evaluated for coronary microvascular dysfunction using pressure wires and then for coronary artery spasm induced by ACh, and it is possible that pressure wires will be used more frequently to induce coronary artery spasm. It will be important to confirm the findings of this study in more cases.

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FOOTNOTES

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Observational Study

Role of fibrinogen, albumin and fibrinogen to albumin ratio in determining angiographic severity and outcomes in acute coronary syndrome

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) pandemic unmasked the huge deficit in healthcare resources worldwide. It highlighted the need for efficient risk stratification in management of cardiovascular emergencies.

AIM

To study the applicability of the old, available and affordable nonconventional biomarkers: albumin and fibrinogen in their ability to predict angiographic severity and clinical outcomes in patients with acute coronary syndrome (ACS).

METHODS

In this prospective, observational study, 166 consecutive patients with ACS were enrolled. Fibrinogen, albumin and their ratio were determined from serum. Patients with underlying chronic liver disease, active malignancy, autoimmune disease, active COVID-19 infection and undergoing thrombolysis were excluded.

RESULTS

Mean age of the population was 60.5 ± 1.5 years, 74.1% being males. ST elevation myocardial infarction (STEMI) was most common presentation of ACS seen in 57% patients. Fibrinogen albumin ratio (FAR) ≥ 19.2 , had a sensitivity of 76.9% and specificity of 78.9% [area under the receiver operating characteristic curves (AUROC) = 0.8, $P = 0.001$] to predict $\leq$ thrombolysis in myocardial infarction

(TIMI) 1 flow in culprit artery in STEMI patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity (AUROC = 0.715, $P = 0.006$).

CONCLUSION

Novel biomarkers, with their high cost, lack of availability and long turn over time are impractical for real-world use. Identifying $\leq$ TIMI 1 flow in the culprit artery has significant impact of management and outcome. Our study has shown that readily available biomarkers like fibrinogen and albumin can help identify these high-risk patients with good accuracy. This allows risk-stratification and individualization of treatment in ACS.

Key Words: Acute coronary syndrome; Albumin; Fibrinogen; Fibrinogen to albumin ratio; Total occlusion of culprit artery

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Core Tip: The study highlights the role of cost-effective, readily available biomarkers fibrinogen and albumin in predicting angiographic severity and clinical outcomes in patients with acute coronary syndrome. Fibrinogen to albumin ratio independently predicted outcomes with greater accuracy compared to fibrinogen or albumin alone. Fibrinogen albumin ratio (FAR) ≥ 19.2 , had a sensitivity of 76.9% and specificity of 78.9 % to predict $\leq$ thrombolysis in myocardial infarction 1 flow in culprit artery in ST elevation myocardial infarction (STEMI) patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity.

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INTRODUCTION

Tremendous progress has been made in the management of acute coronary syndrome (ACS) over last six decades[1]. The success is attributed to be due to improved overall health care facilities, availability of stronger antiplatelet agents and other cardioprotective medications, improved revascularization strategies including both advances in thrombolytic therapy and the ever-improving stent design and technologies which have led to drastic decrease in morbidity and mortality associated with ACS[2-4]. However, despite the obvious progress, gaps exists and ACS continues to be the leading cause of death worldwide with considerable short and long-term mortality and morbidity. The situation is dismal in the developing world where the health care resources are scarce[5]. The coronavirus disease 2019 (COVID-19) pandemic has highlighted the same and the need for efficient triaging and risk-assessment for efficient patient management[6].

Prior to the availability of laboratory resources, the risk stratification was mainly based on the clinical assessment and accordingly clinical risk scores were developed to predict outcomes. Next, with the availability of various laboratory parameters, the risk stratification was further refined by incorporating these biomarkers. Certain novel biomarkers have been recognized ranging from C-reactive protein (CRP) to cysteine rich angiogenic inducer 61 to predict high-risk ACS[7]. Attempt has been made to incorporate these biomarkers to traditional scoring systems to add to their prognostic value, however risk stratification of ACS remains far from perfect[8]. The goal of risk stratification is not only to predict outcomes but also to guide management and more importantly urgency of treatment needed. This is even more relevant in a resource constrained setting. Hence, triaging of patients with ACS and guidance as to which patient needs early intervention and who should be managed medically is a top priority.

Starting from January 27, 2020, when the 1st case of COVID-19 was diagnosed in India, the pandemic had pushed India to the brink, stretching the already thin health care resources. It unmasked the vast deficiencies in our health care system and was a wake-up call to the country to ramp up its preparedness before the next wave. All medical and surgical specialties suffered as result, and acute cardiac care was perhaps the hardest hit[9,10]. Even before the pandemic the condition of cardiac care facilities was suboptimal and registry data of ACS from India showed that only 20% of patients of ACS undergo coronary angiography[11]. In comparison to developed nations, we have half the catheterization labs to cater to our second largest population of world[12]. The morbidity and mortality of ACS is significantly higher compared to the western world.

Novel biomarkers used to prognosticate patients often are experimental and real-world use is often not feasible[13]. Thus, we evaluated role of easily available inflammatory biomarkers like fibrinogen, albumin along with fibrinogen albumin ratio (FAR) role in ACS. They were analyzed to assess if they could predict angiographic severity or clinical outcomes among patients. The aim of the present study was to analyze the role of old, readily available biomarkers, fibrinogen, albumin and FAR in determining angiographic severity and clinical outcomes.

MATERIALS AND METHODS

Study design

This was a prospective, single center, observational study conducted between August 2019 and December 2020. Consecutive patients with ACS presenting to Cardiology department were included. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was reviewed and cleared by the Ethics committee of the Post Graduate Institute of Medical education and Research, Chandigarh (ref no INT/IEC/2019/2750). Informed written consent was obtained from all patients or appropriate legally authorized representatives.

ST elevation myocardial infarction (STEMI) was defined by patients presenting with acute chest pain and electrocardiogram showing ST elevation in ≥ 1 mm in two contiguous leads in all leads other than lead V2-V3. Cutoff point for lead V2-V3 was ≥ 2 mm in males and ≥ 1.5 mm in females[14]. Non-STEMI (NSTEMI) and unstable angina (USA) was defined as per 2014 American Heart Association/American college of cardiology non-ST elevation ACS guidelines[15]. Patients were examined by cardiologists to classify patients from Killip class 1 to 4 depending upon severity of heart failure and cardiogenic shock (CS). Patients with CS were subcategorized as per definition of Society of Cardiovascular angiography and Intervention (SCAI) into stage C to E[16]. Patients were excluded from study if they had undergone fibrinolysis, had underlying chronic liver disease, active malignancy or any autoimmune disease. Patients were followed up telephonically or in person visit at 1, 3 and 6 mo to assess their major adverse cardiovascular and cerebral events (MACCE).

Coronary angiographies were assessed by two interventional cardiologists. Culprit artery was identified by finding of angiography, 12-lead electrocardiogram and regional wall motion abnormality on echocardiography. Coronary flow was classified according to thrombolysis in myocardial infarction (TIMI) risk score[17]. Total occlusion was defined by pre percutaneous coronary artery (PCI) TIMI ≤ 1 and spontaneous recanalization (SR) was defined by TIMI score ≥ 2 .

Blood sampling and lab methods

Venous blood samples were taken within 24 h of admission and prior to angiography. Fibrinogen samples were drawn in sodium citrate vacuum tubes and albumin samples in plain serum vials. FAR ratio was calculated by ratio of fibrinogen (gm/dL) and albumin (gm/dL) and multiplying the ratio by 100. Albumin levels were calculated using bromocresol method on a Technicon RA-1000 automated analyzer (Technicon Instruments, Tarrytown, NY, United States). Fibrinogen concentration was measured with turbidimetric assay using ammonium sulphate. Care was taken to ensure all samples collected were processed within 6 h of collection to ensure minimal alteration of the biomarker levels.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL, United States). Variables are presented as mean $\pm$ SD or median (inter-quartile range). Variable were checked for outliers and normalcy using the Shapiro-Wilk test. Continuous variables with normal distribution were compared with the independent samples Student's *t*-test and those with non-normal distribution with the Mann-Whitney *U* test. Comparison between categorical variables was done using chi-square test or Fisher exact test. A two-sided *P* value < 0.05 was considered to be significant for all variables.

RESULTS

Baseline characteristics

A total of 166 patients of ACS were included in this study. The mean age of patients was 60.5 ± 10.5 years, with majority of patients being males (74%). Ninety-five (57.2%) patients presented with STEMI while NSTEMI ACS (NSTEMI) patients constituted the remaining 42.8%. Among risk factors of CAD most common was hypertension present in 63% followed by diabetes mellitus in 50% of the cohort. Rest angina was presenting complaint in over 90% patients while new onset shortness of breath was present in 18%. The mean duration of presentation to our hospital after chest pain onset was 12.8 ± 9.9 h. The mechanical complications of ACS were also assessed and patients presenting with severe left ventricular systolic dysfunction (Ejection fraction $< 30\%$) or significant ischemic mitral regurgitation (MR) were

more common in patients with STEMI compared to NSTEMI (44.2% *vs* 21%, $P = 0.005$ and 31.6% *vs* 15%, $P = 0.014$ respectively). Patients with classical CS (SCAI stage-C) or worse was present in 26 (15.6%) patients. Angiography was done in around 88% while 62% underwent PCI. The detailed demographic details and key investigation details are presented in [Table 1](#).

Inflammatory biomarkers

Fibrinogen levels were significantly elevated in patients with STEMI compared to NSTEMI and USA (6.3 ± 1.2 *vs* 5.3 ± 1.1 and 5.3 ± 1.3 in gm/L, respectively; $P = 0.001$). FAR was found to be significantly higher in patients with STEMI (19.1 ± 4.8) compared to NSTEMI (15.4 ± 4) and USA (15.1 ± 4.3), $P = 0.001$. Patients with significant ischemic MR and classical CS or worse at presentation had significantly higher levels of fibrinogen and FAR and lower level of albumin as shown in [Table 1](#).

Role of biomarkers to predict outcomes

Angiography showed complete occlusion of culprit artery more commonly in patients with STEMI compared to NSTEMI 41% *vs* 21%, $P = 0.019$. Among patients with STEMI, a fibrinogen value of ≥ 6.55 gm/dL predicted TIMI ≤ 1 flow in the culprit artery with a sensitivity of 74.4% and specificity of 74.2% [area under the receiver operating characteristic curves (AUROC) = 0.805, $P < 0.001$]. FAR also predicted total occlusion of culprit artery with a higher accuracy compared to fibrinogen. A FAR value ≥ 19.2 had a 76.9% sensitivity and 78.2% specificity in predicting TIMI ≤ 1 flow in the culprit artery (AUROC = 0.808, $P < 0.001$). Similar to STEMI patients in NSTEMI too, both fibrinogen and FAR were able to predict total occlusion of culprit artery as shown in [Figure 1](#). Fibrinogen ≥ 6.10 gm/dL had a 75.3% sensitivity and 55.6% specificity (AUROC of 0.68, $P = 0.024$) in predicting $\leq$ TIMI -1 flow in the culprit artery in NSTEMI patients, while fibrinogen alone was not able to predict complete occlusion in patients with USA. Likewise, FAR ≥ 18.85 predicted $\leq$ TIMI -1 flow in the culprit artery with a greater accuracy than fibrinogen [80% sensitivity and 63% specificity (AUROC of 0.715, $P = 0.006$)] in patients with NSTEMI. FAR ≥ 17.3 predicted $<$ TIMI -1 flow in culprit artery with 76.4 % sensitivity and 54.3% specificity in patients with USA. Further FAR correlated with angiographic severity as determined by the SYNTAX scores. FAR increased significantly with increasing SYNTAX scores. Accordingly, the FAR values in low SYNTAX (< 22), intermediate SYNTAX (22-33) and high SYNTAX (> 33) groups were 15.8 ± 2.9 , 18.4 ± 3.3 and 22.9 ± 4.2 respectively ($P < 0.001$).

The mean FAR and fibrinogen was significantly higher and mean serum albumin was significantly lower in patients with CS and significant ischemic mitral regurgitation as shown in [Table 2](#) and [Figure 2](#). The overall, 30-d mortality among patients of ACS was higher in patients with was 9.5% in STEMI compared to NSTEMI 2.8%, $P = 0.004$. Among inflammatory markers albumin was significantly less in patients who succumbed to illness compared to survivors (3.2 ± 0.33 *vs* 3.4 ± 0.33 , $P = 0.03$). Another inflammatory biomarker assessed in our study was the CRP. CRP levels were significantly higher in non-survivors compared to survivors (56.4 ± 24.3 *vs* 35.2 ± 18.4 , $P = 0.04$). However, there was no correlation of CRP with angiographic severity or the TIMI flow in our study. Thirty-day mortality of the cohort was 6.6%. MACCE occurred in 10.3% patients at a mean follow up of 6.6 ± 1.5 mo.

DISCUSSION

In last sixty years, since first biomarkers of ACS were identified, their role has undergone drastic change and are now integral to management of ACS patients. They not only have a role in early diagnosis but also provide means to gain insights to underlying causes and consequences of ACS. Novel biomarkers are coming up at a rapid rate including myeloperoxidase, pregnancy-associated plasma protein-A, matrix metalloproteinases, tissue inhibitor of metalloproteinases, various interleukins and the novel exosomal micro RNAs[18]. However, the long turn-around time and easy accessibility besides the high cost makes them impractical for real-world use.

Pre procedural TIMI flow in culprit artery is strongly related to patient outcomes[19,20]. SR of culprit artery in STEMI patients occurs in 26% those undergoing primary PCI[21]. SR of culprit artery results from endogenous fibrinolytic system leading to dissolution of arterial thrombi. The ST resolution on 12-lead electrocardiogram is not a reliable marker to predict SR, thus necessitating the development of other biomarkers which can help in early identification of the recanalization status of the vessel and guide in patient management and prognostication[22]. Various biomarkers have been tested to predict SR; however, the results are dismal. In our study fibrinogen and FAR were able to predict total occlusion of culprit artery in STEMI with reasonably good accuracy.

The statistics on revascularization by thrombolysis or primary PCI are dismal in the country. Thrombolysis is performed in around 50% patients of STEMI while primary PCI is performed in less than 15% patients in our country[12]. COVID-19 deepened the crises further and these figures are likely to get worse during and post pandemic[6,23,24]. Moreover, the number of patients presenting late to medical facilities after STEMI are likely to increase. It has been seen that patient presenting with STEMI and occluded artery TIMI flow ≤ 1 fear worse as compared to those who have SR and benefit most from early invasive strategy[19,20]. Hence, the importance of early identification of TIMI flow in culprit

Table 1 Baseline characteristics and laboratory profile of patients with acute coronary syndrome, *n* (%)

	STEMI (<i>n</i> = 95)	NSTEMI (<i>n</i> = 38)	USA (<i>n</i> = 33)	<i>P</i> value
Risk factors				
Age, yr (mean ± SD)	61.2 ± 10.1	60.2 ± 11.0	60.5 ± 10.5	0.5
Males	73 (76.8)	25 (65.8)	25 (75.8)	0.5
Diabetes	49 (52)	20 (52.6)	14 (42.4)	0.5
Hypertension	61 (64)	22 (58)	21 (64)	0.8
Smoking	31 (32.6)	12 (31.6)	10 (30.3)	0.9
Prior history of CAD	2 (2.2)	6 (16.2)	9 (27.3)	0.001
Clinical features on presentation				
Rest angina	89 (93.6)	36 (94.7)	26 (78.8)	0.013
Ejection fraction < 30%	42 (44.2)	10 (26.3)	5 (15.2)	0.005
Significant ischemic MR	30 (31.6)	9 (23.7)	2 (6.1)	0.014
Killip class ≥ 2	24 (25.3)	7 (18.4)	2 (6)	0.057
SCAI stage C	11 (11.6)	7 (18.4)	0	0.04
SCAI stage D	3 (3.2)	0	0	0.3
SCAI stage E	5 (5.3)	0	0	0.14
Key investigations				
Creatinine, mg/dL (mean ± SD)	1.17 ± 0.6	1.2 ± 0.6	1.05 ± 0.47	0.42
CK-MB, (mean ± SD)	112 ± 98	71 ± 57	25 ± 24	0.001
Fibrinogen, gm/L (mean ± SD)	6.3 ± 1.2	5.3 ± 1.1	5.3 ± 1.3	0.001
Albumin, gm/dL (mean ± SD)	3.3 ± 0.33	3.4 ± 0.36	3.5 ± 30	0.075
FAR (mean ± SD)	19.1 ± 4.8	15.4 ± 4.0	15.1 ± 4.3	0.001

CAD: Coronary artery disease; MR: Mitral regurgitation; CK-MB: Creatinine kinase; FAR: Fibrinogen to albumin ratio; SCAI: Society of Cardiovascular angiography and Intervention; STEMI: ST elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; USA: Unstable angina.

arteries.

In NSTEMI complete occlusion of culprit artery varies from 19% to 30%. These patients are at increased risk of mortality and adverse events. Risk scoring systems and electrocardiogram are not able to identify these high-risk patients[25]. In our study similar to STEMI, both fibrinogen and FAR were able to identify patients with total occlusion in NSTEMI with reasonable accuracy. Identification of this high-risk group is rather difficult with the currently available tools. Easily accessible, readily available, cost-effective biomarkers can help better manage these patients.

High thrombus burden has remained Achilles-heel of coronary intervention since its advent in 1977 [26]. Fibrinogen being precursor of fibrin has been shown to be precursor of thrombosis, inflammatory response during ACS often leads to structural changes in fibrinogen rendering it resistant to fibrinolysis [27]. Albumin also apart from being a reflection of ongoing inflammation has pathophysiological role in thrombosis[28]. In our study only albumin amongst inflammatory biomarkers could predict short term mortality, this was similar to earlier studies showing hypoalbuminemia to be predictor of poor prognosis in patients with ACS and other cardiovascular diseases[29,30]. Thus, these inflammatory biomarkers are not merely bystanders of ongoing inflammation but have potential role in pathophysiology of ACS. The pandemic has made a call for an efficient triage system for better management of cardiac emergencies to avoid putting a strain on already this health care resources in the country. Accordingly, low risk (those who have SR) NSTEMI and STEMI should be managed medically initially while the high-risk group should receive an early invasive strategy. Using fibrinogen, albumin and their composite (FAR) could enable us to better understand and identify these high-risk ACS patients as was shown in the index study.

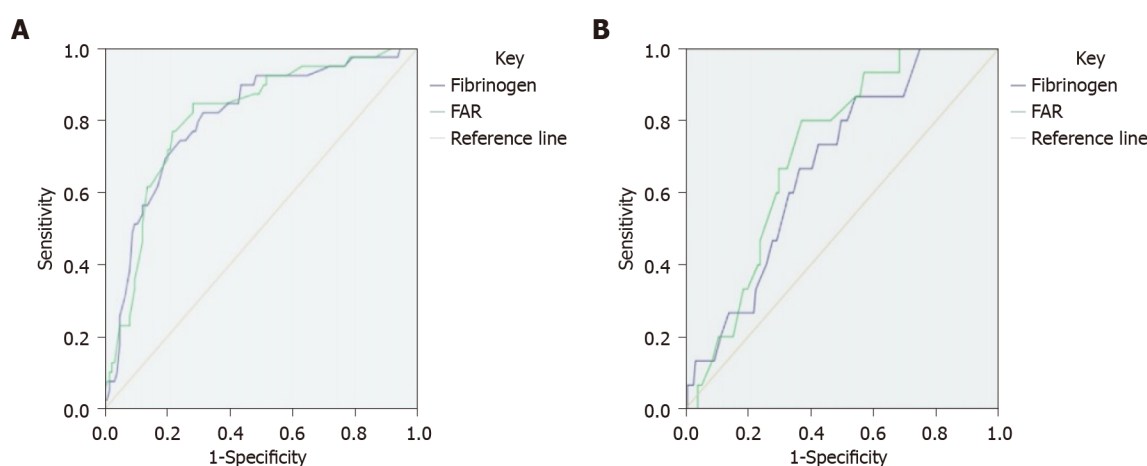
Study limitations

Our study is a single center study, with a small sample size. Thus, to generalize our results to a large population is not feasible. Serial sampling of these biomarkers was not done to assess their change in level with clinical improvement or deterioration.

Table 2 Comparison between patients with total occlusion of culprit artery compared to patients with > thrombolysis in myocardial infarction 2 flow

	Patients with TIMI- ≤ 1 flow (n = 54)	Patients with TIMI- ≥ 2 flow (n = 98)	P value
Age, yr	60.5 $\pm$ 10.2	60.5 $\pm$ 10.7	0.9
Time of presentation to hospital after chest pain onset (h)	13.4 $\pm$ 11.2	12.3 $\pm$ 8.8	0.24
Hypertension	33 (61)	71 (65)	0.3
Active smokers	16 (29.6)	36 (32.4)	0.3
EF < 30%	23 (42.6)	33 (29.7)	0.1
Cardiogenic shock	10 (18.5)	15 (13.5)	0.4
Complete heart block	8 (14.8)	7 (6.3)	0.07
Time to initiation of medical treatment, h	77.3 $\pm$ 63	74.5 $\pm$ 66	0.87
Time to angiography, h	107 $\pm$ 79	113 $\pm$ 141	0.84
CK-MB	101.2 $\pm$ 90	75 $\pm$ 83.4	0.11
Platelet ($\times 10^9$ /L)	1.89 $\pm$ 0.7	2.0 $\pm$ 0.91	0.17
Procalcitonin (ng/mL)	0.59 $\pm$ 0.7	1.0 $\pm$ 2.6	0.27
TLC ($\times 10^9$ /L)	10.6 $\pm$ 3.8	10.7 $\pm$ 3.9	0.8
CRP (mg/dL)	47.2 $\pm$ 34.3	39.7 $\pm$ 28.4	0.16
Fibrinogen (gm/L)	6.9 $\pm$ 1.04	5.4 $\pm$ 1.2	0.001
Albumin (gm/dL)	3.3 $\pm$ 0.35	3.4 $\pm$ 0.32	0.014
FAR	21.1 $\pm$ 3.9	15.6 $\pm$ 4.1	0.001

EF: Ejection fraction; CK-MB: Creatinine kinase; TLC: Total leukocyte count; FAR: Fibrinogen to albumin ratio; CRP: C-reactive protein; TIMI: Thrombolysis in myocardial infarction.



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Figure 1 Receiver operating characteristic curve demonstrates the good accuracy of fibrinogen and fibrinogen to albumin ratio in predicting total occlusion in culprit artery. A: ST elevation myocardial infarction; B: Non-ST elevation myocardial infarction acute coronary syndrome. FAR: Fibrinogen to albumin ratio.

CONCLUSION

To efficiently manage cardiovascular emergencies in a resource constrained setting like ours, there is an ardent need to identify patients at high risk and prioritize resource allocation. Our study shows that by using old, easily available biomarkers we can effectively triage and identify this high-risk subgroup. This should pave way for further large-scale studies to affirm role of fibrinogen and FAR in predicting total occlusion of the culprit artery in patients with ACS.

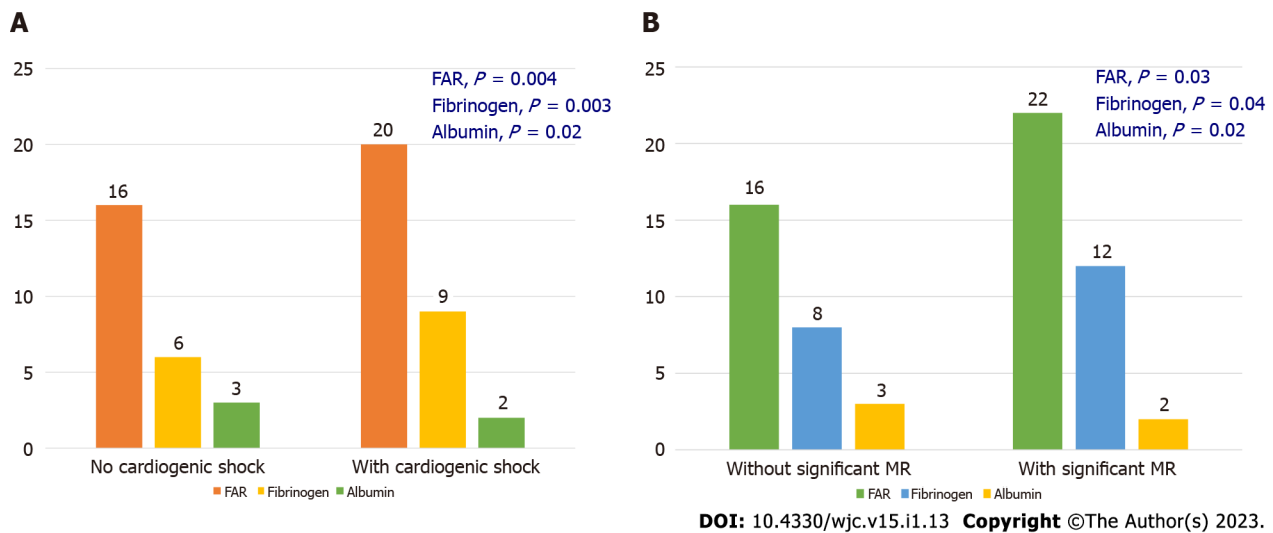


Figure 2 Bar graphs showing the differences in mean levels of fibrinogen, albumin and fibrinogen to albumin ratio in patients. A: Patients with and without cardiogenic shock; B: Patients with and without significant ischemic mitral regurgitation. FAR: Fibrinogen to albumin ratio; MR: Mitral regurgitation.

ARTICLE HIGHLIGHTS

Research background

Despite the obvious progress in our management of acute coronary syndrome (ACS), it continues to be the leading cause of death worldwide with considerable short and long-term mortality and morbidity. The situation is dismal in the developing world where the health care resources are scarce. There is dire need for resource sensitive, readily available, reliable and easily affordable biomarkers to enable appropriate resource allocation in cardiac emergencies.

Research motivation

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the huge deficit in health care resources worldwide and made a strong case developing efficient triaging and risk-assessment for effective patient management.

Research objectives

The present study aimed to study the applicability of the old, available and affordable nonconventional biomarkers: albumin and fibrinogen in their ability to predict angiographic severity and clinical outcomes in patients with ACS.

Research methods

In this prospective, observational study, 166 consecutive patients with ACS were enrolled. Fibrinogen, albumin and their ratio were determined from serum. Patients with underlying chronic liver disease, active malignancy, autoimmune disease, active COVID-19 infection and undergoing thrombolysis were excluded.

Research results

Mean age of the population was 60.5 ± 1.5 years, 74.1% being males. ST elevation myocardial infarction (STEMI) was most common presentation of ACS seen in 57% patients. Fibrinogen albumin ratio (FAR) ≥ 19.2 , had a sensitivity of 76.9% and specificity of 78.9% [area under the receiver operating characteristic curves (AUROC) = 0.8, $P = 0.001$] to predict $\leq$ TIMI 1 flow in culprit artery in STEMI patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity (AUROC=0.715, $P = 0.006$).

Research conclusions

Our study has shown that readily available biomarkers like fibrinogen and albumin and their ratio can help identify these high-risk patients with good accuracy. This allows risk-stratification and individualization of treatment in ACS.

Research perspectives

Our study makes a strong case for the readily available and cost-effective biomarkers: Fibrinogen, albumin and their ratio (FAR) to guide appropriate clinical decision making in real world setting. It

showed excellent accuracy for predictive angiographic severity and outcomes which are the most valuable piece of Information any clinician needs.

FOOTNOTES

Author contributions: Batta A, Makkar K and Sharma YP contributed conception and design; Batta A, Makkar K, Sharma YP, Panda PK and Hatwal J contributed analysis and interpretation; Batta A contributed data collection; Batta A and Makkar K contributed writing the article; Batta A, Makkar K and Sharma YP contributed critical revision of the article; Batta A and Sharma YP contributed final approval of the article; Makkar K, Panda PK and Hatwal J contributed statistical analysis; Batta A, Makkar K and Sharma YP contributed overall responsibility.

Institutional review board statement: The protocol was approved by the institution Ethics Committee [Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh-160012, INDIA. Reference number: INT/IEC/2019/2750]

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 report no relevant conflicts of interest for this article.

Data sharing statement: All participants gave their written informed consent for enrollment in the study. The dataset and statistical code will be made available to the readership of the journal upon reasonable request from the corresponding author.

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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Prospective Study

Feasibility and efficacy of delayed pharmacoinvasive therapy for ST-elevation myocardial infarction

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Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) refers to a clinical syndrome that features symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. In patients with STEMI who could not receive primary percutaneous coronary intervention (PCI) on time, pharmacoinvasive strategy (thrombolysis followed by timely PCI within 3-24 h of its initiation) is an effective option.

AIM

To analyze the role of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis.

METHODS

This was a physician-initiated, single-center prospective registry between January 2017 and July 2017 which enrolled 337 acute STEMI patients with partially occluded coronary arteries. Patients received routine pharmacoinvasive therapy (PCI within 3-24 h of thrombolysis) in one group and delayed pharmacoinvasive therapy (PCI within 24-72 h of thrombolysis) in another group. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d of the procedure. The secondary endpoints included major bleeding as defined by Bleeding Academic Research Consortium classification, angina, and dyspnea within 30 d.

RESULTS

The mean age in the two groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, $P = 0.426$). Diabetes was present among 20.2% and 22.1% of patients in the routine and delayed groups, respectively. Smoking rate was 54.6% and 55.8% in the routine and delayed groups, respectively. Thrombolysis was initiated within 6 h of onset of symptoms in both groups ($P = 0.125$). The mean time from thrombolysis to PCI in the routine and delayed groups was 16.9 ± 5.3 h and 44.1 ± 14.7 h, respectively. No significant difference was found for the occurrence of measured clinical outcomes in the two groups within 30 d (8.7% *vs* 12.9%, $P = 0.152$). Univariate analysis of demographic characteristics and risk factors for patients who reported MACCE in the two groups did not demonstrate any significant correlation. Secondary endpoints such as angina, dyspnea, and major bleeding were non-significantly different between the two groups.

CONCLUSION

Delayed PCI pharmacoinvasive strategy in a critically diseased but not completely occluded artery beyond 24 h in patients who have been timely thrombolysed seems a reasonable strategy.

Key Words: Coronary artery disease; ST-elevation myocardial infarction; Primary percutaneous coronary intervention; Pharmacoinvasive strategy; Thrombolysis; Atherosclerosis

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Core Tip: Pharmacoinvasive strategy with percutaneous coronary intervention (PCI) within 3 to 24 h after successful thrombolysis has been proven to be a viable alternative to primary PCI. In resource poor countries, patients often present to the interventionist beyond 24 h of thrombolysis due to logistic reasons. The results of this study demonstrate that the clinical outcomes of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) are comparable to those of routine pharmacoinvasive (3-24 h of initiation of thrombolysis) in patients with acute ST-elevation myocardial infarction (STEMI). Hence, in critically diseased acute STEMI patients who have been timely thrombolysed, delayed PCI (24-72 h following thrombolysis) appears a reasonable strategy.

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INTRODUCTION

ST-elevation myocardial infarction (STEMI), a potentially lethal diagnosis, refers to a clinical syndrome that encompasses symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. Primary percutaneous coronary intervention (PCI) is the global standard of care for patients presenting with acute STEMI[1,2]. However, the practicality of all patients reaching the PCI-capable center within 1 h is a challenge. Thus, in patients with acute STEMI who cannot get primary PCI in a timely manner, pharmacoinvasive strategy is considered as an effective and viable option[3,4]. This is particularly true in developing nations where this delay often crosses the golden period of 24 h due to the exponentially increasing disease burden and limited availability of resources. The famous Occluded Artery Trial (OAT), failed to show any advantage of performing PCI (beyond 72 h) + optimal medical therapy compared to optimal medical therapy alone[5].

Therefore, in the present study we analyzed a novel concept of 'delayed pharmacoinvasive therapy' in acute STEMI patients with partially occluded coronary vasculature who had received thrombolysis within the first 12 h of symptoms onset and underwent PCI in a window period of 24-72 h, and compared both routine and delayed pharmacoinvasive strategies in such patients.

MATERIALS AND METHODS

This was a physician-initiated, single-center prospective registry which enrolled STEMI patients who were thrombolized within 12 h of symptom onset and subsequently underwent PCI between January 2017 and July 2017. The study protocol was approved by the local Institutional Review Board and was performed in accordance with Declaration of Helsinki. Written informed consent was obtained from all patients or from their designees before enrollment.

The enrolled patients with STEMI were either admitted to peripheral hospitals, thrombolized, and referred to us; or else were directly admitted to our hospital but could not undergo primary PCI and thus received thrombolysis. For various nonspecific reasons, some of them could not undergo PCI within 3–24 h of initiation of thrombolytic therapy. The common reasons for this delay were financial constraints and imbalance between the service seekers and providers which does not support 24 h functioning of catheterization laboratory, even in tertiary care centers. The period of 24–72 h has remained a grey area for the decision of primary PCI in the literature but is one of the usually encountered strategy in low resource clinical setup and used in many centers with PCI, if vessels are still found to be occluded on angiography. We called this group as delayed pharmacoinvasive group. To evaluate the effectiveness of this strategy, we compared the results with those obtained in the cohort who underwent routine pharmacoinvasive therapy (thrombolized within 12 h of symptom onset followed by PCI within 3–24 h initiation of thrombolysis). The groups were not randomized. Stated simply, Group 1 (routine) represented those patients undergoing PCI < 24 h of symptom onset and Group 2 (delayed) consisted of those subjects undergoing PCI between 24–72 h of symptom onset.

Patients who underwent primary PCI were excluded from the study. Other exclusion criteria included contraindication for thrombolysis, patients presenting beyond the window period for thrombolysis, or patients with totally occluded arteries on angiogram within 24–72 h.

Clinical endpoints and definitions

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d that included composite of death, rehospitalization due to reinfarction and congestive heart failure, target vessel revascularization, and stroke. The secondary endpoints included individual primary endpoints, major bleeding as defined by Bleeding Academic Research Consortium classification, and angina and dyspnea within 30 d. The impact of time of thrombolysis to PCI on the clinical outcome (< 24 h, 24–48 h, and 48–72 h) was also assessed.

Statistical analysis

The statistical review of this study was performed by a biomedical statistician from King George's Medical University. All the data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows version 20.0; Chicago, IL, United States). Categorical and continuous variables are summarized as frequency (percentage) and the mean $\pm$ SD, respectively. The difference between groups was verified using Chi-square test for categorical variables and independent sample *t*-test for continuous variables. $P < 0.05$ was considered statistically significant.

RESULTS

The flow chart of selection of study patients is demonstrated in [Figure 1](#). Among 880 STEMI patients who presented at our tertiary care center in the given period, 337 were divided into two groups: (1) 183 patients in the routine group who underwent PCI within 3–24 h of initiation of thrombolysis; and (2) 154 patients in the delayed group who underwent PCI within 24–72 h of initiation of thrombolysis.

Demographic characteristics of the study cohorts (routine group *vs* delayed group) are compared in [Table 1](#). Mean age in the two groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, $P = 0.426$), with a predominance of male patients in both groups (87.4% in routine group and 89.6% in delayed group). The occurrence of anterior wall STEMI and non-anterior STEMI was almost equally distributed in the routine and delayed groups (53.6% *vs* 57.1% and 46.4% *vs* 42.9%; $P = 0.509$, respectively). In both groups, around 58% of patients had single vessel disease while 42% had multiple vessel disease. A statistically significant difference was noted in mean left ventricular ejection fraction between the two groups (routine: 46.9 ± 4.7 and delayed: 45.8 ± 4.5 ; $P = 0.034$).

In both the routine and delayed groups, thrombolysis was initiated within 6 h of onset of symptoms (5.2 ± 3.4 h *vs* 5.8 ± 4.5 h, $P = 0.125$). The mean time from thrombolysis to PCI was 16.9 ± 5.3 h in the routine group while it was 44.1 ± 14.7 h (an average 27 h late) in the delayed group.

The clinical outcomes within 30 d of the procedure in the two groups are depicted in [Table 2](#). The primary endpoint, *i.e.*, MACCE, was reported in 16 (8.7%) patients in the routine group and in 20 (12.9%) patients in the delayed group ($P = 0.152$). Angina occurred in 4 (2.2%) patients in the routine group and in 1 (0.6%) in the delayed group ($P = 0.381$). Dyspnea occurred in 6 (3.3%) and 5 (3.2%) in the routine and delayed groups, respectively ($P = 0.99$).

Table 1 Comparison of baseline characteristics of the two study groups (mean $\pm$ SD)

Characteristic	Routine (<i>n</i> = 183)	Delayed (<i>n</i> = 154)	<i>P</i> value
Age, years	55.1 $\pm$ 10.1	54.2 $\pm$ 10.5	0.426
Age group, <i>n</i> (%)			
20–29 yr	0	2 (1.3)	0.197
30–39 yr	13 (7.1)	10 (6.5)	
40–49 yr	38 (20.8)	34 (22.1)	
50–59 yr	47 (25.7)	52 (33.8)	
60–69 yr	71 (38.8)	43 (27.9)	
70–79 yr	14 (7.7)	13 (8.4)	
Gender, <i>n</i> (%)			
Male	160 (87.4)	138 (89.6)	0.533
Female	23 (12.6)	16 (10.4)	
Risk factors, <i>n</i> (%)			
Diabetes	37 (20.2)	34 (22.1)	0.677
Hypertension	49 (26.8)	43 (27.9)	0.814
Smoking	100 (54.6)	86 (55.8)	0.825
Killip class, <i>n</i> (%)			
Class 1	165 (90.2)	129 (83.8)	0.176
Class 2	11 (6.0)	10 (6.5)	
Class 3	5 (2.7)	10 (6.5)	
Class 4	2 (1.1)	5 (3.2)	
Left ventricular ejection fraction (%)	46.9 $\pm$ 4.7	45.8 $\pm$ 4.5	0.034
Type of myocardial infarction, <i>n</i> (%)			
AWMI	98 (53.6)	88 (57.1)	0.509
Non-AWMI	85 (46.4)	66 (42.9)	
Type of coronary artery disease, <i>n</i> (%)			
SVD	105 (57.4)	89 (57.8)	0.939
MVD	78 (42.6)	65 (42.2)	
Symptoms to needle time, h	5.2 $\pm$ 3.4	5.8 $\pm$ 4.5	0.125
Thrombolysis to PCI time, h	16.9 $\pm$ 5.3	44.1 $\pm$ 14.7	0.001

AWMI: Anterior wall ST segment elevation myocardial infarction; Non-AWMI: Non-anterior wall ST segment elevation myocardial infarction; SVD: Single vessel disease; MVD: Multi-vessel disease; PCI: Percutaneous coronary intervention.

To analyze the effect of time from thrombolysis to PCI on clinical outcomes, we further divided the delayed group into two subgroups based on the time from thrombolysis to PCI: (1) 24– $\leq$ 48 h (*n* = 96); and (2) 48–72 h (*n* = 58). The two subgroups were both compared with the routine group (thrombolysis to PCI time < 24 h; *n* = 183). However, no statistically significant difference was observed in measured clinical outcomes among the three groups (Table 3).

Univariate analysis of demographic characteristics and risk factors for patients who reported MACCE in the two groups are outlined in Table 4. A significant correlation was reported between Killip class II and the occurrence of primary outcomes in the routine group (odds ratio: 4.59; 95% confidence interval: 1.08–19.40).

Table 2 Outcomes based on primary and secondary endpoints in the two study groups

Clinical outcome	Routine (n = 183)	Delayed (n = 154)	P value
Primary endpoints, n (%)			
MACCE	16 (8.7)	20 (12.9)	0.152
Secondary endpoints, n (%)			
Death	5 (2.7)	3 (1.9)	0.732
Myocardial infarction	2 (1.1)	7 (4.5)	0.085
Target vessel revascularization	3 (1.6)	3 (1.9)	0.999
Congestive heart failure	6 (3.3)	7 (4.5)	0.547
Stroke	0	0	0.999
Angina	4 (2.2)	1 (0.6)	0.381
Dyspnea	6 (3.3)	5 (3.2)	0.999
Major Bleeding ¹	1 (0.5)	3 (1.9)	0.335

¹As defined by Bleeding Academic Research Consortium (BARC) classification.

MACCE: Major adverse cardiac and cerebrovascular events.

Table 3 Outcomes based on primary and secondary endpoints among study groups

	Routine	Delayed		P value		
	Group A (≤ 24.0 h), n = 183	Group B (24.0 ≤ 48.0 h), n = 96	Group C (48.0–72.0 h), n = 58	Group A vs Group B	Group A vs Group C	Group B vs Group C
Primary outcomes, n (%)						
MACCE	16 (8.7)	13 (13.5)	7 (12.06)	0.212	0.263	0.965
Secondary outcomes, n (%)						
Death	5 (2.7)	2 (2.1)	1 (1.7)	0.999	0.999	0.999
Myocardial infarction	2 (1.1)	3 (3.1)	4 (6.9)	0.343	0.093	0.427
Target vessel revascularization	3 (1.6)	2 (2.1)	1 (1.7)	0.999	0.999	0.999
Congestive heart failure	6 (3.3)	6 (6.3)	1 (1.7)	0.245	0.999	0.256
Stroke	0	0	0	-	-	-
Major bleeding ¹	1 (0.5)	1 (1.0)	2 (3.4)	0.999	0.145	0.557

¹As defined by Bleeding Academic Research Consortium (BARC) classification.

MACCE: Major adverse cardiac and cerebrovascular events.

DISCUSSION

Primary PCI within 1 h of symptom onset is the standard of care strategy in acute STEMI[1,6]. However, the real world scenarios are not always ideal, thus decision making in such cases is a challenge for interventional cardiologists[7-10]. As per guidelines, pharmacoinvasive therapy (thrombolysis followed with PCI within 3-24 h) is recommended as an effective option in patients with acute STEMI who could not receive primary PCI within this golden hour[6]. Furthermore, there is a lacuna in the literature regarding the role of PCI, in patients who present in a window of 24-72 h of thrombolysis. This period is critical and the benefits of reperfusion of partially occluded artery must be balanced against the potential harm from procedure-related complications, myocardial injury because of distal embolization of athero-thrombotic debris, and loss of recruitable collateral flow to other coronary territories[11,12]. In our study, we compared the effectiveness of routine (PCI within 24 h of thrombolysis) and delayed (PCI within 24-72 h of thrombolysis) pharmacoinvasive therapies and the results revealed no statistically significant difference in the clinical outcome between two therapies within 30 d of the procedure.

Table 4 Univariate analysis for prediction of primary endpoints as a measure of outcome

Variable	Events (16/183)	Routine (3-24 h)	Events (21/154)	Delayed (> 24 h)
		OR (95%CI)		OR (95%CI)
Age (> 65 yr)	1/16	0.68 (0.08-5.48)	3/18	1.31 (0.34-4.98)
Age (55-65 yr)	9/81	1.70 (0.62-4.77)	8/47	1.48 (0.57-3.86)
Age (45-55 yr)	1/41	0.21 (0.03-1.65)	5/56	0.50 (0.17-1.46)
Age (35-45 yr)	4/38	1.30 (0.40-4.30)	4/26	1.19 (0.36-3.87)
Age (< 35 yr)	1/7	1.79 (0.20-15.86)	1/7	1.06 (0.12-9.26)
Male	15/160	2.28 (0.29-18.10)	17/138	0.42 (0.12-1.46)
KILLIP Class-1	13/165	0.43 (0.11-1.67)	17/132	0.67 (0.20-2.20)
KILLIP Class-2	3/11	4.59 (1.08-19.40)	1/9	0.78 (0.09-6.59)
AWMI	9/99	1.10 (0.39-3.09)	10/88	0.64(0.25-1.61)
Type 2 DM	3/37	0.9 (0.24-3.35)	2/34	0.33(0.07-1.50)
Smoking	10/100	1.43 (0.50-4.10)	14/86	1.69 (0.64-4.47)
HTN	4/49	0.90 (0.28-2.95)	4/43	0.57 (0.18-1.79)
LVEF (35-45)	3/70	0.34 (0.09-1.25)	7/73	0.51 (0.19-1.34)
LVEF (> 45)	12/112	2.01 (0.62-6.50)	14/78	2.16 (0.82-5.68)
MVD	7/78	1.05 (0.37-2.96)	11/65	1.61 (0.64-4.05)
SVD	9/98	1.13 (0.40-3.17)	10/87	0.66 (0.26-1.66)
CrCl (30-60)	1/29	0.33 (0.04-2.61)	5/30	1.35 (0.45-4.03)
CrCl (60-90)	11/113	1.40 (0.47-4.22)	11/78	1.08 (0.43-2.72)
CrCl (> 90)	4/40	1.21 (0.37-3.99)	5/42	0.81 (0.28-2.37)

AWMI: Anterior wall ST-elevation myocardial infarction; DM: Diabetes mellitus; HTN: Hypertension; LVEF: Left ventricular ejection fraction; MVD: Multi-vessel disease; SVD: Single vessel disease; CrCL: Creatinine clearance.

Almost a decade ago, OAT-trial was published to test whether opening a totally occluded infarct related artery, 3-28 d following acute STEMI, will improve the clinical outcome or not. The results of that trial cautioned about a trend towards excess non-fatal re-infarction when PCI was performed in stable patients with a totally occluded infarct related artery, 3 to 28 d after STEMI, and did not show any reduction in major cardiovascular events during a mean follow-up of 3 years among these patients[5, 13]. Furthermore, in an analysis from the Melbourne Interventional Group registry of 4307 patients with STEMI who underwent PCI, no mortality hazard was reported where PCI was delayed beyond the first 24 h but was performed within the index admission. However, they have not defined/specified the index admission in terms of time/hours[14].

A meta-analysis of ten randomized controlled trials on timing of PCI in non-STEMI patients showed no reduction in death or re-infarction rate in early *vs* delayed intervention. However, recurrent ischemia and length of stay were significantly reduced with an early invasive strategy[15]. In non-STEMI cases, a delayed invasive approach is recommended, with an early invasive strategy within 24 h in high-risk patients and a delayed invasive strategy within 72 h in intermediate risk patients[16]. As randomized controlled trials of these kinds are difficult to plan for STEMI patients, decisions must be based on observational studies or clinical registries. Recently, a randomized controlled trial was published for transient STEMI in which the outcomes of a STEMI-like approach (with an immediate invasive strategy) were compared with a non-STEMI like approach (with a delayed invasive strategy) and the results showed no difference in clinical outcomes[17].

PCI in any scenario after 72 h is not recommended as it can be more detrimental than beneficial to vascularize the myocardium which is already dead[18]. In the present study, the mean time from symptom onset to angiography was 22.0 ± 6.6 h and 49.4 ± 15.5 h in the routine and delayed groups, respectively. Contrary to this, these time windows are significantly less in the reported literature [3,19]. Notably, it is difficult to compare the triage and referral facilities between developed and developing countries. Delayed presentation was one of the most important factors in our study determining the poor primary outcomes as compared to Western data. The delay in reaching STEMI care hospital in our country is multifactorial: (1) Delay in recognition of chest symptom by patients themselves; (2) unavail-

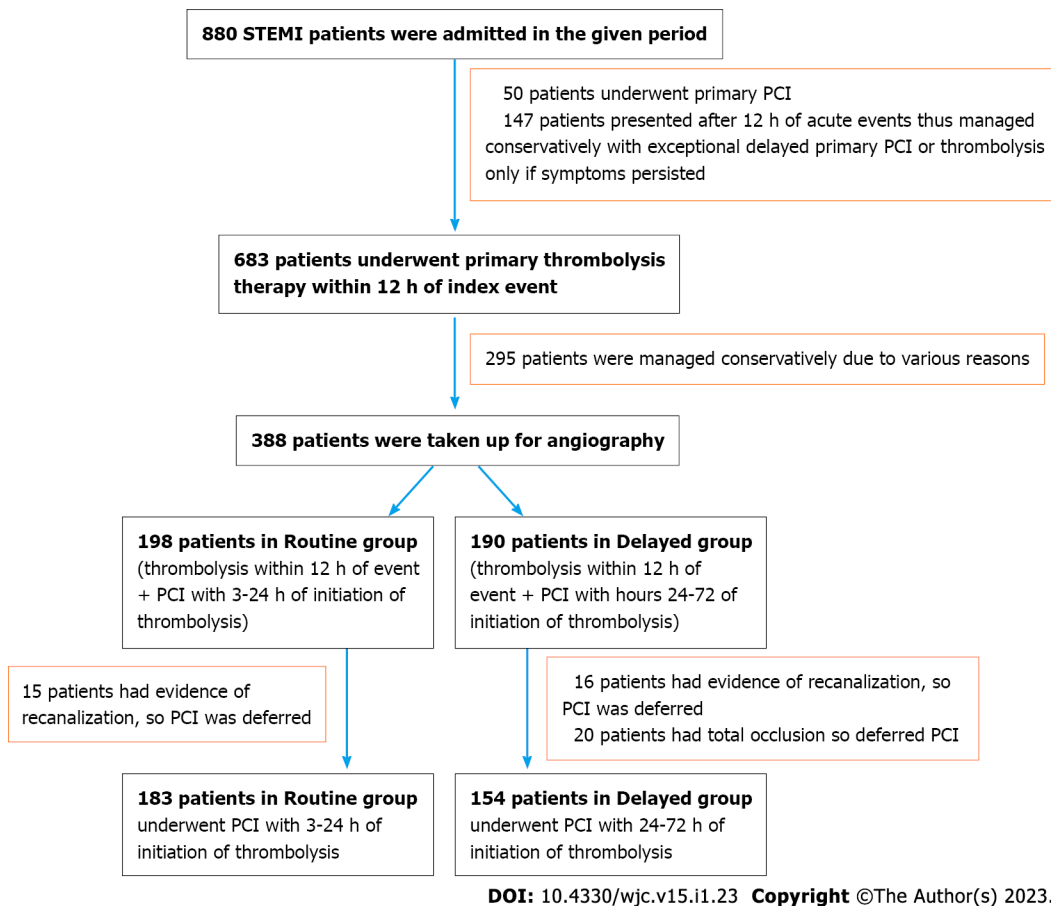


Figure 1 Flow chart of patient enrollment in the study. STEMI: ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention.

ability of electrocardiogram machine at peripheral health care centers; (3) incompetency in diagnosing and taking decision for referral to higher centers by the health care provider; and (4) poor transportation services. However, in our opinion these loopholes in our systems are not too difficult to handle. The lag time for patient presentation can be reduced by creating public awareness regarding symptoms of acute coronary syndrome, educating the grass root level health care providers, ensuring the availability of an electrocardiogram machine at peripheral health care centers, and strengthening the ambulance services. Increasing the number of catheterization laboratories and their working hours by increasing the number of work force will also prevent the procedural delays.

The primary outcome, *i.e.*, MACCE within 30 d, was reported in 8.7% in the routine group and 13.6% in the delayed group ($P = 0.152$). The STEMI patients undergoing primary PCI have witnessed a wide range of MACCE (1.6% to 23.3%) with in 30 d, in various studies and variation depends on the baseline risk factors of the study population and pharmacological intervention prior to PCI[20-22]. Furthermore, in our cohort Killip class was the most important predictor of worse outcomes among all the clinical parameters analyzed by univariate analysis. Killip class II patients had larger infarct and poorer left ventricular function as compared to Killip class I and it is a well-recognized fact that the outcome of STEMI with high Killip class ($\geq$ class II) is poor[23,24]. Male sex and left ventricular ejection fraction $> 45\%$ were the other two parameters which reported moderate significance in predicting the outcomes.

Our study is the first of its kind to clearly document the useful role of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) in patients with acute STEMI, which is extremely important and practical in low resource high burden settings.

Limitations

There were several limitations to our study. First, we enrolled a comparatively small number of patient population and had a shorter duration of the study. As randomized controlled trials are difficult to conduct in these subjects because of ethical and legal issues, keeping in mind our preliminary results which support delayed pharmacoinvasive therapy in a specified group of population, prospective registries must be encouraged to conclude further. Second, despite a prospective design, we did not use Cox proportional hazard model which has been shown to have more statistical power than logistic regression model in cross sectional studies[25]. However, when the follow-up period is short and event rates are low (as in our study), both methods may be comparable[26]. Third, we did not evaluate the psychological impact of a delayed PCI or the Post Traumatic Stress Disorder symptoms during the extra

waiting period. Fourth, despite a high rate of smoking at baseline, data regarding persistent smoking at 30 d was not available. However, counselling for smoking cessation was provided to all smokers as a protocol.

CONCLUSION

The results of the present study specifically established that the clinical outcomes of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) are comparable to those of routine pharmacoinvasive (3-24 h of initiation of thrombolysis) in patients with acute STEMI. Delayed PCI (24-72 h following thrombolysis) in critical diseased but not completely occluded arteries, which have been timely thrombolysed, seems a reasonable strategy in acute STEMI patients.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) when untreated is a potentially fatal condition and timely primary percutaneous coronary intervention (PCI) is the key to improving outcomes.

Research motivation

In developing countries, despite multiple guidelines and interventions, the primary PCI coverage in STEMI remains low in clinical practice. PCI within 24 h of thrombolysis (pharmacoinvasive approach) has emerged as a viable alternative to primary PCI. However, due to logistic and financial reasons, patients in developing world may undergo PCI late (> 24 h) after thrombolysis.

Research objectives

This study aimed to analyze the safety and feasibility of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis. Group 1 (routine) represented those patients undergoing PCI < 24 h of symptom onset and Group 2 (delayed) consisted of those subjects undergoing PCI between 24-72 h of symptom onset.

Research methods

This was a single center, prospective registry at a tertiary care center. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d of the procedure.

Research results

Among 337 patients with STEMI who underwent thrombolysis, there was no difference in measured clinical outcomes (MACCE) at 30 d between the routine pharmacoinvasive and delayed pharmacoinvasive groups (8.7% *vs* 12.9%, $P = 0.152$). The mean time from thrombolysis to PCI in the routine and delayed groups was 16.9 ± 5.3 h and 44.1 ± 14.7 h, respectively.

Research conclusions

Delayed PCI pharmacoinvasive strategy in a critical diseased but not completely occluded artery beyond 24 h in patients who have been timely thrombolysed seems a reasonable strategy.

Research perspectives

Late PCI after thrombolysis in STEMI is common in developing world due to logistic and financial reasons. This study demonstrates the safety and feasibility of such delayed pharmacoinvasive PCI, lending credibility to this approach utilized in daily practice.

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FOOTNOTES

Author contributions: Sethi R and Mohan L conceived the project; Pradhan A, Vishwakarma P, Singh A, and Mohan L were involved in data collection; Shukla A, Bhandari M, Sharma S, and Chaudhary G analyzed the data; Pradhan A and Mohan L performed the literature search; Pradhan A and Sethi R drafted the manuscript; Narain VS, Dwivedi

SK, and Chandra S critically reviewed the manuscript; Sethi R, Mohan L and Pradhan A prepared the final manuscript; Sethi R and Pradhan A submitted the initial version; Sethi R, Pradhan A, and Vishwakarma P revised the manuscript; Pradhan A and Vishwakarma P prepared the rebuttal; Pradhan A submitted the revised version.

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Takotsubo cardiomyopathy following envenomation: An updated review

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Abstract

BACKGROUND

Takotsubo cardiomyopathy (TTC) can be diagnosed in patients presenting with clinical features of acute coronary syndrome (ACS) by using Mayo clinic criteria. Multiple precipitators have been attributed to causing TTC. Rarely it has been reported to occur following an acute envenomation.

AIM

This review describes the various patterns, mechanisms, and outcomes of envenomation induced TTC.

METHODS

In this review, we included all studies on "TTC" and "envenomation" published in the various databases before June 2022. To be included in the review articles had to have a distinct diagnosis of TTC and an envenomation

RESULTS

A total of 20 patients with envenomation induced TTC were identified. Most episodes of envenomation induced TTC were reported following a bee sting, scorpion sting, and snake envenomation. Fear and anxiety related to the sting, direct catecholamine toxicity and administration of exogenous beta-adrenergic agents have been commonly postulated to precipitate TTC in these patients. 95%

of these patients presented with a clinical picture of ACS. Most of these patients also fulfill at least 3 out of 4 criteria of Mayo clinic criteria for TTC. Echocardiographic evidence of Apical TTC was noted in 72% of patients. 94% of these patients had clinical improvement following optimal management and 35% of these patients were treated with guideline directed medications for heart failure.

CONCLUSION

Envenomation following multiple insect stings and reptile bites can precipitate TTC. Most reported envenomation related TTC has been due to bee stings and scorpion bites. Common mechanisms causing TTC were fear, anxiety, and stress of envenomation. Most of these patients present with clinical presentation of ACS, ST elevation, and elevated troponin. The most common type of TTC in these patients is Apical, which improved following medical management.

Key Words: Takotsubo cardiomyopathy; Envenomation; Mechanism; Outcome

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Core Tip: Multiple envenomations following insect stings and reptile bites can cause Takotsubo cardiomyopathy. Bee stings, wasp stings, scorpion stings, snake bites, spider bites, and jellyfish stings are the commonly reported precipitators of this cardiomyopathy. Multiple mechanisms have been postulated to cause this of which fear, anxiety, and stress of envenomation are the predominant ones. Patients usually present with clinical presentation of acute coronary syndrome, ST elevation, and elevated troponin. Echocardiography commonly shows an apical pattern of cardiomyopathy. This cardiomyopathy improves with medical management.

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INTRODUCTION

Takotsubo cardiomyopathy (TTC), aka stress cardiomyopathy, is a reversible left ventricular dysfunction syndrome precipitated by multiple emotional and environmental triggers[1]. Patient with TTC presents with the clinical picture of an acute coronary syndrome (ACS) including chest pain, abnormal cardiac enzymes, and electrocardiography (EKG) following a distinct trigger or acute stress [2]. It is most commonly reported in postmenopausal women worldwide. TTC has been reported in around 2% of patients presenting with an initial diagnosis of ACS[3].

As per the Revised Mayo Clinic Criteria, TTC can be diagnosed in the presence of the following four criteria: (1) Transient left ventricular (LV) dyskinesia extending beyond a single coronary distribution, (2) Absence of acute plaque rupture or obstructive coronary artery disease, (3) New EKG abnormalities or significant troponin elevation, and (4) absence of myocarditis or pheochromocytoma[4]. Most of the time with conservative medical management recovery of LV function occurs within 21 d in up to 95% of patients[3].

While the exact mechanisms resulting in the precipitation of TTC are not fully understood, most often it has been reported following an episode of sudden physical and emotional stressors resulting in high-catecholamine states. Over the last two decades, multiple different physical stressors have been reported to precipitate TTC[3,5]. Although uncommon TTC has been reported in patients following an episode of acute envenomation[6,7]. In this narrative review, we aimed to describe the current literature on the pattern, mechanism, and outcomes of envenomation induced TTC.

MATERIALS AND METHODS

We searched the PubMed and Medline databases for the terms “TTC” and “envenomation”. We expanded our search using the names of various agents of envenomation including “snake”, and “scorpion” and “wasp” and “bee” and “spider” and “jellyfish”. We also searched in the google scholar and Reference Citation Analysis database with similar terms. We screened the references of the initially identified manuscripts for additional manuscripts. To be included in the review articles had to have a

distinct diagnosis of TTC and envenomation. Revised Mayo Clinical Criteria was used to screen for diagnosis of TTC. Envenomation had to be confirmed based on the toxidrome specific and unique to the agent. Although evidence of the absence of coronary artery disease based on cardiac catheterization was preferred, we did include reports using an alternating modality of imaging as well. All the studies published in English, including adults with an episode of recent envenomation and subsequent diagnosis of TTC were eligible to be included in this review. In this review, we included all studies published before June 2022. All the articles were independently screened by 2 different physicians. Articles lacking clinical details, opinions, comments, and letters were excluded from this review.

RESULTS

As shown in the strobe diagram a total of 37 articles were identified (Figure 1). Among these 18 articles were eligible to be included in the review. Six of these articles were on bee sting precipitating TTC, 3 articles each on snake envenomation and scorpion sting, and 2 articles each on wasp, spider, and jellyfish envenomation induced TTC. A total of 20 patients with envenomation induced TTC were reported from thirteen different countries around the world. Tables 1 and 2 describe the details of the presentation, pattern, management, and outcome in each of these envenomations. We have described the characteristics of each of these individual envenomation related TTC below.

On bee sting precipitating TTC the total number of articles identified from various databases was 10, among which 6 articles with complete patient details were eligible to be included in the study. A total of 6 patients were reported to have TTC following a bee sting[8-12]. All these patients fulfilled at least 3 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of these patients was 57, and all of them were females. The most common pattern of TTC noted was an apical type (67%). The various mechanisms that were postulated to precipitate TTC episodes were an anaphylactic reaction, epinephrine injection, catecholamine storm, cytokine storm, and direct cardiotoxic effect of the venom. Treatment details were available in 4 out of the 6 patients. Beta-blockers (BB) were used in 3 patients; Angiotensin converting enzyme inhibitors (ACEI) were used in 2 patients. Good outcome was reported in 4 patients, but multiorgan failure and death by cardiac rupture was reported in 1 patient. Interestingly improvement in a patient with cardiogenic shock was reported following mechanical circulatory support and extracorporeal membrane oxygenation.

The total number of articles on wasp envenomation and TTC identified from various databases was 5, among which 2 articles were eligible to be included in the study. A total of 2 patients were reported to have TTC following wasp envenomation[12-15]. Both the patient's fulfilled at least 3 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of the patients was 75 and one of them was male. An apical pattern of TTC was noted in both patients. The mechanisms postulated to precipitate TTC episodes were an anaphylactic reaction and epinephrine injection secondary to the effect of the venom. Treatment details were available for both patients. BB and ACEI were used in both patients. No mortality was reported, and both patients had clinical improvement.

The total number of articles identified from various databases describing spider bite and TTC was 4, among which 2 articles had patient details and were eligible to be included in the study. A total of 3 patients were reported to have TTC following spider envenomation[16,17]. All these patients fulfilled at least 2 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of the patients was 37 and two of them were female. Details of the pattern of TTC were not available in 2 of the 3 patients. The various mechanisms that were postulated to precipitate TTC episodes were a direct cardiotoxic effect of the venom, catecholamine storm, epinephrine, and anti-venom injection. Treatment details were not available for most of the patients. BB and ACEI were used in one patient. All three patients had improvement following treatment.

Snake envenomation precipitating TTC related articles identified from databases were 4, among which 3 articles were eligible to be included in the study. A total of 3 patients were reported to have TTC following snake bite and subsequent envenomation[18-20]. All patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 60 and two of them were female. An apical type of TTC was noted in all patients with additional involvement of the mid left ventricle in two. Catecholamine surge secondary to emotional stress because of snake bite was thought to be the underlying pathology of TTC. Only one patient was treated with guideline directed therapy for LV dysfunction with BB, ACEI, and a diuretic, while others received supportive care. All the patients recovered completely.

Scorpion sting related TTC articles that were identified from databases were 6. Three articles were eligible to be included in our study. A total of four patients were reported to have TTC following scorpion bite related envenomation[6,7,21-23]. All patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 31 and the gender distribution was equal. Apical type of TTC was noted in 2 patients and basal type of TTC in the other two patients. Abnormal response to catecholamines mediated through microvascular dysfunction, alpha toxins acting on sodium channels in the autonomic center leading to sympathetic excitation and release of catecholamines as well as a massive outpouring of catecholamines were suggested to be the precip-

Table 1 Baseline demographic characteristics and presenting features of study participants demographic characteristics of study participants

Ref.	Year of publication	Country	Age	Gender	Comorbidity	Clinical presentation
Bee						
Mishra <i>et al</i> [8]	2016	USA	63	F	Unknown	Rash, diaphoresis, chest pain, dyspnea
Aono <i>et al</i> [9]	2019	Japan	87	F	Unknown	Multiple bee stings with multi-organ failure
Seecheran <i>et al</i> [10]	2021	Caribbean	48	F	None	Obtunded, somnolent
Winogradow <i>et al</i> [12]	2011	Germany	37	F	Unknown	Local itching, spreading hives
Winogradow <i>et al</i> [12]	2011	Germany	70	F	Unknown	Swelling of throat, chest pain
Ghanim <i>et al</i> [11]	2015	Israel	37	F	None	Rash, dyspnea, impaired consciousness
Wasp						
Scheiba <i>et al</i> [13]	2011	Germany	81	M	Unknown	Absent pulses, gasping, unconsciousness
Geppert <i>et al</i> [14]	2010	Germany	70	F	Unknown	Chest pain and dyspnoea
Spider						
Alexakis <i>et al</i> [16]	2015	Greece	64	F	Hyperthyroidism	Nausea, tremor, infraorbital edema, diffuse abdominal pain, lower extremity muscle cramps
Isbister <i>et al</i> [17]	2015	Australia	33	M	Unknown	Perioral paresthesia, widespread fasciculation, diaphoresis, hypersalivation, dyspnea
Isbister <i>et al</i> [17]	2015	Australia	13	F	Unknown	Localized intense pain, urinary incontinence, profuse sweating, and vomiting
Snake						
Van Rensburg <i>et al</i> [18]	2015	South Africa	58	M	None	Bilateral ptosis
Murase <i>et al</i> [19]	2012	Japan	56	F	Unknown	Swelling of left foot
Delumgahawaththa <i>et al</i> [40]	2021	Sri Lanka	66	F	Hypertension, hyperlipidemia	Central chest pain
Scorpion						
Abroug <i>et al</i> [29]	2018	Tunisia	36	F	Unknown	Pulmonary edema, shock
Abroug <i>et al</i> [29]	2017	Tunisia	45	F	Unknown	Altered level of consciousness, respiratory failure, shock
Miranda <i>et al</i> [23]	2015	Brazil	7	M	Unknown	Localized pain, vomiting, profuse sweating, dyspnea
Jain <i>et al</i> [27]	2006	India	35	M	Unknown	Mild local pain, irritation
Jellyfish						
Bianchi <i>et al</i> [24]	2011	Italy	53	F	Unknown	Chest pain, fatigue, localized intense itch
Tiong <i>et al</i> [25]	2009	Australia	26	M	Unknown	Localized pain, restlessness, agitation, palpitations

USA: United States of America, M: Male, F: Female.

itators of TTC. Among the four patients, the first patient was treated with continuous positive airway pressure and dobutamine infusion, the second patient with intravenous furosemide, and the third patient with systemic steroids along with inotropic drugs. Except for the utilization of diuretics, these 3 patients were not treated with guideline directed therapy for LV dysfunction. However, complete recovery was reported in all patients within seven days.

Regarding Jelly Fish envenomation precipitating TTC, three articles were identified from databases. Two articles with one patient each had TTC following a jellyfish envenomation[24,25]. These patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 40 and one of them was male. Mid ventricular ballooning was noticed in both patients, with one patient showing apical involvement as well. Precipitators of TTC in these patients were thought to be secondary to stress, venom, and excess endogenous catecholamine release. These 2 patients were not treated with any medications for guideline directed therapy for LV dysfunction. Both patients were treated symptomatically and completely recovered within a week.

Table 2 Details of diagnosis, treatment, and outcome in study participants

Ref.	Agent	Mayo criteria	Type	Mechanism	Rx	Outcome
Mishra <i>et al</i> [8]	Bee	Apical hypokinesia, LVEF – 40 to 45%; Absence of CAD; ST elevation, T wave inversion Troponin elevation	Apical	-Cytotoxic storm; - Direct cardiotoxic effects of bee venom; - Anaphylactic reaction	-ACEI; -BB	Improved
Aono <i>et al</i> [9]	Bees (Multiple)	Apical hypokinesia; Absence of CAD; ST elevation in I, II, aVL, aVF, V2 to V6 and raised Troponin	Apical			-Multi organ failure; - Death by cardiac rupture
Seecheran <i>et al</i> [10]	African Bee	Apical hypokinesia; Absence of CAD; ST elevation in V1, V2, V3, raised Troponin	Apical	-Cytokine storm; - Anaphylaxis	-ARNI; - Eplerenone; - Bisoprolol; - Dapagliflozin	Improved
Winogradow <i>et al</i> [12]	Bee	Anterior, lateral, and Posterior hypokinesia; Absence of CAD; ST elevation in VI and raised Troponin	Reverse	-	-BB; -ACEI; - Aldosterone agonist	-
Winogradow <i>et al</i> [12]	Bee	Apical wall hypokinesia; Absence CAD; VFIB	Apical	-Hypersensitivity; - Epinephrine Injection	-	-
Ghanim <i>et al</i> [11]	Bees	Basal and Mid hypokinesia; Absence of CAD; ST elevation in lateral leads and depression in anterior and inferior leads and raised Troponin	Reverse	-Catecholamine storm; -Epinephrine injection	-IABP; - VAECMO; - Adrenaline; - Norepinephrine and Dopamine	Improved
Scheiba <i>et al</i> [13]	Wasp	Apical and anteroseptal hypokinesia, LVEF – 45%; Absence of CAD; ST elevation in I, aVL, V2-V4 and Troponin elevation	Apical	-Hypersensitivity; - Epinephrine Injection	-BB; -ACEI; - Aspirin	Improved
Geppert <i>et al</i> [14]	Wasp	Apical (anterior and inferior) and anteroseptal hypokinesia (46%); Absence of CAD; ST segment elevations in the leads, V1–V3, T-negatives in leads I, aVL and V2 –V4 and raised Troponin	Apical	-Epinephrine injection	-Bisoprolol; - Ramipril; - Aspirin	Improved
Alexakis <i>et al</i> [16]	Black widow spider	Hypokinesia of the basal and middle segments of the LV wall with apical sparing, LVEF – 36%; CAG not done; T wave flattening in aVL, and Troponin elevation	Reverse	-Alpha-ladrot toxin mediated catecholamine storm; -Cytokine storm	- BB; -ACEI; - Aspirin; - Clopidogrel	Improved
Isbister <i>et al</i> [17]	Funnel web spider	Diffuse global hypokinesia with LVEF of 20%; CAG not done; Diffuse ST changes and troponin elevation	-	-Toxin; -Antivenom; -Catecholamine storm		Improved
Isbister <i>et al</i> [17]	Funnel web spider	Reduced EF- 45%; CAG not done; ST depression in the inferior and anterior leads and elevated troponin	-	-Toxin; -Antivenom; -Adrenaline	-	Improved
Van Rensburg <i>et al</i> [18]	Cape Cobra	Mid and apical LV segment hypo or akinetic, LVEF: 27%, Absent CAD; New ST elevation across anterolateral leads, subsequent EKG showing T wave inversions in anterolateral leads, raised troponin	Mid ventricular and apical; (Apical ballooning)	-Catecholamine storm; -Cytokine storm; - Catecholamine release associated with Intensive Care Unit medication	Supportive care; Anti-snake venom administered for snake bite	Recovery of RWMA within a week (ECHO)
Murase <i>et al</i> [19]	<i>Gloydius blomhoffii</i> Snake (<i>Mamushi</i>)	Abnormal LV systolic function, apical akinesis, hyperdynamic basal segment of LV; No stenotic lesions noted on the CT scan; EKG changes T inversions in I, a	Apical	-Unknown	Supportive management; No Anti snake venom	Complete recovery (ECHO); (4 d)

VL, V1-6, raised troponin						
Delumgahawaththa <i>et al</i> [40]	<i>Unidentified (Possibly Russel Viper)</i>	Hypokinetic mid and apex of LV segments, with ballooning, LVEF: 35%; Absence of CAD; EKG changes with ST elevation in 1 and a VL, T wave inversion II, III, a VF, V 2-6, Troponin elevation	Mid LV and Apical LV	-Catecholamine storm; -Direct myocardial toxicity; -Microvascular spasm	ACEI, BB, Diuretic, single antiplatelet, statin; Anti-snake venom	Partial recovery in 1 mo and complete in 5 mo (ECHO)
Abroug <i>et al</i> [29]	<i>Androctonus australis</i>	Patient 1: Basal ballooning of left and right ventricles; CAG not done; Troponin elevation; ST depression in four precordial leads; No other causes to explain the cardiac dysfunction. Patient 2: Impaired systolic function on echocardiogram. Basal ballooning on cardiac MRI in 24 hours; CAG not done; Troponin and ProBNP elevation; No other causes to explain the cardiac dysfunction	Basal ballooning in both patients	-Catecholamine storm; - Microvascular dysfunction	-CPAP, Dobutamine infusion; -No management mentioned	Patient 1: Discharged in 5 d, MRI in one month was normal. Patient 2: Discharged in 4 d with normal LV function on repeat echocardiography examination before discharge
Miranda <i>et al</i> [23]	<i>Tityus serrulatus</i>	Apical ballooning with hypokinesia; CAG not done; ST segment elevation in V1-V3, DI and aVL; No other causes to explain the cardiac dysfunction	Apical	-Alpha toxins act on voltage-gated sodium channels causing catecholamine storm; -Cytokine storm	-IV furosemide	Day 6 - asymptomatic, discharged; Cardiac MRI in 7 mo showed complete recovery of wall motion in apical region
Jain <i>et al</i> [27]	<i>Mesobuthus tamulus</i>	Apical, apicolateral hypokinesia; CAG not done; ST segment elevation in V1-V3 and T wave inversion; Absence of other causes of cardiac dysfunction	Apical	-Catecholamine storm; - Microvascular dysfunction	-Systemic steroids, inotropic drugs;	-Improved LVEF in 7 d; -Cerebellar infarction with clinical signs
Bianchi <i>et al</i> [24]	<i>Pelagia noctiluca</i> - A common Mediterranean jellyfish	Apical akinesis with severe left ventricular dysfunction; Absence of CAG; Acute myocardial infarction including persistent ST elevation despite thrombolysis performed for symptom relief and raised Troponin	Apical and mid-ventricular	-Direct toxicity; - Catecholamine storm; -Cytokine storm	-Symptomatic management	Improved. Completely symptom free, improved LVEF in 7 d
Tiong <i>et al</i> [25]	<i>Carukia barnesi</i> - A cubozoan/box jellyfish found in Australia	Mid-ventricular stress cardiomyopathy with apical sparing; No CAG; Persistent hyperacute T waves, rise in troponin	Mid-ventricular ballooning with apical sparing	-Sympathetic overdrive; - Catecholamine storm	-Supportive with high flow oxygen, morphine; - Magnesium sulfate IV	- Improved, discharged in 3 d

aVL: Augmented unipolar lead L; aVF: Augmented unipolar lead F; LV: Left Ventricle; LVEF: Left ventricular ejection fraction; ACEI: Angiotensin converting enzyme inhibitor; BB: Beta blocker; CAD: Coronary artery disease; CAG: Coronary angiogram; ARNI: Angiotensin receptor-neprilysin inhibitor; VFIB: Ventricular fibrillation; ECHO: Echocardiography; EKG: Electrocardiogram; IV: intravenous; RWMA: Regional wall motion abnormality; CT: Computed tomography; MRI: Magnetic resonance imaging; CPAP: Continuous positive airway pressure; Pro BNP: Pro brain natriuretic peptide; IABP: Intra-aortic balloon pump; VAECMO: Veno-arterial extra corporeal membrane oxygenation.

DISCUSSION

TTC, aka stress induced cardiomyopathy, transient apical ballooning syndrome, and broken heart syndrome is a reversible cardiomyopathy that is increasingly being diagnosed in patients presenting with ACS following a triggering event, precipitator. Multiple emotional, environmental, physical, and iatrogenic triggers have consistently been reported to precipitate such events[1-3,5,26]. While multiple stressors have been known to predispose TTC, in this review article, we highlight the multiple reported cases of TTC following envenomation which has not been reviewed before. In this descriptive review, we also discuss the various mechanisms of envenomation that have been postulated to precipitate TTC in the medical literature. Envenomation and stings have various cardiac complications including vasovagal episodes, myocarditis, ACS, and TTC. In this review, we have specifically focused on their implications in the presence of TTC. As mentioned in **Figure 2** multiple mechanisms have been postulated to result in sympathetic activation which ultimately precipitates the transient LV

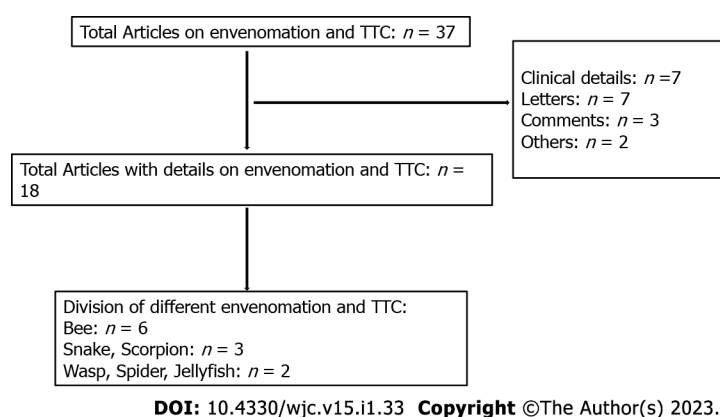


Figure 1 Strobe diagram showing the flow of the articles. TTC: Takotsubo cardiomyopathy.

Agent	Fear/Anxiety	Cytokine storm	Direct Injury	Anaphylaxis/Hypersensitivity	Epinephrine
Bee	+	+	+	+	+
Wasp	+	-	-	+	+
Spider	+	+	+	-	+
Snake	+	-	+	-	+
Scorpion	+	+	+	-	+
Jelly fish	+	-	+	-	-

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Figure 2 Various mechanisms precipitating takotsubo cardiomyopathy following envenomation.

dysfunction. Excessive sympathetic stimulation in these patients could be initiated by stress and subsequently worsen in the presence of another mechanism. Five distinct mechanisms have been consistently reported across the literature.

Fear, Anxiety, emotional stress

The sudden and accidental exposure to a sting or a bite that is perceived as threatening can result in peak stress. Acute emotional stress is known to increase regional cerebral blood flow in the hippocampus, brainstem, and basal ganglia and increase brain activation along with an increasing concentration of epinephrine and norepinephrine in the brain simultaneously. After an episode of acute stress, the interaction of the neocortex, limbic system, reticular activating system, brain stem, and spinal cord results in the interpretation of the stimulus as a threat. Subsequently, activation of the brainstem results in a neural stress response which results in the secretion of norepinephrine from locus coeruleus in the brain which then stimulates the hypothalamic-pituitary-adrenal axis. The sympathetic pathway through the posterior hypothalamus descends to the spinal cord and facilitates the release of norepinephrine. This increased catecholamine secretion from sympathetic nerve endings and secretion of epinephrine and norepinephrine from chromaffin cells in the adrenal medulla can subsequently affect the cardiac adrenergic receptors. Which subsequently contributes to the classical presentation of TTC. As shown in [Figure 2](#), emotional stress was the precipitator of TTC across all the bites[18,27-29].

Cytokine storm

During an animal bite or an envenomation, venom is injected with the help of stinging apparatus into the dermal-epidermal junction, subcutaneous tissues, vessels, or muscle fibers. Venoms are chemically a diverse mixture of proteins, amines, and salts produced for predation or protection and can result in significant injury on injection to humans as well. Following the bite metalloproteinase, and L-Amino acid oxidase present in these venoms result in local dermal proteolysis, tissue destruction, and apoptosis, subsequently providing access to toxins to circulation, and target organ. Once within circulation, these toxins can alter the structure and function of endothelial cells. These agents are not only highly proinflammatory resulting in the secretion of excessive inflammatory markers they also precipitate dysregulation of neutrophils, mononuclear phagocytic system, and granulocytes thus

accelerating inflammation and cell damage. Dysregulation and excessive stimulation of these cytokines, and pro inflammatory mediators result in cytokine storm causing multiorgan dysfunction. Multiple infections [including Novel coronavirus disease 19 (COVID-19)], toxins, cancers, and diseases are known to cause TTC due to cytokine storms precipitated by endothelial dysfunction[18,30,31].

Direct catecholamine injury/toxicity

Emotional stress like pheochromocytoma is associated with an excessive outburst of catecholamine. In patients with TTC, catecholamine levels can be extremely high as compared to other cardiac diseases. Similarly, patients with TTC have been shown to have higher ventricular catecholamine sensitivity. Alpha ladarotoxin in spider venom and alpha toxin in scorpion venom has been reported to precipitate catecholamine storm. Subsequently, excessive norepinephrine released from cardiac sympathetic nerve terminals can result in a reduction of cardiac myocyte viability. Transient elevations of catecholamines in TTC result in localized focal mononuclear inflammatory cells, fibrosis, and contractions bands in cardiac myocytes. This is evident with elevated cardiac enzymes and localized areas of edema, without late enhancement in magnetic resonance imaging. Direct catecholamine injury was also commonly reported to be the precipitate TTC following all the envenomations[28,31-33].

Anaphylaxis/ Hypersensitivity

Anaphylaxis secondary to bites and envenomation is immunoglobulin E (IgE) mediated. In patients with prior sensitization, systemic reactions can occur in up to 9% of patients. Major allergens like Antigen 5, phospholipase A1, phospholipase A2, hyaluronidase, and acid phosphatase can precipitate classic Ig E mediated anaphylactic response. Subsequently, mast cells and basophils degranulate releasing proinflammatory markers including histamine and proteases. Which results in the activation, influx, and migration of neutrophils and lymphocytes and the secretion of chemokines and cytokines. Anaphylaxis induced myocardial injury can be diverse. In a study including 300 patients with anaphylaxis myocardial injury was reported in 7.3% of patients. The etiologies of myocardial injury were anaphylactic cardiomyopathy, TTC, and Kounis syndrome. The causes of excessive catecholamine release precipitating TTC in anaphylaxis are multifactorial. Histamine can stimulate the adrenal medulla directly to produce catecholamine, compensatory catecholamine release due to activation of the renin-angiotensin-aldosterone axis, and external administration of adrenaline for anaphylaxis and norepinephrine for persistent shock. This form of TTC was only reported following bee and wasp stings [3,28,31,33].

Exogenous Beta-adrenergic receptor stimulation

In normal patients beta1-adrenergic receptor (B1AR) and B2AR receptors density are highest in the apex, thus making it susceptible to exposure to higher levels of catecholamine. Following exposure to supratherapeutic doses of catecholamine signal trafficking of catecholamine receptors occurs, which is a form of protective response of cardiac myocytes to stress. This switching of Gs to Gi coupling of B2AR receptors results in reduced inotropy and apoptosis of cardiac myocytes. This supratherapeutic level of catecholamine surge is classical of pheochromocytoma thus requiring evaluation of the same and has been incorporated into the Mayo clinic criteria for diagnosis of TTC. Exogenous catecholamines have been consistently reported to precipitate TTC. TTC has been reported following the administration of epinephrine to patients subcutaneously, intravenously, and through inhalation. Iatrogenic large volume adrenaline injection has also been reported to precipitate TTC. As shown in Image 2 exogenous catecholamine injection was the second most reported mechanism of TTC after emotional stress in these patients[11-13,28,31,34-37].

Multiple other mechanisms including microvascular dysfunction and spasm, abnormal myocardial metabolism and intracellular lipid accumulation, myocardial inflammation, estrogen excess, and endothelial dysfunction have been postulated[28,31,38]. In patients with envenomation induced TTC, multiple mechanisms can initiate and precipitate cardiac dysfunction.

Clinical Profile

In this narrative review, we summarized the clinical features following envenomation induced TTC. Most insect stings and reptile bites are accidental. Following these bites and stings, clinical manifestations can vary from an asymptomatic state and mild local reactions to severe multiorgan dysfunction based on the dose and the characteristics of the venom. TTC can occur irrespective of prior cardiac comorbidities and in absence of traditional cardiac risk factors. To summarize the clinical features of these envenomations with TTC we combined the episodes of TTC following all the envenomation. To date envenomation resulting in TTC has been described in the above-mentioned animals. Almost all these patients presented with a clinical picture of ACS (95%) and had EKG changes and elevated troponin (100% each). Sixty percent of these patients had ST segment elevation ($n = 12$), and 15% of them had ST depression and T wave inversion simultaneously ($n = 3$). Among patients with echocardiographic evidence of TTC ($n = 18$), Apical TTC was found in 72% of patients ($n = 13$), reverse TTC in 28% ($n = 5$), and midventricular TTC was reported in 17% ($n = 3$) of patients. Details of Coronary angiogram (CAG) were mentioned in 85% of patients ($n = 17$) and all the CAG were negative for any acute

obstructive disease.

Conservative medical management was initially done on all the patients. Management was mostly physician directed and clinical feature driven. Medications for heart failure management were given to 35% ($n = 7$) of patients. These 7 patients were treated with ACEI, and BB together. Inotropic agents were used in 15% ($n = 3$) and aldosterone agonist was used in 10% ($n = 2$) of patients. Details of clinical outcomes were available for 18 patients among whom 17 (94%) had clinical improvement. Improvement in LV ejection fraction (LVEF) and regional wall motion abnormality was reported in all patients with clinical improvement. Death occurred in one patient following multi organ dysfunction and cardiac rupture after multiple bee stings. As *per* the author's knowledge, this is the first review summarizing the various mechanisms, clinical features, management, and outcome following envenomation's precipitating TTC[34,35,39].

This review has a few limitations. All patients with TTC secondary to envenomation were included from case studies spanning more than a decade. Most studies did not rule out pheochromocytoma. Most of these patients did not have baseline echocardiography before admission. Studies also lacked details of CAG at presentation and echocardiographic details during follow up. Even though multiple mechanisms of TTC were considered, case studies did not report levels of inflammatory markers, catecholamine levels, IgE levels, Eosinophil counts, or advanced cardiac imaging. Most of these reports did not mention the different components of the venom which were instrumental in the precipitation of TTC[39,40]. Classification of the severity of these toxidromes, varied treatment protocols and non-availability of recurrence, functional status at discharge, and long term follow up data continue to be a challenge[3,4,26,33,33,39-41]. However, this review has the strength of describing the patterns and mechanisms of envenomation related TTC and their outcome. We also recommend that future case studies should focus on using a uniform diagnostic criterion for diagnosing and reporting TTC from episodes of stings or envenomation. Future studies should identify specific components in the venom precipitating catecholamine storm, microvascular injury, and myocardial damage[42-44]. Uniform echocardiography at diagnosis and follow up should be done consistently. All available details including imaging modalities and pattern of cardiac involvement should be consistently reported[45]. Given the rarity of these events, randomized trials on these specific etiologies might be difficult, interim optimal medical management during the envenomation and goal directed therapy for heart failure should be considered in patients who have evidence of LV dysfunction with low ejection fraction, unless complete recovery of clinical symptoms, signs, and LVEF is documented at the time of discharge from hospital. Guideline directed heart failure medications including BB and ACEI can be administered and consistent reporting of these subgroups of patients should be encouraged.

CONCLUSION

In conclusion, multiple insect stings and reptile bites related envenomation can precipitate TTC. Most envenomation related TTC has been due to bee stings and scorpion bites. Fear and anxiety related to the sting, direct catecholamine toxicity, and administration of exogenous beta-adrenergic agents have been commonly postulated to precipitate TTC in these patients. Most of these patients present with clinical presentation of ACS, ST elevation, and elevated troponin. Most of these patients also fulfill at least 3 out of 4 criteria of Mayo clinic criteria for TTC. The most common type of TTC in these patients is Apical, which improves following medical management. One third of these patients were treated with ACEI and BB with reported improvement in outcome.

ARTICLE HIGHLIGHTS

Research background

Multiple different physical, emotional and iatrogenic stressors have been known to precipitate stress induced cardiomyopathy also called takotsubo cardiomyopathy (TTC).

Research motivation

Rarely TTC has been reported in patients following an episode of acute envenomation secondary to insect stings and reptile bites.

Research objectives

This review aimed to narrate the current literature on the patterns, mechanisms, and outcomes of envenomation induced TTC.

Research methods

This review included all studies on "TTC" and "envenomation" published in PubMed, Google Scholar,

and Reference Citation Analysis databases before June 2022. Articles had to have a distinct diagnosis of TTC with Revised Mayo Clinical Criteria and documented envenomation.

Research results

Envenomation related TTC was reported from all over the world. The reports of envenomation induced TTC were reported mostly following a bee sting, scorpion sting, and snake envenomation. Fear and anxiety related to the sting, direct catecholamine toxicity, and administration of exogenous beta-adrenergic agents were postulated to precipitate TTC in these patients. Most patients presented with a clinical picture of acute coronary syndrome (ACS), ST elevation, and elevated troponin. Echocardiographic evidence of Apical TTC was noted in most of the patients. Almost all of these patients had clinical improvement following optimal management.

Research conclusions

Envenomation following multiple insect stings and reptile bites can precipitate TTC. Most reported envenomation related TTC has been due to bee and scorpion stings. Common mechanisms causing TTC following envenomation are fear, anxiety, and stress. Most of these patients present with clinical presentation of ACS. The most common type of TTC in these patients is Apical, which improved following medical management.

Research perspectives

Multiple envenomations following insect stings and reptile bites can cause TTC. Worldwide bee stings, wasp stings, scorpion stings, snake bites, spider bites, and jellyfish stings are the commonly reported precipitators of this cardiomyopathy. Multiple mechanisms have been postulated to cause this of which fear, anxiety, and stress of envenomation are the predominant ones. Patients usually present with a clinical presentation of ACS. Echocardiography commonly shows an apical pattern of cardiomyopathy. This cardiomyopathy improves with medical management.

FOOTNOTES

Author contributions: Mishra AK, George AA, Hadley M planned and formulated the study; GeorgeAA, John KJ, ArunKumar P, Dasari M, Pasha MA collected and analyzed the data; Mishra AK, George AA completed the manuscript; Mishra AK, Hadley M reviewed the manuscript and Hadley M approved the manuscript; All authors reviewed and agreed with the final content of the article.

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Cardiac arrest and cardiopulmonary resuscitation in “hostile” environments: Using automated compression devices to minimize the rescuers’ danger

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Abstract

Mechanical automated compression devices are being used in cardiopulmonary resuscitation instead of manual, “hands-on”, rescuer-delivered chest compressions. The -theoretical- advantages include high-quality non-stop compressions, thus freeing the rescuer performing the compressions and additionally the ability of the rescuer to stand reasonably away from a potentially “hazardous” victim, or from hazardous and/or difficult resuscitation conditions. Such circumstances involve cardiopulmonary resuscitation (CPR) in the Cardiac Catheterization Laboratory, especially directly under the fluoroscopy panel, where radiation is well known to cause detrimental effects to the rescuer, and CPR during/after land or air transportation of cardiac arrest victims. Lastly, CPR in a coronavirus disease 2019 patient/ward, where the danger of contamination and further serious illness of the health provider is very existent. The scope of this review is to review and present literature and current guidelines regarding the use of mechanical compressions in these “hostile” and dangerous settings, while comparing them to manual compressions.

Key Words: Automated compression devices; Cardiopulmonary resuscitation; Cathlab; Computed tomography; Transfer; COVID-19

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Core Tip: The use of automated compression devices in ‘hostile’ environments, both in in- and out-of-hospital cases of cardiac arrest, seems to be beneficial both regarding compressions’ quality but especially the rescuers’ safety. So far, while experimental data is extensive, real-life studies examining their use in non-friendly situations are still limited. Since high-quality cardiopulmonary resuscitation remains the key to a successful resuscitation, their use such difficult and “hostile” situations should be seriously taken into consideration. Noteworthy, such a use is indeed implied by guidelines.

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INTRODUCTION

Cardiopulmonary resuscitation (CPR) is the pillar of cardiac arrest treatment. High numbers of people sustain cardiac arrest both inside and outside of the hospital every year[1] thus, making the need for high-quality CPR crucial, in order to save human lives.

The cornerstone of high-quality CPR is effective chest compressions (CC). The characteristics of great-quality CCs are proper rate, adequate depth, full chest recoil, and minimal interruptions[2]. However, during the highly demanding resuscitation setting optimal quality of CCs is not always achieved. Rescuer exhaustion is the main reason for suboptimal CCs, as compressions are extremely demanding and tiring for the providing rescuer. In a study of manual compressions, the vast majority of rescuers reported serious back discomfort, mostly related to the duration of CPR, while approximately 20% of the rescuers suffered back injury or reported a prolapsed-disk diagnosis[3].

Besides operator exhaustion, hostile settings related to cardiac arrest are often the reason for CCs of suboptimal quality. Those settings include but are not limited to, resuscitation in a moving ambulance during patient transportation, inside the computed tomography (CT) scanner, or in the cardiac Catheterization Laboratory (CathLab). Especially for the CathLab, it is not only difficult for the operator to perform high-quality CCs due to the existence of the equipment, but it is also very dangerous, due to the hazardous ionizing radiation.

Mechanical automated chest compression devices (ACDs) implement all the necessary qualifications to solve all the aforementioned problems and have been implemented in clinical practice. Many studies, reviews, and meta-analyses have contemplated the use of ACDs in the clinical setting of a cardiac arrest, presenting both the upsides of their use and the potential obstacles. ACDs can deliver high-quality compressions, of consistent rate and depth, lasting up to one hour when disconnected from their energy source[4,5].

There are mainly two device types of ACDs, based on the compressions' delivery style (Figure 1). The first type is piston-driven (PD) (Lucas® Stryker Medical, United States, Life-Stat® Michigan Instruments, United States) –thus applying anteroposterior thrust on the sternum. A recent study showed that the use of a piston-driven ACD (which uses a suction cup) is associated with higher coronary perfusion pressure[6]. The second type of ACD uses a load-distribution band (LDB) (Autopulse® Zoll Medical Corp, United States) and distributes the force applied to the patients' torso more evenly[7]. Both types have been studied in the settings of both the in-hospital cardiac arrest (IHCA) and the out-of-hospital cardiac arrest (OHCA) and they seem to be more beneficial in the setting of IHCA[7]. A novel idea, however, is that they can be of great value in a 'non-friendly' setting of a cardiac arrest, either IHCA or OHCA. In this review, we present current data and literature regarding the implementation of ACDs in cardiac arrest in a 'hostile' environment.

IN-HOSPITAL CARDIAC ARREST

The use of ACDs in the hospital environment (Figure 1) combines various advantages. The devices can be deployed fast, and they solve the problem of energy loss, as the in-hospital hospital-bed mattresses tend to absorb up to 40% of the force produced during chest compressions[8]. They are easier to use and considerably less invasive than the Extracorporeal Membrane Oxygenation that is used in cardiac arrest settings, and they additionally require easier training[9]. Furthermore, the infrastructure of the hospital environment is highly advanced, offering high-quality post-resuscitation care, a well-trained resuscitation team, very efficient airway management, and minimized response times; thus, in-hospital setting CPR, assisted by ACDs, can offer a superior, more organized peri-arrest care to patients. So far, data indicated that the use of ACDs in the IHCA setting can be beneficial when compared to manual cardiac compressions, although further data could elucidate more on the standing debate[7].

However, although the ACDs can offer a sustainable solution to the very important constant-high-quality-compressions problem, they can pose limitations. Patient safety has been studied, and patient injuries (such as rib fractures, liver lacerations, or vertebral body fractures) have sporadically been reported[9]. Furthermore, device failure has also been reported[10,11]. A learning curve required for the correct use and placement of the devices, with minimum interruptions of the ongoing manual compressions, has also been brought to attention[10]. The randomized COMPRESS-RCT study[12], although prematurely terminated due to unfavorable outcomes in the use of a certain ACD type (Lucas) in the hospital environment, did accentuate important aspects and limitations regarding the implementation of efficient ACD-study protocols. Hospital survival was low, while the identified problems were delays in the intra-arrest randomization, non-superior compressions quality in the Lucas arm, and low overall recruitment[12].

In-hospital 'hostile' environment

Radiation exposure: Despite the limitations arising from using ACDs in the hospital environment, data suggest that their use in special settings and non-friendly situations is beneficial and even suggested. More specifically, although improved techniques, equipment, and training led to a fall in cardiac arrest cases in the cardiac cath lab[13], prolonged CPR may still be required[13]. The presence of the equipment as well as the ionizing radiation constitute a 'hostile' environment. Radiation exposure during manual CCs is a major concern, as accumulated doses over time have been associated with multiple health hazards[14]. As a result, the protection of the rescuers from radiation should be a priority. The use of ACDs in the CathLab can substitute manual compressions, thus eliminating the need for extra personnel during the resuscitation process. Furthermore, ACDs can offer good-quality compressions during the ongoing catheterization process (*i.e.* primary PCI), as they are greatly translucent[15]. The Lucas device has been reported to allow free movement of the radiation detector and allow all views during catheterization, except for the straight anteroposterior[16]. The device compressions do not affect the interventions during catheterization, although minor interruptions for coronary stenting may be warranted[16]. Although the initial device deployment delay has been reported as a drawback, the time needed can be reduced to a median of seven seconds with proper staff training[17]. So far, the Lucas device has been mainly studied in the CathLab in the form of case reports. During PCI arrest, it has been shown that the device, when compared to manual CCs, has better outcomes in terms of both return of spontaneous circulation (ROSC) and survival rates at hospital discharge[18]. The blood pressure levels that the device can maintain during resuscitation are also of vital importance[19]. The device can also assist the resuscitation process as it can be used during the transportation of the patient to the cath lab. A study contemplated that better ROSC rates are achieved for patients transferred to the CathLab with ongoing mechanical compressions[20]. In the event of PCI, a Lucas case series argued that the device was beneficial for patients[16]; Autopulse case reports also argue that uninterrupted visualization during catheterization is achieved thus allowing all interventions [21,22]. On the other hand, a study stated that ongoing CPR upon arrival at the CathLab and continuous mechanical compressions for over 10-20 min in the CathLab were both predictive of poor outcomes[23]. Of interest, a recent study revealed that for patients undergoing PCI under mechanical compressions,

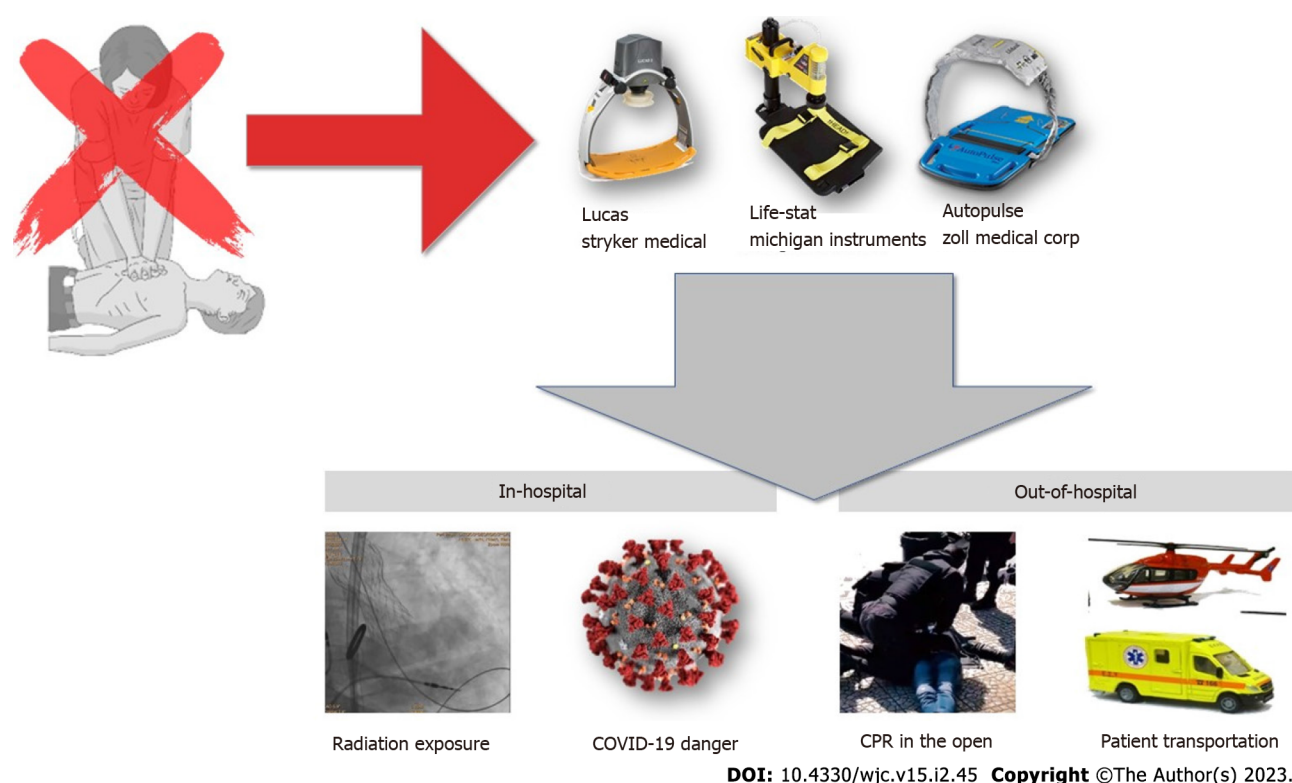


Figure 1 Automated compression devices instead of hands-on manual cardiopulmonary resuscitation to minimize the rescuers' danger in in-hospital and out-of-hospital cardiac arrest resuscitation. COVID-19: Coronavirus disease 2019; CPR: Cardiopulmonary resuscitation.

mild hyperkalemia might be beneficial, identifying the potassium (KCl) concentration of 5.1 mmol/L to be the optimal cut-off, for the prediction of survival to hospital discharge[24].

The topic of ACD compressions inside the CT scanner has not been studied as extensively. So far, a case report of a pulmonary embolism that sustained cardiac arrest suggested that contrast-enhanced CT imaging with ongoing chest compressions is feasible after cardiac arrest[25]. Experimental data suggest that an ECG-triggered protocol allows almost artifact-free chest evaluation during mechanical compressions[26].

Coronavirus disease 2019 danger: CPR is a complex intervention, requiring extensive skills from quite a few knowledgeable healthcare providers. The risks of viral transmission through aerosol and droplet generation during CPR have not yet been fully identified, but a transmission can be detrimental to these valuable and scarce CPR team members[33]. On the other hand, patients with coronavirus disease 2019 (COVID-19) who require intubation and ventilation have extremely poor survival rates[27-29]. The best way to express this concept has already been written, and we also stand for[30]: This pandemic has changed the risk-benefit balance for CPR: from "there is no harm in trying" to "there is little benefit to the patient and potentially significant harm to staff".

During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus pandemic, the advanced life support algorithm must be followed with extreme caution to personal protection, especially regarding personal protective equipment, airway management, and compressions, and an ACD should be used, as soon as the device is available[31-32]. The high contagiousness of the SARS-CoV-2 virus changed significantly every day clinical practice and the CPR process. Occupational exposure of healthcare and other personnel to all airborne transmitted pathogens is not by any means negligible but can be minimized through a high index of suspicion, preparedness, and appropriate protection[33].

Regarding changes and additions to the already existing OHCA protocol, it is suggested that cardiac arrest recognition should be performed by searching for the absence of pulse and normal breathing while completely avoiding listening to or feeling breath sounds, by placing one's ear and cheek near the victim's mouth[31]. A cloth should also be placed on the unconscious victim's mouth during the resuscitation process. CPR should be performed only through chest compressions and quick and effective use of an AED is of vital importance without any additive risk to the resuscitation process. Hand sanitizing is an efficient alternative to soap-based hand washing, which is advised immediately after the process[31,34].

Regarding the IHCA CPR process, advanced airway management is mainly endotracheal intubation should be performed by the most trained and experienced physician, as the risk of cross-infection is high. The use of PPE is highly advised in the hospital setting, while participants in the CPR process

should be trained on how to correctly handle, put on and safely remove all PPE equipment[31,34]. As the need for protection through PPE use may delay CPR initiation for patients with COVID-19, "donning/doffing" training can help minimize those delays. Regarding the algorithm, adjustments have been made to accommodate those newly surfaced needs; no CPR should commence without the use of PPE, and for shockable rhythms, up to three back-to-back shocks are allowed to restore the patient's rhythm. CPR should start only with chest compressions, while defibrillation for all shockable rhythms should be given with only minimal delays[31,32].

A mechanical compression device should be used as soon as it becomes available in any setting that allows their safe and efficient use, especially in the need for prolonged CPR[7,34]. The obvious advantage, besides the ones already discussed earlier, is the need for one less –COVID-19 exposed– person in the CPR team. Furthermore, this at-risk person would be the one the closest for the longest duration, to the SARS-CoV-2 infected victim. Therefore, automated chest compression devices have been proposed to be used during COVID-19 CPR[35,36]. When they are not available it was discussed to reduce the duration of the CPR cycles from two to one minute as the quality of chest compressions can deteriorate fast if the rescuer wears PPE[33,35,36].

OUT-OF-HOSPITAL CARDIAC ARREST

The ACDs have been studied quite extensively in the setting of an OHCA (Figure). So far the results are mixed, as a study suggested that a load distribution band presents worse neurological outcomes and worse survival when compared to manual CCs; however, a meta-analysis concluded that ACDs are associated with better ROSC outcomes, provided that the staff applying them is sufficiently trained[37,38]. In the same meta-analysis, load-distribution devices outperformed piston-driven devices, a finding that may be associated with the necessary pause for application[38,39]. Interestingly, in another meta-analysis of survival to thirty days, it was found that survival to hospital admission or survival to discharge was comparable between the two arms (manual CCs and the Lucas device), although manual CPR proved superior to the Autopulse device; regarding patient safety, manual CCs were superior to the devices[7,40].

Out-of-hospital 'hostile' environment

The OHCA setting is at its core the most challenging one. Compressions, of undetermined quality, are most often initiated by bystanders after significant delays. ACDs, brought by the rapid response EMS (emergency medical system *e.g.* ambulances or motorcycles) can offer continuous high-quality compressions, on the scene of a cardiac arrest, while defibrillation can take place simultaneously; in this way, quality is maintained at a high standard and the need for pauses is minimized[38]. However, in the randomized ASPIRE trial the deployment of the load-distribution device created a delay of 2.1 min to the first shock in ventricular fibrillation. As a result, the trial was prematurely terminated due to neurological and survival adverse outcomes[37]. In another randomized trial no difference regarding early survival between the manual and the mechanical arm was noted[41]. Prolongation of time to first shock was also prominent in CIRC and LINC trials[42,43]. Applicability factors, such as body weight, have also been highlighted and they may also cause delays[42,43]. In a recent study, the mechanical (Lucas) arm did not show added benefit regarding the ROSC rate, but its use did not lead to a higher risk of traumatic injury. The same study suggested that ACDs may be more useful in cases of delayed ambulance response times, or events happening in remote locations[44]. However, liver lacerations, occasionally associated with massive post-resuscitation hemorrhage, have been twice reported in the Lucas arm along with one Autopulse-associated tension pneumothorax that caused an air embolus[45]. The pre-hospital use of ACDs has been associated with worse neurological outcomes to hospital discharge when compared to manual compressions[46,47]. The LINC trial randomized SCA victims into manual compression *vs* Lucas-mediated compressions on the scene and showed no differences in either four-hour survival, six-month survival, or neurological outcomes between the two arms[43]. Similarly, in the PARAMEDIC trial (2:1 randomized trial of manual CCs: Lucas) no superiority of the device was proven in the primary outcome of thirty-day survival[48]. Furthermore, in the randomized CIRC trial (LDB device *vs* manual CPR) the two arms of the study displayed similar survival rates and neurological outcomes to discharge[42]. However, ACDs have been proposed to improve both pre-hospital and admission-to-hospital survival, especially when operated by a two-member paramedic team, the victim is young and the arrest takes place in a city center[5,7].

Cardiac arrests that are treated within Emergency Departments are considered cases of OHCA[49]. Patients that are treated for cardiac arrest in the Emergency Department are in the vast majority, patients that sustained a cardiac arrest outside of the hospital and were transferred with continuous compressions to the ED; thus, the resuscitation process can be quite challenging and may pose difficulties. Research has not definitively concluded regarding the effect of ACDs in ED departments. While a large randomized trial from Japan concluded that the mechanical arm of patients treated in the ED for an OHCA presented worse survival outcomes possibly due to deployment pauses[50], another randomized trial examined the effect of trained personnel operating LDB devices and concluded that

better CPR quality is delivered to the patient, with shorter interruption times during deployment of the device[51].

However, the most challenging setting is during patient transportation. Cardiac arrest patients are sometimes transferred to the hospital with ongoing CPR, of doubtful quality[52] or they may arrest en route to the hospital. Rather conclusive data showed manual compressions during transfer to be ineffective for the patient and unsafe for the providing staff[53]. Various difficulties -including but not limited to uneven pavements and tight spaces and doorways during the victim transfer to the ambulance, sudden stops, accelerations, turns, and confined ambulance space, adversely affect delivered CPR quality[7]. Those are the exact settings in that an ACD may effectively assist the resuscitation process and favorably alter its course. An observational study found that ACDs use, contrary to manual CPR, minimizes compression interruptions during the extrication of a patient, except for the deployment pause[54]. Research has presented beneficial outcomes so far for the use of ACDs of both types during transportation, in terms of higher ROSC, survival to hospital admission, and quantitative CPR quality irrespective of transportation conditions or vehicle type[55,56]. However, regarding survival and outcomes, the heterogeneity of the included trials still poses a significant challenge to the generalization of the results. In every case, the vast majority of studies highlight the need for proper personnel training. The Danish cardiac arrest registry reported a marked reduction in mortality, when resuscitated OHCA victims were transferred to CathLab-capable tertiary centers rather than when being transferred to the nearest district hospital, irrespective of the overall distance the resuscitated victim had to travel by ambulance[57]. During the resuscitation process, an OHCA victim may need to undergo a large distance transportation by ambulance. ACDs may facilitate the process, thus having a place in the resuscitation process during transportation. Experimental data, using manikins, has concluded that the Lucas-2 device, in use by experienced hands, is a good alternative to manual compressions during a rescue-helicopter transfer and it complies -as a system- with all European Resuscitation Council (ERC) recommendations[58]. A randomized study, also using manikins, concluded that the Lucas system increased CPR quality and reduced pauses during helicopter rescue, but prolonged the time interval to first defibrillation[59]. Similarly, regarding transportation down stairwells and through tight spaces, experimental data proposing a new Lucas-2 system with shoulder strap fixation during non-supine stretcher transportation, allowed uninterrupted compressions, while yielding better chest compression fractions for the overall resuscitation period[60]. A randomized triple cross-over experimental study in an alpine setting revealed that Corpuls and Lucas-3 maintained the adequate quality of CPR during transportation and the piston was placed correctly even during challenging terrestrial transport[61]. Furthermore, a manikin-based study contemplated that while ambulance speed can affect manual compressions quality during transportation, devices of both types can resolve quality issues[62]. A similar experimental study showed good device performance during transport on a soft stretcher or gurney involving a stairwell, trips with a turntable ladder, a rescue basket, and an ambulance including loading/unloading of the patient, but underlined the need to check patient-device connection and stability[63]. All experimental studies highlight the need for real-world data. A retrospective observational study in Switzerland concluded that the implementation of mechanical compression devices in helicopter transportation can be beneficial, especially for non-trauma patients[64]. However, a recent German registry reported that mechanical devices are not associated with better survival rates when used during transport, but are associated with better survival in prolonged resuscitation. They are, however, associated with worse survival when a fibrinolytic was used; rescuer safety could be a sufficient reason for their use[65].

The use of mechanical compression devices has been used as a bridge to uncontrolled organ donation [66]. Although both ethical and clinical challenges are raised, the use of ACDs can reduce the time of warm ischemia[67]. During the insertion of extracorporeal CPR (cardiopulmonary bypass), the use of an ACD may be useful and it is applied with positive results, although data are still scarce[7]. In the case of refractory cardiac arrest, ethical dilemmas require very careful consideration[68].

GUIDELINES

Regarding current guidelines for in-hospital practice, the American Heart Association in 2010 stated that piston-driven or load-distributing band chest compression devices may be considered in patients undergoing PCI or CT scanning, for prolonged resuscitation (class IIa) or when manual resuscitation is challenging (class IIb)[69].

The ERC in its 2015 guidelines strongly recommended the use of ACDs in the cath lab during coronary interventions[70]. It is mandatory for trained personnel to implement the use of such devices, but there is insufficient evidence to support or refute their routine use in cardiac arrest[7].

In the latest (post COVID-19 pandemic) 2021 ERC guidelines the use of ACDs is considered if high-quality manual CPR is not practical or is dangerous for the provider[71].

CONCLUSION

The use of ACDs in 'hostile' environments, both in in- and out-of-hospital cases of cardiac arrest, seems to be beneficial both regarding compressions' quality and especially the rescuers' safety (Figure 1). So far, while experimental data is extensive, real-life studies examining their use in non-friendly situations are still limited. Since high-quality CPR remains the key to successful resuscitation, their use in such difficult and "hostile" situations should be seriously taken into consideration. Noteworthy, such use is indeed implied by guidelines.

FOOTNOTES

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Retrospective Cohort Study

Utility of short-term telemetry heart rhythm monitoring and CHA₂DS₂-VASc stratification in patients presenting with suspected cerebrovascular accident

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Specialty type: Cardiac and cardiovascular systems**Provenance and peer review:** Invited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
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Inpatient telemetry heart rhythm monitoring overuse has been linked to higher healthcare costs.

AIMTo evaluate if CHA₂DS₂-VASc score could be used to indicate if a patient admitted with possible cerebrovascular accident (CVA) or transient ischemic attack (TIA) requires inpatient telemetry monitoring.**METHODS**A total of 257 patients presenting with CVA or TIA and placed on telemetry monitoring were analyzed retrospectively. We investigated the utility of telemetry monitoring to diagnose atrial fibrillation/flutter and the CHA₂DS₂-VASc scoring tool to stratify the risk of having CVA/TIA in these patients.**RESULTS**

In our study population, 63 (24.5%) of the patients with CVA/TIA and telemetry monitoring were determined to have no ischemic neurologic event. Of the 194 (75.5) patients that had a confirmed CVA/TIA, only 6 (2.3%) had an arrhythmia detected during their inpatient telemetry monitoring period. Individuals with a

confirmed CVA/TIA had a statistically significant higher CHA₂DS₂-VASc score compared to individuals without an ischemic event (3.59 *vs* 2.61, *P* < 0.001).

CONCLUSION

Given the low percentage of inpatient arrhythmias identified, further research should focus on discretionary use of inpatient telemetry on higher risk patients to diagnose the arrhythmias commonly leading to CVA/TIA. A prospective study assessing event rate of CVA/TIA in patients with higher CHA₂DS₂-VASc score should be performed to validate the CHA₂DS₂-VASc score as a possible risk stratifying tool for patients at risk for CVA/TIA.

Key Words: Telemetry monitoring; CHA₂DS₂-VASc score; Arrhythmia; Atrial fibrillation

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Core Tip: Inpatient telemetry monitoring can be a costly resource in hospitals. Inappropriate use of this clinical tool only increases burgeoning healthcare costs both to the patient and the hospital. Atrial fibrillation is a risk factor for stroke which is why telemetry is indicated for 24-48 h after a cerebrovascular accident. However, telemetry for all patients for this short period of time can be non-diagnostic. Our study shows telemetry can be better utilized in patients with higher risk factors for atrial fibrillation as seen with higher CHA₂DS₂-VASc scores, and this stratification of telemetry monitoring may allow appropriate allocation and use for patients in whom benefit will be derived.

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INTRODUCTION

Non-intensive-care inpatient telemetry monitoring is a widely used observation tool in cardiovascular medicine. The use of non-intensive-care telemetry is widely utilized in the setting of suspected cerebrovascular accident (CVA) or transient ischemic attack (TIA)[1]. One of the most common causes of CVA/TIA is atrial fibrillation (AFib). The 2018 stroke guidelines states that cardiac monitoring is recommended for atrial fibrillation as part of in-hospital secondary prevention. Cardiac monitoring should be performed for at least the first 24 h[2]. Telemetry monitoring is utilized in these cases to assess whether undiagnosed atrial fibrillation was the cause of their ischemic event. Past studies have demonstrated that the use of telemetry inpatient post-stroke to assess for the presence of these arrhythmias may contribute to an increased healthcare cost burden[3,4].

The overutilization of telemetry monitoring has been a frequent discussion regarding our nation's ever-increasing healthcare costs. The American Board of Internal Medicine's 2013 Choosing Wisely campaign emphasized avoiding inappropriate continuous use of telemetry monitoring in an attempt to decrease the cost of care and number of false positive errors which could negatively impact patient care [5]. In 2004, the American Heart Association (AHA) first issued a statement on telemetry monitoring indications in intensive care settings[3]. Since then, updated recommendations in 2017 have been published by the AHA in order to address the overuse of arrhythmia monitoring as well as other issues. The AHA recommends monitoring arrhythmias for 24-48 h after a stroke[6]. Dhillon *et al*[7] formulated inclusion and exclusion guidelines for which patients should need telemetry monitoring outside of the intensive care unit in an effort to decrease costs from overuse. The efficacy of these guidelines was tested in a retrospective study of 562 patients and found that no patient that was not indicated for telemetry had a clinically significant arrhythmia. This suggests that it is possible to narrow the indications for which patients should be on telemetry monitoring.

As atrial fibrillation is a common etiology of CVA/TIA, CHA₂DS₂-VASc is a clinical scoring tool used to evaluate the one-year risk of having a thromboembolic event in a non-anticoagulated patient with nonvalvular atrial fibrillation[8,9]. This clinical scoring tool uses age, sex, congestive heart failure, hypertension, thromboembolism history, vascular disease, and diabetes as risk factors, and assigns points to each risk factor. If the total score is greater than or equal to 2 points, current literature states that an oral anticoagulation strategy should be employed to reduce the annual risk of stroke[10]. In our study, we sought to evaluate if CHA₂DS₂-VASc scoring could be used to risk stratify patients with a possible diagnosis of CVA or TIA into telemetry monitoring indicated *vs* nonindicated group.

MATERIALS AND METHODS

A retrospective cohort study was performed at a tertiary-care safety-net community hospital between January 2014 and December 2016 with a total of 257 consecutive patients admitted with suspected CVA or TIA. Criteria for patient inclusion in the study was an admission diagnosis of CVA or TIA, lack of pre-existing atrial fibrillation, and admission with telemetry monitoring employed. Telemetry monitoring was performed for at least 24 h, consistent with current standards of care. CVA or TIA was confirmed *via* current diagnostic guidelines (including patient evaluation by the neurology consulting service and/or non-invasive brain imaging studies). The CHA₂DS₂-VASc score was calculated for each patient. Independent variable *t*-tests were performed using SPSS Statistics, version 16.0, when comparing patients with and without a final diagnosis of CVA or TIA.

RESULTS

The demographics of our study population can be seen in Table 1 and includes age, ethnicity, sex, body mass index, smoking, and history of dyslipidemia. Of the 257 patients included in our study, 75.5% (*n* = 194) patients had a confirmed ischemic event (CVA or TIA). Of these patients, only 2.3% (*n* = 6) were found to have atrial fibrillation or atrial flutter during their inpatient telemetry monitoring.

The mean and median CHA₂DS₂-VASc scores were found to be significantly different between patients that did and did not have a confirmed CVA/TIA (Table 2). The mean CHA₂DS₂-VASc score was higher in the group with confirmed CVA/TIA than in the group without an ischemic event (3.59 *vs* 2.61, *P* < 0.001). The median score was also found to be higher, with median score of 4 in patients with CVA/TIA compared to median score of 2 in patients without an event (*P* < 0.001).

DISCUSSION

Atrial fibrillation affects over 5 million people in the United States and increases the risk of stroke by 5-fold compared to the rest of the population[10,11]. The initial presentation of atrial fibrillation can be asymptomatic or subclinical[12]. The economic burden of people with previously unknown and asymptomatic atrial fibrillation is estimated to be over 3 billion dollars[13,14]. Of those with atrial fibrillation, female sex is an established risk factor for stroke, cognitive dysfunction, and dementia[15-17]. Patients diagnosed with atrial fibrillation with a concerning CHA₂DS₂-VASc score should be treated with anticoagulation therapy to avoid major adverse cardiac and cerebrovascular events (MACCE). The AFIRE trial showed a temporal association between major bleeding and MACCE events, demonstrating the importance of optimal antithrombotic therapy and managing bleeding risk in patients with atrial fibrillation and stable coronary artery disease[18]. Direct oral anticoagulants are shown to be at least as efficacious and safe as warfarin among patients with non-valvular atrial fibrillation[19]. DOACs are shown to have lower MACE rates *vs* warfarin[20].

The CHA₂DS₂-VASc scoring tool has been validated to estimate the patient's stroke risk with atrial fibrillation[21,22]. Limited research has been done to demonstrate its utility in predicting the risk of ischemic stroke in patients without atrial fibrillation. Our findings show that there is a statistically significant increase in the CHA₂DS₂-VASc score for patients with a confirmed ischemic event (3.59 *vs* 2.61, *P* < 0.001). Patients with ischemic events had their CHA₂DS₂-VASc score clustered on the higher end of the scores. Similarly, those patients without an ischemic event had their scores clustered towards the lower end of the score.

Of the 75.5% (*n* = 193) of patients that had a confirmed CVA/TIA, only 2.3% (*n* = 6) of these were found to have newly diagnosed atrial fibrillation. In a 2016 meta-analysis, Demeestere *et al*[23], detected atrial fibrillation in only 2.2% of patients with large-vessel CVA, and 2.4% of patients with small-vessel CVA. Moreover, a 2016 meta-analysis by Korompoki *et al*[24], found that atrial fibrillation was detected in 4% of patients post-TIA. These detection rates increased over time with an increased duration of monitoring. A meta-analysis of 32 studies showed the atrial fibrillation detection after CVA/TIA was better detected with more prolonged periods of monitoring compared to standard telemetry[25]. A study conducted by Simova *et al*[1] showed ECG telemonitoring after cryptogenic stroke or TIA only resulted in detection of AF in 10 of 36 patients (27%). The therapeutic implication of this finding suggests the benefit of routine prolonged ECG monitoring in this group as opposed to short-duration (24-48 h) inpatient telemetry.

The yield of telemetry use in this patient population is low, despite atrial fibrillation being a common cause of CVA/TIA. This presents a possible area in which we can safely reduce the amount of telemetry monitoring to only 24 h while inpatient or even possibly forgo monitoring completely in very low risk patients. Given the burden atrial fibrillation has on the general population, novel methods of screening are available and can be more cost effective[26]. Employment of wearable wireless continuous electrocardiographic (EKG) patches allows for one-to-two-week telemetry monitoring compared to the traditional 24-48-h Holter monitoring. This patient friendly approach can transmit telemetry recordings

Table 1 Demographics of the study population, *n* (%)

Variable	Confirmed CVA/TIA (<i>n</i> = 194)	Absent CVA/TIA (<i>n</i> = 63)
Mean age (yr)	67.54	58.54
<i>Ethnicity</i>		
White	105 (54.12)	32 (50.79)
Black	70 (36.08)	22 (34.92)
Other	19 (9.80)	9 (14.29)
<i>Gender</i>		
Men	93 (47.94)	24 (38.10)
Women	101 (52.06)	39 (61.90)
Mean BMI	27.36	29.10
Dyslipidemia	108 (55.70)	22 (34.90)
Smoking	54 (27.83)	14 (22.20)

CVA: Cerebrovascular accident; BMI: Body mass index; TIA: Transient ischemic attack.

Table 2 CHA₂DS₂-Vasc scores of patients with confirmed cerebrovascular accident /transient ischemic attack vs absent cerebrovascular accident /transient ischemic attack, *n* (%)

CHA ₂ DS ₂ -Vasc	Confirmed CVA/TIA (<i>n</i> = 194)	Absent CVA/TIA (<i>n</i> = 63)
0	11 (5.70)	4 (6.35)
1	26 (13.40)	19 (30.16)
2	24 (12.37)	10 (15.87)
3	29 (14.95)	15 (23.81)
4	42 (21.65)	4 (6.35)
5	26 (13.40)	4 (6.35)
6	20 (10.31)	4 (6.35)
7	11 (5.67)	3 (4.76)
8	5 (2.55)	0 (0.00)
Mean	3.59	2.61 ^a
Median	4	2 ^a

^a*P* value < 0.001 on Mann-Whitney *U* Test. CVA: Cerebrovascular accident; TIA: Transient ischemic attack.

to health care providers for real time detection of cardiac events[27]. Studies have shown that the adhesive patch monitors detect more events than the conventional Holter monitor[28]. Recent developments have shown that wearables, such as smart watches, are an effective method of screening for atrial fibrillation in the general population. The Apple Heart Study used the Apple Watch in concurrent use with the current standard of diagnosing paroxysmal arrhythmias, the EKG patch, and showed that the positive predictive value of the tachograms was 0.71 (95%CI: 0.76-0.92)[29]. In addition to smart watches, portable single lead EKGs and phone applications can also be used to record palpitation events[26]. The Kardia Band designed by AliveCor mimics lead I and was designed to be used as an accessory for the Apple Watch. It was able to correctly detect atrial fibrillation with a sensitivity of 93% (95%CI: 86%-99%) and an 84% specificity (95%CI: 73%-95%)[30]. The Cardio Rhythm app for the iPhone uses the phone's camera to act as a light sensor in order to obtain heart rate measurements. The app is not used for continuous rhythm monitoring but can be used for sporadic heart rate checks or during symptoms of palpitations. It was able to detect atrial fibrillation with a sensitivity of 92.9% (95%CI: 77%-99%) and a specificity of 97.7% (95%CI: 97%-99%)[31]. Significant gaps of knowledge remain regarding the optimal length and yield of long-term inpatient monitoring beyond the recommended 24-h inpatient telemetry monitoring[32]. Future research should be done to evaluate

the percentage of detected atrial fibrillation in patients with confirmed ischemic events with outpatient cardiac rhythm monitoring of different lengths of time.

A total of 24.5% ($n = 63$) of patients in this study that were placed on telemetry monitoring for suspected CVA/TIA did not have a confirmed ischemic event per neurology evaluation. Given that the use of telemetry requires additional staff and hospital resources, increased cost burden, and is a limited resource in hospitals, efforts should be made to limit its use. Our findings suggest that the CHA₂DS₂-VASc score may be a valuable scoring tool to help risk stratify patients at risk for CVA/TIA and could thereby reduce the need of inpatient telemetry monitoring in patients suspected to have a CVA/TIA that have a low CHA₂DS₂-VASc score. Our study was limited by the small sample size of the study group. Additional studies with a larger sample size would allow for more statistical analysis of the utility of CHA₂DS₂-VASc in predicting CVA/TIA. Risk stratifications of patients can help reduce the use of unnecessary telemetry monitoring, especially in resource-limited hospitals.

CONCLUSION

Inpatient telemetry monitoring can be a costly resource in hospitals. Inappropriate use of this clinical tool only increases burgeoning healthcare costs both to the patient and the hospital. Atrial fibrillation is a risk factor for stroke which is why telemetry is indicated for 24-48 h after a CVA. However, telemetry for all patients for this short period of time can be superfluous and costly. Our study shows telemetry can be better utilized in patients with higher risk factors for atrial fibrillation as seen with higher CHA₂DS₂-VASc scores, and this stratification of use of telemetry monitoring will allow appropriate allocation and use for patients in whom benefit will be derived.

ARTICLE HIGHLIGHTS

Research background

Non-intensive-care inpatient telemetry monitoring is a widely used observation tool in cardiovascular medicine.

Research motivation

Inpatient telemetry heart rhythm monitoring overuse has been linked to higher healthcare costs.

Research objectives

Our study aimed to evaluate if CHA₂DS₂-VASc score could be used to indicate if a patient admitted with possible cerebrovascular accident (CVA) or transient ischemic attack (TIA) requires inpatient telemetry monitoring.

Research methods

A retrospective cohort study was performed at a tertiary-care safety-net community hospital between January 2014 and December 2016 with a total of 257 consecutive patients admitted with suspected CVA or TIA. Telemetry monitoring was performed for at least 24 h, consistent with current standards of care. CVA or TIA was confirmed *via* current diagnostic guidelines (including patient evaluation by the neurology consulting service and/or non-invasive brain imaging studies). The CHA₂DS₂-VASc score was calculated for each patient. Independent variable *t*-tests were performed using SPSS Statistics, version 16.0, when comparing patients with and without a final diagnosis of CVA or TIA.

Research results

Individuals with a confirmed CVA/TIA had a statistically significant higher CHA₂DS₂-VASc score compared to individuals without an ischemic event (3.59 *vs* 2.61, $P < 0.001$).

Research conclusions

Given the low percentage of inpatient arrhythmias identified, further research should focus on discretionary use of inpatient telemetry on higher risk patients to diagnose the arrhythmias commonly leading to CVA/TIA.

Research perspectives

A prospective study assessing event rate of CVA/TIA in patients with higher CHA₂DS₂-VASc score should be performed to validate the CHA₂DS₂-VASc score as a possible risk stratifying tool for patients at risk for CVA/TIA.

FOOTNOTES

Author contributions: Aydin T, Zeltser R, Makaryus AN performed the research; Bhuiya T and Zeltser R performed the statistical analyses in the paper; Zeltser R and Makaryus AN designed the research and contributed to the analysis; Bhuiya T, Roman S, Aydin T, Patel B, Makaryus AN, wrote the paper; Zeltser R, and Makaryus AN supervised the report.

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Safety and efficacy of balloon angioplasty compared to stent-based-strategies with pulmonary vein stenosis: A systematic review and meta-analysis

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Abstract

BACKGROUND

Pulmonary vein stenosis (PVS) is an uncommon but known cause of morbidity and mortality in adults and children and can be managed with percutaneous revascularization strategies of pulmonary vein balloon angioplasty (PBA) or pulmonary vein stent implantation (PSI).

AIM

To study the safety and efficacy outcomes of PBA vs PSI in all patient categories with PVS.

METHODS

We performed a literature search of all studies comparing outcomes of patients evaluated by PBA vs PSI for PVS. We selected all published studies comparing PBA vs PSI for PVS with reported outcomes of restenosis and procedure-related

complications in all patient categories. In adults, PVS following atrial fibrillation ablation and in children PVS related to congenital etiology or post-procedural PVS following total or partial anomalous pulmonary venous return repair were included. The patient-centered outcomes were risk of restenosis requiring re-intervention and procedural-related complications. The meta-analysis was performed by computing odds ratios (ORs) using the random effects model based on underlying statistical heterogeneity.

RESULTS

Eight observational studies treating 768 severe PVS in 487 patients met our inclusion criteria. The age range of patients was 6 months to 70 years and 67% were males. The primary outcome of the re-stenosis requiring re-intervention occurred in 196 of 325 veins in the PBA group and 111 of 443 veins in the PSI group. Compared to PSI, PBA was associated with a significantly increased risk of re-stenosis (OR 2.91, 95%CI: 1.15-7.37, $P = 0.025$, $I^2 = 79.2\%$). Secondary outcomes of the procedure-related complications occurred in 7 of 122 patients in the PBA group and 6 of 69 in the PSI group. There were no statistically significant differences in the safety outcomes between the two groups (OR: 0.94, 95%CI: 0.23-3.76, $P = 0.929$, $I^2 = 0.0\%$).

CONCLUSION

Across all patient categories with PVS, PSI is associated with reduced risk of re-intervention and is as safe as PBA and should be considered first-line therapy for PVS.

Key Words: Pulmonary veins; Pulmonary vein stenosis; Constriction; Balloon angioplasty; Stents; Drug-eluting stents

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Core Tip: 81.5% of patients with pulmonary vein stenosis undergoing a transcatheter intervention reported symptom of dyspnea. Pulmonary vein stent implantation (PSI) was superior to pulmonary vein balloon angioplasty (PBA) in preventing restenosis of the pulmonary vein. No difference in procedural related complications was noted between PSI and PBA. Differences in peri-procedural anticoagulation strategies between studies could have affected the outcome.

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INTRODUCTION

Catheter ablation for atrial fibrillation in adults involves the use of radiofrequency energy to electrically isolate the pulmonary vein[1]. As injured tissue heals scar tissue extends deeper into vein from the ostium leading to pulmonary vein stenosis (PVS). Cryoballoon ablation therapy for atrial fibrillation can have similar consequences[2]. With increased utilization of techniques aimed to reduce PVS such as antral isolation, 3-dimensional mapping and use of intra-cardiac ultrasound, the incidence of PVS has declined substantially from 20%-40% to 1%-1.5% currently[3]. In children, PVS can be primary (idiopathic) or secondary (post-surgical) following repair of total or partial anomalous pulmonary venous return[4], post pulmonary vein isolation and in Fibrosing Mediastinitis, where the patients develop severe pulmonary vein stenosis which is challenging to treat. Patients with severe PVS report symptoms of pleuritic chest pain, cough, hemoptysis and dyspnea on exertion. Untreated severe PVS can be progressive leading to irreversible lung parenchymal damage, pulmonary hypertension, heart failure and death[5].

Percutaneous intervention with balloon angioplasty (PBA) or pulmonary vein stent implantation (PSI) is the current treatment modality in adults. Re-stenosis risk after percutaneous interventions is higher in all patient categories and there is increasing adoption of stent-based strategies[6]. Available literature on this topic reports risk of restenosis with balloon angioplasty in the range of 44%-73%[6-8] and risk of re-stenosis of stent-based strategies over 16 years is 18%[8]. PVS confers poor prognosis in children and is conventionally treated with catheter intervention including PBA/PSI and/or surgery.

The former has been considered as a palliative approach. The mortality rate is as high as 47% at a median follow-up of 2 mo and re-intervention appeared to improve survival[5] and children with bare metal stents had better survival compared to drug-eluting stents (DES) and biliary atresia (BA)[9]. This may be dependent on the vessel size and on adjunctive therapy. The aim of this study is to perform a comprehensive analysis of safety and efficacy outcomes of percutaneous re-vascularization strategies of BA *vs* stent-based strategies for PVS in all patient categories.

MATERIALS AND METHODS

Protocol and registration

The protocol detailing the methods of the systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews. The current meta-analysis was performed using the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10]. Ethical review and approval were waived for this study, as our study is a meta-analysis and involves no interaction with human subjects and access to any subject identifiers.

Study identification and search strategy

We performed a comprehensive search for studies comparing PBA *vs* PSI in patient with PVSs using scientific databases (PubMed, EMBASE, Cochrane, Web of science, Scopus) from inception to December 2019. The search terms were pulmonary vein stenosis, balloon angioplasty, pulmonary balloon angioplasty, stents. The last search was run on December 31st, 2019. The authors (PA and SS) developed the search strategy along with a clinical information specialist (DA-D). The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist. Details of the search strategy are provided in the [Supplementary Table 1-PRISMA checklist](#).

Study selection

Initial screening of the search results was performed by two reviewers (PA and SS). Title and abstract screening were first performed followed by comprehensive review of the entire manuscripts. When inconsistencies in screening were found and no consensus was reached a third reviewer (RA) casted the deciding vote.

Eligibility criteria

We selected all published studies comparing PBA *vs* PSI for PVS with reported outcomes of re-stenosis and procedure-related complications in all patient categories. In adults, PVS following atrial fibrillation ablation and in children PVS related to congenital etiology or post-procedural PVS following total or partial anomalous pulmonary venous return repair are included. All types of stents are included. No restrictions on study selection based on outcomes were used. Studies which assessed stent-based strategies without PBA group, abstracts which are published without full text publications and studies lacking endpoint measures were excluded.

Data extraction and quality assessment

For all the studies included, we extracted: (1) Study participants characteristics including age, gender, imaging modality after ablation, frequency of clinical symptoms related to PVS, study's inclusion criteria; (2) types of intervention- PBA *vs* PSI, stent size, post-intervention antiplatelet therapy and follow up imaging; and (3) outcome measures including re-stenosis requiring re-intervention and procedure-related complications. Cochrane Consumers and Communication Review Group's data extraction template was used to develop a standardized data extraction sheet for screening studies. The two authors independently collected the data and kappa values were used to report agreement measures. The primary outcome was re-stenosis requiring re-intervention and the secondary outcome was major complications related to procedures including death, major adverse cardiac and cerebrovascular events, major in-hospital complications requiring prolonged hospitalization or additional therapy (*i.e.* major bleeding or vascular complication, cardiac tamponade)

Quality assessment of studies, risk of bias

The study quality of included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies as shown in [Supplementary Table 2](#) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Briefly, studies were quoted using prespecified items on patients' selection (representativeness and selection of patients, ascertainment of exposure, demonstration that outcome of interest was not present at the start of the study), comparability of cohorts based on the design or analysis, and assessment of outcomes (recording, adequacy of follow-up including length of follow up). Ratings for each item were added to provide a study quality score (maximal score, 9). Two independent reviewers (PA and SS) performed the Newcastle-Ottawa Scale grading. Discrepancies were resolved by consensus.

Method of analysis

The meta-analysis was performed by computing odds ratios (ORs) using the random effects model based on underlying statistical heterogeneity. A biomedical statistician performed the statistical review of the study. We calculated the OR and 95% confidence intervals (CIs) for each treatment effect for each study and pooled the point estimates of OR from each study using the generic inverse-variance method of Der Simonian and Laird[10,11]. Stata SE Statistical Software: Release 14.1, College Station, TX: StataCorp LP, StataCorp 2015. I^2 statistics were used to test statistical heterogeneity. The I^2 statistics describes the percentage of variation across studies that is because of heterogeneity rather than those expected by random chance [$I^2 = 100\% \times (Q-df)/Q$].

A CI for I^2 was constructed using either (1) noncentral chi-squared distribution method of Hedges and Piggott (2001) or (2) test-based method of Higgins and Thompson. The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%-50\%$, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity)[12]. Publication bias was assessed using a funnel plot and Egger's regression test[13] ($P < 0.05$ was considered significant). A summary of evidence table was created to summarize the main results (patient-centered outcomes) using the GRADE Pro tool [Guideline Development Tool (Software), McMaster University, 2015 (developed by Evidence Prime, Inc)][14]. Sensitivity analysis was performed for primary analysis through an influence analysis by omitting one study at a time.

RESULTS

Study selection

A total of 856 Citations were identified using Pubmed, EMBASE, Scopus, Web of Science, and Cochrane databases. We excluded 415 studies based on the title and abstracts. After these exclusions and screening rest of the studies in detail we found eight studies that met the inclusion criteria mentioned above. The PRISMA diagram was created for the systematic review [Figure 1](#). Kappa for agreement on full text, and abstract inclusion was 0.89 (95%CI: 0.86-0.94).

Study and patient characteristics

[Table 1](#) and [2](#) summarizes the study characteristics. The trials that were included were published between 2003 and 2019. Studies were observational prospective and retrospective cohort studies and had a follow-up duration of 6 mo to 48 mo. A total of 487 patients were included in this meta-analysis. Study population included children and adults; the age range of patients was 6 mo to 70 years. 67% of the study population were males, 81.5% of the study population reported symptoms of dyspnea and 8.4% of patients were asymptomatic. 768 severe PVS lesions were included from all studies. Severe pulmonary vein was defined as $> 70\%$ luminal stenosis of the pulmonary vein based on computed tomography (CT) imaging. For adults with PVS, the time between atrial fibrillation ablation/pulmonary vein isolation to the development of clinical symptoms ranged from 1 mo to 18 mo. The imaging protocols used to diagnose PVS were contrast-enhanced spiral CT scans, magnetic resonance imaging, lung perfusion scans. PVS was confirmed by invasive angiography. Procedural aspects consisted of right heart hemodynamic monitoring, selective pulmonary angiography, and access of left atrium by transseptal puncture. Interventions performed were predilation, gradual balloon dilation, stenting in a stepwise manner or primary stenting. Pulmonary vein surgery was required in 5 children in re-intervention group with pericardial well procedure[5] and hybrid stenting was performed after cardiac arrest in the operating room in some children with precluding anatomic factors, difficult vascular access, multiple closely spaced ostium[9]. Post-procedural antiplatelet and anticoagulant therapy was employed to ensure vessel patency. CT imaging and other imaging modalities were employed to follow up patients ([Table 3](#)).

Structure of the meta-analysis

The study compared PBA with PSI for patients with PVS. Bare metal stents, DES and hybrid stents placed surgically in children were included in this meta-analysis.

Patient-centered outcomes

Risk of re-stenosis requiring re-intervention: The data were available for all the 8 studies including 487 patients. 196 events occurred in 325 PBA interventions and 111 events occurred in 443 PSI interventions. Results show that PBA is associated with a significantly higher risk of re-stenosis compared to PSI (OR 2.91, 95%CI: 1.15-7.37, $P = 0.025$). A high degree of heterogeneity was noted ($I^2 = 79.2\%$). [Figure 2](#) shows the forest plots analysis for this outcome.

Risk of procedure-related complications: The data was available for 3 studies, 7 events occurred in 122 PBA interventions and 6 in 69 PSI interventions. Overall results show that there is no difference in procedure-related complications between PBA vs PSI for PVS (OR: 0.94, 95%CI: 0.23-3.76, $P = 0.929$),

Table 1 Main demographics of patients treated with either balloon angioplasty or stenting included in meta-analysis

Ref.	Patients (n)	Mean age (yr)	Males (%)	Frequency of clinical symptoms; Dyspnea (%)	Hemoptysis (%)	Asymptomatic (%)	Severe PVS treated (n)
Qureshi <i>et al</i> [19]	19	51 ± 13	NA	95	63	5	37
Prieto <i>et al</i> [7]	44	53 ± 11	70	88	23	7	68
Neumann <i>et al</i> [6]	12	58	70	77	8	17	15
Fender <i>et al</i> [20]	113	50	77	67	27	0	178
Cory <i>et al</i> [5]	30	Median age- 6.4 m	50	NA	NA	NA	58
Schoene <i>et al</i> [15]	39	62.1 ± 9.0	60	79	26	NA	61
Kurita <i>et al</i> [9]	31	7 mo	65	NA	NA	NA	53
Suntharos <i>et al</i> [8]	199	55 ± 12	78	83	13	13	319

NA: Not available; PVS: Pulmonary vein stenosis.

without heterogeneity ($I^2 = 0.0\%$). The forest plot analysis for this outcome is shown in [Figure 3](#). In a study by Prieto *et al* [7], one patient in PBA group while undergoing pulmonary vein (PV) dilation developed an intimal flap needing stenting and had a transient ischemic event without permanent debility. Two patients in the stenting group developed tamponade requiring evacuation of pericardial space but there was no mortality. In a study by Neumann *et al* [6], there were 3 adverse events- one patient developed hemoptysis immediately after dilation of the left upper PV which stopped 10 min after protamine administration, one patient developed small dissection of the left upper PV during dilation before stenting distally with clinical hemoptysis which resolved by additional stenting of the vein distal to the original stenosis and allergic reaction to the contrast agent used was seen in one patient. In a study by Schoene *et al* [15], major events in PBA group were 2 wire-induced PV perforations with tamponade managed by pericardiocentesis and 2 balloon-induced PV ruptures with tamponade managed by urgent surgical repair in one and emergency stenting and pericardiocentesis in another. In the stent group, an acute stent thrombosis resulting in a stroke occurred which was complicated by intracerebral bleeding with thrombolytic therapy use but there was no mortality. [Supplementary Tables](#) provide further information regarding outcomes in the included studies ([Supplementary Tables 3 and 4](#)).

Sensitivity analysis: The funnel plot distribution of outcomes was derived from the standard error of the logarithm OR plotted against the OR of re-stenosis and procedure-related complications, respectively ([Supplementary Figures 1 and 2](#)). Influence analysis demonstrated that no single study significantly altered the summary ORs for the primary or secondary outcome, because the exclusion of each study did not alter the point estimate outside the 95% CI ([Figure 4 and 5](#)).

DISCUSSION

The analysis examines the safety and efficacy of intervention with PBA *vs* PSI in patients with PVS. The principal findings of our study include (1) Similar safety profile of PBA *vs* PSI in the management of PVS; and (2) A higher risk of re-stenosis with PBA in comparison to PSI in patients with PVS. The PSI demonstrated a lower risk of re-stenosis can be attributed to the use of stents in patients with higher risk and the use of devices not particularly designed for PVS intervention. A follow-up with cardiac imaging every 3-6 mo is usually done in patients with asymptomatic PVS with about 50%-70% stenosis, particularly with ipsilateral PVS, and revascularization is considered when the PVS progress to severe grade defined as luminal stenosis > 70% by CT imaging [16]. Intervention needs to be performed urgently in patients with concomitant ipsilateral PVS in order to prevent potential progressive vascular fibrosis, occlusion, atrophy, and congestion with consequent lung infarction [17].

In the advent of suboptimal results of angiography and the occurrence of complications post-dilation, an acute mechanical benefit is provided well by stents compared to PBA. In addition, it is suggested that there is a time-dependent reduction in patency of the vessel post-PBA, making stenting favored in terms of long-term advantages [18]. This can be ascribed to the pathophysiological mechanisms of the venous

Table 2 Clinical characteristics of patients treated with either balloon angioplasty or stenting included in meta-analysis

Ref.	Study type	Enrolment Period	Main inclusion criteria	Imaging after ablation	Mean time between PVI and clinical symptoms	Revascularization approach	Stent size	Acute angiographic success	Primary outcome at follow-up	Follow-up
Qureshi <i>et al</i> [19], 2003	Observational retrospective study	2000-2002	Severe PVS with clinical symptoms	CT-scans in symptomatic patients	4 mo	Stepwise	4-10 mm	NA	Freedom of reintervention	10 ± 9 mo
Prieto <i>et al</i> [7], 2008	Observational retrospective study	2000-2007	Severe PVS with clinical symptoms	CT-scans, lung perfusion scans in symptomatic patients	11.5 mo	Stepwise/primary stenting	8-10 mm	Residual stenosis ≤ 30%	Recurrence of symptoms requiring reintervention	25 ± 21 mo
Neumann <i>et al</i> [6], 2009	Observational prospective study	2003-2005	Severe PVS (> 70%) with clinical symptoms and/or significant perfusion defect	Surveillance imaging with MRI, lung perfusion scans, CT scans, TTE every 3 mo	NA	Stepwise (if rebound stenosis was observed after balloon dilatation)/primary stenting	8-12 mm	NA	Clinically symptomatic restenosis	48 mo
Fender <i>et al</i> [20], 2016	Observational prospective study	2000-2014	Severe PVS (> 75%) with clinical symptoms	Surveillance imaging with CT-scans at 3 mo + CT-scans and lung perfusion scans in symptomatic patients	4.0 ± 3.0 mo	Stepwise	6-10 mm + DES 4 mm	Residual stenosis < 20%	Clinically symptomatic restenosis	48 mo
Cory <i>et al</i> [5], 2017	Observational retrospective study	2005-2016	Catheter intervention for PVS for patients < 18 yr	NA	NA	Stepwise/primary stenting	Median-DES 4 mm, BMS 5 mm	NA	Mortality following transcatheter PV intervention	Median of 30.6 mo
Schoene <i>et al</i> [15], 2018	Observational retrospective study	2004-2017	Symptomatic PVS with > 70% in a single stenosis or > 60% in multiple ipsilateral stenosis	Initial screening process from 2004-2007- TEE 6-12 mo after PVI or when symptomatic, subsequent CT or MRI. Screening terminated in 2008, symptomatic patients underwent CT, MRI and/or PV angiography	10.2 ± 8.0 mo	Stepwise/primary stenting	Median stent- 7 mm × 20 mm, DES 5 mm	Residual stenosis < 10%-20%	Restenosis rate following transcatheter intervention	Median of 6 mo
Kurita <i>et al</i> [9], 2019	Observational retrospective study	2001-2017	PVS associated with total anomalous pulmonary venous connection and isolated congenital PVS	Combination of ultrasound, CT and angiography	Median 7 from birth	Stepwise/primary stenting-PCI/hybrid surgery	3-8 mm	NA	In-stent restenosis following stent placement using CT or angiography ≥ 50% higher stenosis of stent size	19 mo
Suntharos <i>et al</i> [8], 2019	Observational retrospective study	2000-2016	PVS after PVI undergoing PCI	CT-scan pulmonary vein protocol, quantitative lung perfusion scan	NA	Stepwise/primary stenting	3-16 mm	NA	Freedom of reinvention	Median follow up- 17 mo

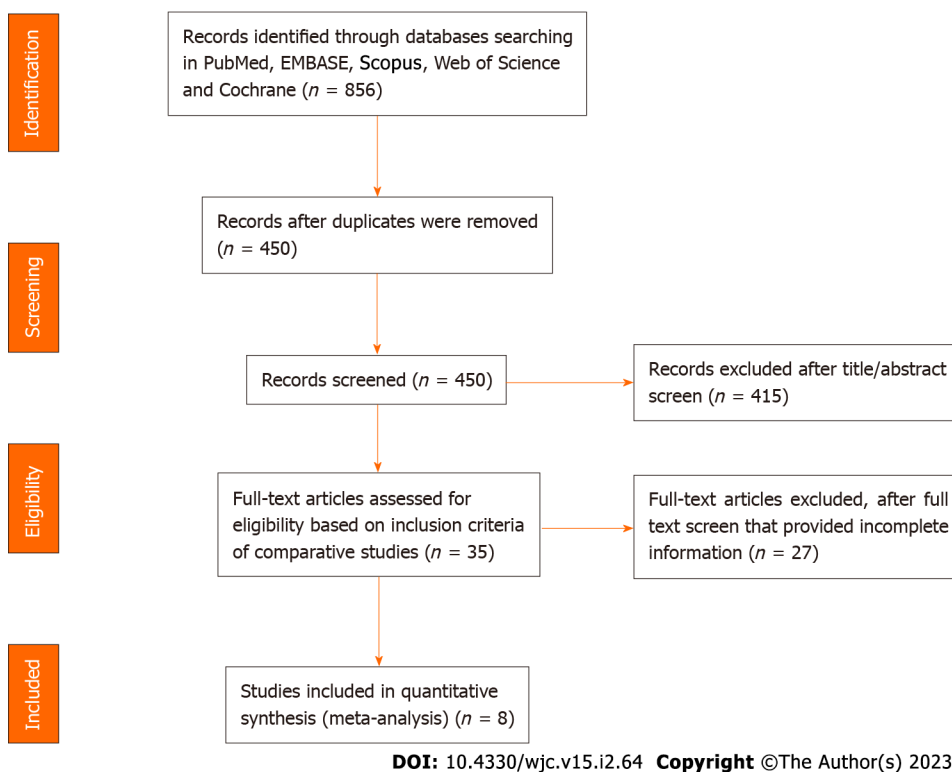
CT: Computed tomography; DES: Drug-eluting stents; NA: Not available; PVI: Pulmonary vein isolation; PVS: Pulmonary vein stenosis; PV: Pulmonary vein; TEE: Transesophageal echocardiography; MRI: Magnetic resonance imaging; PCI: Percutaneous interventions.

system as well as the histological features. This ensues from post-thrombotic fibrosis inside and around the vein, with extravenous compressive bands and accompanying perivenous fibrosis leading to the obstructive processes in intima at ablation sites, which also involves the distal sites to PV ostia. Stenting

Table 3 Follow up characteristics after revascularization

Ref.	Antiplatelet therapy	Imaging modalities	Restenosis definition
Qureshi <i>et al</i> [19], 2003	NR	CT-scans every 3 mo	PV narrowing > 70% of the original PV lumina
Prieto <i>et al</i> [7], 2008	NR	CT-scans, lung perfusion scans at 3-12-24 mo	NR
Neumann <i>et al</i> [8], 2009	ASA+Clopidogrel+Coumadin for 3 mo	CT-scans, lung perfusion scans every 3 mo	PV narrowing > 70% of the original PV lumina before PVI
Fender <i>et al</i> [20], 2016	Coumadin+Clopidogrel	CT-scans, lung perfusion scans at 3-12-24 mo	PV narrowing > 75% in the previously treated PV
Cory <i>et al</i> [5], 2017	NA	Angiography	Vein loss defined as PV atresia or PVs of uncertain status in deceased patients
Schoene <i>et al</i> [15], 2018	ASA 4 weeks+Clopidogrel 6 mo+Coumadin or DOACs	CT-scans, MR imaging	PV narrowing > 70% in the previously treated PV
Kurita <i>et al</i> [9], 2019	ASA, Ticlopidin, Warfarin	CT or angiography	In stent restenosis: $\geq 50\%$ luminal narrowing
Suntharos <i>et al</i> [8], 2019	Anticoagulation followed by low-dose aspirin	CT-scans, lung perfusion scans, angiography based on intervention-3 mo, 6 mo, 1yr	Severe restenosis/ concern for progression to total occlusion

ASA: Acetyl salicylic acid; CT: Computed tomography; NA: Not available; NR: Not reported; PV: Pulmonary vein; PVI: Pulmonary vein isolation.

**Figure 1** PRISMA flow diagram for clinical study selection for meta-analysis.

may be able to provide an advantage against these pathophysiological mechanisms.

Studies show a high success rate and low re-stenosis rates of PSI compared to PBA, with longer freedom from re-stenosis[6]. Hence, stenting can be considered a first-line strategy. Studies have also consistently shown that large stent sizes, have excellent clinical outcomes and long-term patencies. Meta-analyses showed that long-term patency is better with large stent sizes of 9-10 mm[6,7]. The incidence of in-stent re-stenosis is shown to be less in large stents, as opposed to small stents[17,19,20]. Although stenting is widely used in the pulmonary vein, the operator needs to be careful due to the risk of protruding into the LA, jailing PV side branches, and crossing a low-flow distal side branch[18]. Other frequent complications, such as hemoptysis and self-limiting hemorrhages, have been found to be similar between the two groups. Revascularization is indicated in the advent of elevated PA pressure

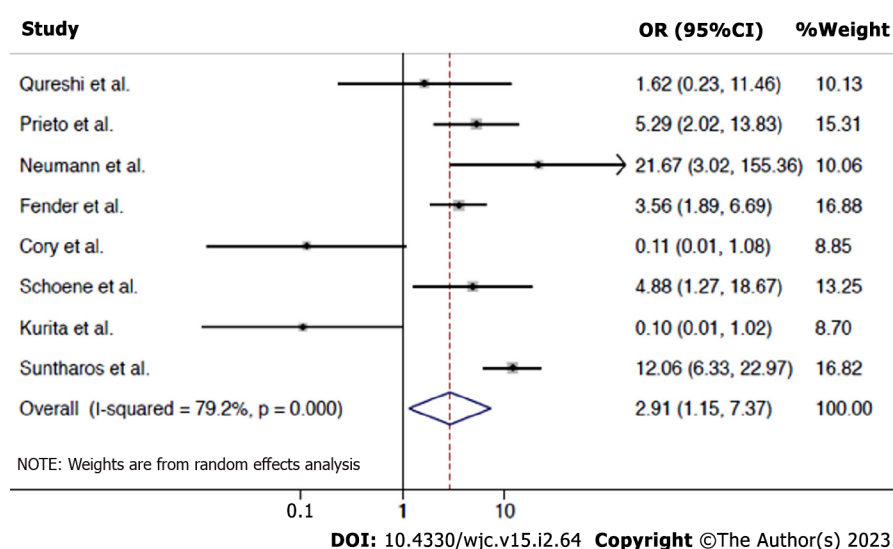


Figure 2 Forest plot for recurrent pulmonary vein stenosis in pulmonary vein balloon angioplasty group compared to pulmonary vein stent implantation group.

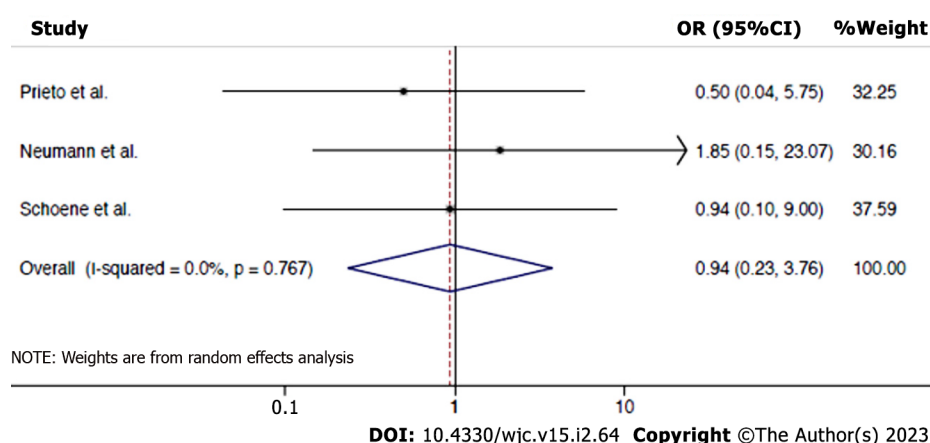


Figure 3 Forest plot for procedure related complications in pulmonary vein balloon angioplasty group versus pulmonary vein stent implantation group.

levels or the presence of typical symptoms. There is a chance of missing the diagnosis as the progression is unpredictable, and clinical symptoms may be atypical and can appear late. But early diagnosis and intervention are essential to prevent irreversible pulmonary damage.

Limitations of the study need to be acknowledged. The present study analyzes data comparing PBA and PSI from observational studies, but not randomized controlled trials. The analysis tends to be challenging to interpret when patients are treated with stenting after trial and failure of BA, as observed in some studies. In addition, procedural success and severe PVS definitions differ widely in studies, subsequently causing substantial heterogeneity. Also, the follow-up imaging techniques and protocols vary widely in the studies, which come into play when diagnosing post-procedural re-stenosis. Lastly, the antiplatelet/anticoagulation regimens post-procedure varies considerably in studies which might have possibly modified the treatment effect. The regimens were not consistently reported among different studies (Cory *et al*[5], Prieto *et al*[7], and Qureshi *et al*[19] didn't mention their regimens). The reported antiplatelet/anticoagulation regimens were also various, including 3 mo of dual-antiplatelet therapy[6], warfarin and aspirin/ticlopidine[9], and at least 6 mo of anticoagulation followed by long term aspirin[8]. Interestingly, the re-stenosis rates varied between the two studies included an anticoagulation agent (70% at 5 years, and 27% at 5 years), whereas the dual-antiplatelet regimen was associated with a 23% restenosis at about 4 years. This observation implies the post-procedural antiplatelet/anticoagulation regimens may have a minor role for restenosis.

Summary of evidence

The current analysis updates the summary of evidence by incorporating two recent observational

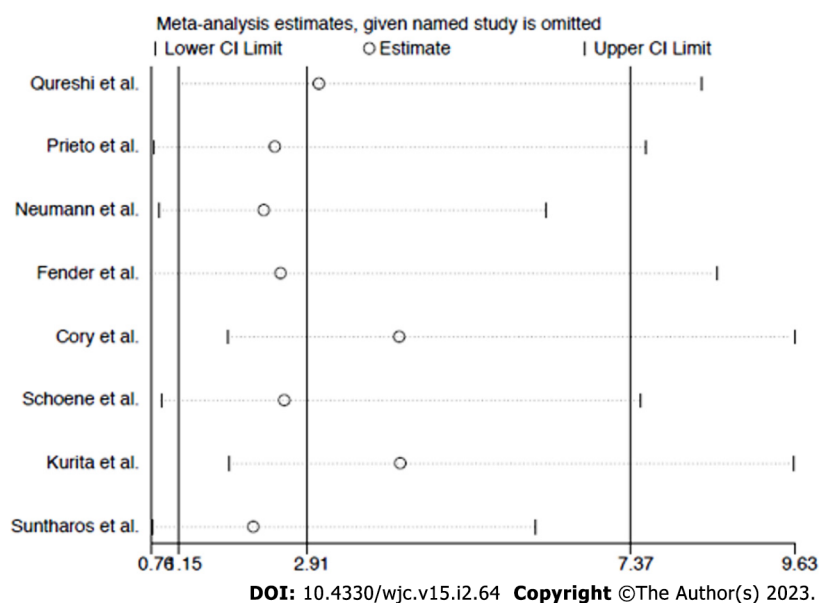


Figure 4 Sensitivity analysis for recurrent pulmonary vein stenosis.

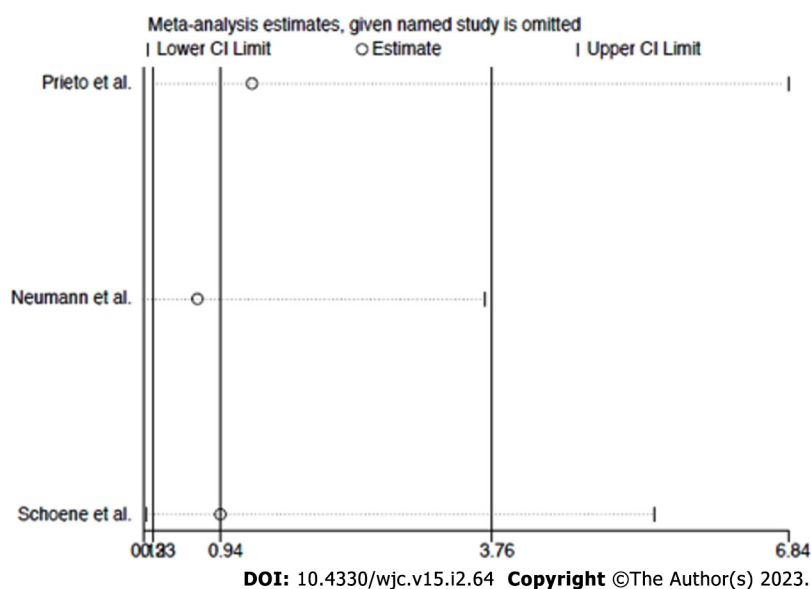


Figure 5 Sensitivity analysis for procedure related complications.

studies. Overall, we found sufficient evidence evaluating the comparative efficacy of pulmonary vein isolation (PVI) and PBA in treating patients with PVS. The outcomes with a moderate grade of certainty of evidence include pulmonary restenosis and procedure-related complications (Table 4).

CONCLUSION

Percutaneous re-vascularization with stents appears to be superior to PBA, in regard to re-stenosis and the need for re-intervention. Hence, stenting should be considered as the first line of choice over BA. A further follow-up to ascertain the real success of the intervention and the re-stenosis patterns is crucial.

Table 4 Summary of evidence

Outcomes	Anticipated absolute effects ^a (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Certainty of the evidence (GRADE) ^b
	Risk with PSI	Risk with PBA			
Restenosis	251 per 1000	493 per 1000 (278 to 711)	OR 2.91 (1.15 to 7.37)	487 (8 observational studies)	⊕ ⊕ ⊕ ○ MODERATE ^c
Procedure related complications	87 per 1000	82 per 1000 (21 to 264)	OR 0.94 (0.23 to 3.76)	191 (3 observational studies)	⊕ ⊕ ⊕ ○ MODERATE ^c

^aThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

^bGRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; (2) Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; and (4) Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^cRated down for imprecision as the 95% confidence interval overlaps with no effect and fails to exclude important benefit or important harm. PBA: Pulmonary vein balloon angioplasty; PSI: Pulmonary vein stent implantation.

ARTICLE HIGHLIGHTS

Research background

Pulmonary vein balloon angioplasty (PBA) and pulmonary vein stent implantation (PSI) are the two re-vascularization strategies used to manage pulmonary vein stenosis.

Research motivation

Both these strategies are widely used to treat pulmonary vein stenosis. Our study tends to explore outcomes and complications with each of these strategies

Research objectives

Our study tried to explore the safety and efficacy outcomes of two re-vascularization strategies Pulmonary vein balloon angioplasty *vs* pulmonary vein stent implantation in the management of pulmonary vein stenosis.

Research methods

The meta-analysis was performed by computing odds ratios using the random effects model based on underlying statistical heterogeneity.

Research results

The primary outcome of the re-stenosis requiring re-intervention occurred in 196 of 325 veins in the PBA group and 111 of 443 veins in the PSI group. Compared to PSI, PBA was associated with a significantly increased risk of restenosis (OR 2.91, 95%CI: 1.15-7.37, $P = 0.025$, $I^2 = 79.2\%$).

Research conclusions

Percutaneous re-vascularization with stents appears to be superior to PBA, in regard to re-stenosis and the need for re-intervention. Hence, stenting should be considered as the first line of choice over balloon angioplasty.

Research perspectives

A further follow-up to ascertain the real success of the intervention and the re-stenosis patterns is crucial.

FOOTNOTES

Author contributions: Agasthi P and Sridhara S contributed equally to this work; Agasthi P, Sridhara S, Mookadam F, Fortuin FD and Arsanjani R, designed the research study; Agasthi P, Sridhara S, Rattanawong P, Venepally NR, Chao C, Ashraf H and Pujari S performed the research; Douglas DA, Allam Mohamed, Alla Y, Kumar A contributed new reagents and analytic tools; Agasthi P, Sridhara S, Rattanawong P, Venepally NR, Chao C, Ashraf H, Pujari S and Allam M analyzed the data and wrote the manuscript; Mookadam F, Packer DL, Holmes DR Jr, Hagler DJ, Fortuin FD and Arsanjani R reviewed the manuscript before submission; All authors have read and approved the final

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Redefining the therapeutic strategies against cardiorenal morbidity and mortality: Patient phenotypes

Dimitra Bacharaki, Ioannis Petrakis, Kostas Stylianou

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Abstract

Chronic kidney disease (CKD) patients face an unacceptably high morbidity and mortality, mainly from cardiovascular diseases. Diabetes mellitus, arterial hypertension and dyslipidemia are highly prevalent in CKD patients. Established therapeutic protocols for the treatment of diabetes mellitus, arterial hypertension, and dyslipidemia are not as effective in CKD patients as in the general population. The role of non-traditional risk factors (RF) has gained interest in the last decades. These entail the deranged clinical spectrum of secondary hyperparathyroidism involving vascular and valvular calcification, under the term “CKD-mineral and bone disorder” (CKD-MBD), uremia *per se*, inflammation and oxidative stress. Each one of these non-traditional RF have been addressed in various study designs, but the results do not exhibit any applied clinical benefit for CKD-patients. The “crusade” against cardiorenal morbidity and mortality in CKD-patients is in some instances, derailed. We propose a therapeutic paradigm advancing from isolated treatment targets, as practiced today, to precision medicine involving patient phenotypes with distinct underlying pathophysiology. In this regard we propose two steps, based on current stratification management of corona virus disease-19 and sepsis. First, select patients who are expected to have a high mortality, *i.e.*, a prognostic enrichment. Second, select patients who are likely to respond to a specific therapy, *i.e.*, a predictive enrichment.

Key Words: Cardiorenal; Morbidity; Mortality; Phenotype; Precision medicine; Personalized medicine

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Core Tip: Stagnation in the Nephrology field has to be overcome with a new perspective. This new vision takes lessons from the past as personalized medicine, adapts precision medicine from today's lessons from corona virus disease-19 and sepsis and looks into the future with the aid of the big data. Our proposal is that cardiorenal management should be stratified according to patient phenotypes and not as an assembly of individual targets.

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INTRODUCTION

Cardiovascular (CV) disease is a major contributor of mortality in chronic kidney disease (CKD) patients, especially in the late stage 5 on dialysis (5D), mounting up to 58% of causes[1,2]. Aside traditional CV risk factors (RF), as diabetes and arterial hypertension, non-traditional RF related to kidney disease *per se* seem to play a pivotal role in the complex interaction between the kidney and the heart[3]. Non-traditional RF include secondary hyperparathyroidism resulting in vascular and valvular calcification, collectively termed as CKD-mineral and bone disorder (CKD-MBD)[4], uremia *per se*, inflammation, oxidative stress and dysbiotic gut microbiota[5].

THE PROBLEM

CKD patients have long been excluded from cardiovascular clinical trials, for various reasons: (1) Inadequate surrogate outcomes and low event rate, especially in end stage renal disease, demand a prohibitory large sample size and an extensive follow up[6]; and (2) fear for negative results or adverse events, since the aforementioned non-traditional risk factors are recognized as potential disease modifiers[7]. Nephrology practice could be characterized as “low evidence” medicine, which pursues targeting traditional RF with data originating from the general, non-CKD-population[8].

Major clinical problems, such as the choice of treatment for non-valvular atrial fibrillation in dialysis patients, remain unsolved and clinical nephrologists “navigate through darkness” regarding therapeutic strategy[9]. In the case of hyperphosphatemia although there is numerous scientific evidence that “phosphate is a cardiovascular toxin”[10], there has been no randomized control trial (RCT) providing evidence that “correction” will translate into tangible cardiovascular benefit, set the optimal timing of intervention, the different means or the optimal serum phosphate target[11]. Yet the patients endure an overwhelming phosphate binder pills consumption[12] with enormous economic implications for healthcare[13].

A LIGHT IN THE TUNNEL

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially marketed as glucose lowering drugs in diabetes mellitus type2, are a game changer in the field of cardiorenal protection[14]. Their beneficial effects, regarding reduction in CV morbidity and mortality and renal function preservation, have been assessed by RCTs across CKD stages 1-3, notably with empagliflozin (EMPA REG OUTCOME)[15] and dapagliflozin (CAPA-CKD)[16]. The unprecedented success of this novel treatment stems from the pleiotropic effects of SGLT2i, targeting multiple intra-extrarenal pathways[17].

Another promising therapeutic tool is Mediterranean Diet (Med Diet) that has a pivotal role for cardiorenal protection[18]. Targeting all traditional and multiple non-traditional RF of cardiovascular morbidity and mortality along with exercise, Med Diet confers to an anti-inflammatory and anti-oxidative metabolic profile[19]. The level of adherence has been recently linked in an observational study with left ventricular geometry patterns in dialysis patients, a powerful independent risk factor of CV mortality in this particularly vulnerable population[20].

In clinical practice SGLT2i are currently tested as real world experience in advanced stages of CKD [21]. On the other hand nephrologists are still reluctant to prescribe vegetable based diets, as Med Diet, mostly for the fear or ignorance of handling potassium and/or provoking malnutrition[22].

A KEY IN THE PUZZLE: CKD IS AN “INFLAMMAGING” CONDITION

The only positive RCT in the field of CV protection in CKD is the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study)[23], where the inhibition of the pro-inflammatory IL-1 β was more beneficial in post myocardial infarction patients with glomerular filtration rate (GFR) < 60 mL/min/1.73 m². The concept of “inflammaging”, introduced by Franceschi, unified all chronic degenerative conditions, in a common pathophysiology, which could be translated as a low grade sterile chronic inflammation resembling the natural course of ageing[24]. In observational studies IL-6 has been described as an independent predictor of outcome in pre-dialysis[25], hemodialysis[26] and peritoneal dialysis patients[27]. The association of inflammation and outcome seems so strong that a hypothesis proposal was made not to include inflamed and not inflamed patients in the same cohort in an RCT, since inflammation is powerful catalyst for other risk factors in CKD[28]. CKD patients are in a paradox state of both immune - paralysis (driving susceptibility to infections) and immune- activation (linked to CVD)[29].

THE SOLUTION: PRECISION AND PERSONALIZED MEDICINE

Treatment failure, targeting “traditional” RF and nontraditional RF (hyperphosphatemia, CKD-MBD parameters) stems probably from the fact that there is no stratification management that would guide a precision or personalized medicine. Nephrology practice seems to be in a state of involuntary blindness as the crowd that pretends to see the clothes of the naked Emperor in Hans Christian Andersen’s tale [30]. In order to find a solution we propose the following 4 steps: (1) Gather the wisdom of the past in the form of personalized medicine; (2) adapt precision medicine from today’s lessons from corona virus disease 19 (COVID-19); (3) sepsis; and (4) look into the future with the aid of the big data.

Personalized medicine negligence

Historically[31], the therapeutic practices have changed drastically from a “patient-centred” view to those of “evidence-based” medicine. “Germ theory of disease” in the 19th century, changed the “holistic view” perception of disease to a “specific cause for a specific disease”. The treatment approach shifted therefore, to a narrow approach that targeted a specific cause. The patient’s role diminished from an active contributor, through personal beliefs, adaptation and lifestyle choices, to a mere passive recipient of the treatment. Patients became “numbers” in any given trial, which will eventually provide the necessary information to form “therapeutic guidelines”[32]. Ironically and paradoxically, the contemporary nephrologist is called to manage CKD patients, who are at very high risk of cardiovascular morbidity and mortality, with guidelines based on weak evidence[6]. As mentioned Nephrology field lacks RCTs and the Cardiology field excludes CKD patients[7]. Furthermore, during the decision-making process the patient is a passive recipient of the diagnostic decision[32].

Precision medicine: Lessons from COVID-19

The pandemic of COVID-19 has taught us a great example of precision medicine. First it was discovered that patients respond differently to the “viral-intruder” and the host’s immune response, whether regulated or dysregulated leads to a favorable or unfavorable outcome respectively[33]. Later on, two distinct pathways were revealed[34] as well as an early biomarker for disease prediction (SUPAR-Soluble urokinase plasminogen activator receptor)[35]. This approach led to precision guided therapy with anakinra that showed remarkable benefit regarding respiratory failure and mortality[36].

Lessons from sepsis

In many aspects “sepsis” and “CKD” have many similarities. Both are heterogeneous syndromes with underlying “inflammation”. Sepsis is defined as “organ dysfunction caused by a dysregulated host response to infection”[37]. CKD is defined as kidney damage or GFR < 60 mL/min/1.73 m² for 3 mo or more, irrespective of cause[38]. Based on this definition half of people over 75 are “labelled” as CKD, but there is debate if they can be regarded as “same risk” for renal deterioration or CV morbidity and mortality as younger people with the same stage of CKD[39]. At the same time CKD has a “systemic nature”[40] affecting multiple organ pathways, on a specific epigenetic background. In parallel sepsis, despite all the achievements in understanding its pathophysiology, is now regarded as “a multifaceted disruption of the finely tuned immunological balance of inflammation and anti-inflammation”[41]. There is a trend to identify patient phenotypes in order to stratify an accurate management[42].

The promise of big data

The “big data” era of the last decade, a precious gift of the tremendous advances in computational technology has helped enormously diverse medical scientific fields, in terms of diagnosis, risk assessment and treatment, fueling precision medicine, but Nephrology field is lagging behind[43]. As an example, multi-omics data combined with clinical and demographic data helped to generate machine -

Table 1 Proposed Measures of prognostic enrichment

Category	Parameters	Evaluation method	
Laboratory	eGFR	Continuous	Discrete based on trials
		CKD-EPI (mL/min/1.73 m ²)	CKD stages 1,2,3a/b,4,5
	uACR	Mg albumin/g creatinine	Albuminuria stages A1,A2,A3
	hs-CRP		
	Serum magnesium		
Radiology	PTH	Intact PTH (pg/mL)	KDIGO < 150, 150-500, > 500 pg/mL
	Anemia variables	Ht/Hb/TSAT/Ferritin/Hepcidin	
	LVMI	LV mass indexed to body surface area (g/m ²)	Geometry types
	Lateral abdominal X-ray	Scale from 0-24	Leena Kaupilla Score ≤ 4 vs > 4
	Aortic stiffness	Pulse wave velocity carotid-femoral PWV (m/s)	CF-PWV < 8.8, 8.8-12, > 12 m/s
Clinical status	Frailty	Nine-point clinical frailty scale	
	Aortic stiffness	Pulse pressure (mmHg)	
	Physical activity	Handgrip strength	
	Diet	Mediterranean Diet Score Panagiotakos Scale 0-24	
Co-morbidities	DM, CAD, PAD, stroke, COPD		Charlson comorbidity index
Bones	Mineral bone density (DEXA)	Values from DEXA (g/cm ²)	Osteopenia osteoporosis

eGFR: Estimated glomerular filtration rate; uACR: Urinary albumin to creatinine ratio; PTH: Parathyroid hormone; Ht: Haematocrit; Hb: Haemoglobin; TSAT: Transferrin saturation; LVMI: Left ventricular mass index; DM: Diabetes mellitus; CAD: Coronary artery disease; PAD: Peripheral artery disease; COPD: Chronic obstructive pulmonary disease; CKD-EPI: Chronic kidney disease-epidemiology collaboration formula; KDIGO: Kidney Disease: Improving Global Outcomes; CF-PWV: Carotid to femoral pulse wave velocity; DEXA: Dual energy X-ray absorptiometry.

learning models for prediction of preeclampsia[44]. Burning clinical issues regarding CKD patients, especially in advanced stages, as treatment of vascular disease, heart failure with reduced or preserved ejection fraction and prevention of sudden cardiac death do not have solid answers yet[8]. Big data science from electronic health records and longitudinal follow up could be a surrogate of RCTs assisting clinical decision[6].

PRECISION MEDICINE THROUGH PATIENT PHENOTYPES

Our hypothesis is that there could be a paradigm shift in the field of nephrology regarding patient stratification and targeted management. In order to accomplish this transition the search for «biomarkers» could be helpful, as in sepsis[45]. The first step of a “prognostic enrichment”, *i.e.*, select patients who are suspected to have high mortality, could be followed by “predictive enrichment”, *i.e.*, patients who are likely to respond to a specific therapy (Figure 1). In this regard various biomarkers could be tested alone or in combination as: (1) Those already used in clinical practice (Table 1); and (2) the established biomarkers of cardiorenal syndrome[46] and those that could be found from multi-omics technology (blood and/or urine samples)[47].

One example of prognostic enrichment in nephrology involves the “heat map” based on GFR levels and albuminuria. It has been extensively validated and has a broad clinical application[48,49]. The CORD study in hemodialysis patients showed that vascular calcification (assessed from plain lateral abdominal X-ray), and arterial stiffness (measured by carotid-femoral pulse wave velocity) are independent prognostic markers of adverse outcome[50].

Regarding predictive enrichment one could utilize CORD study as an implementation paradigm (Figure 2). The authors showed that increased arterial stiffness -associated CV risk, is less pronounced at higher levels of calcification. Also an impressive number (19% of 993 pts “non - calcifiers” *i.e.*, with no visible calcification deposits in lateral X-ray) was identified[51]. This implies the existence of genetic predisposition. This heterogeneity of the dialysis patient population could be contributing to the inconclusive results of the EVOLVE trial. In this study, lowering parathormone levels and targeting adverse CKD-MBD parameters as serum phosphorus and vascular calcification did not produce a statistically significant benefit in preventing CV events[52]. Another example is the interaction between

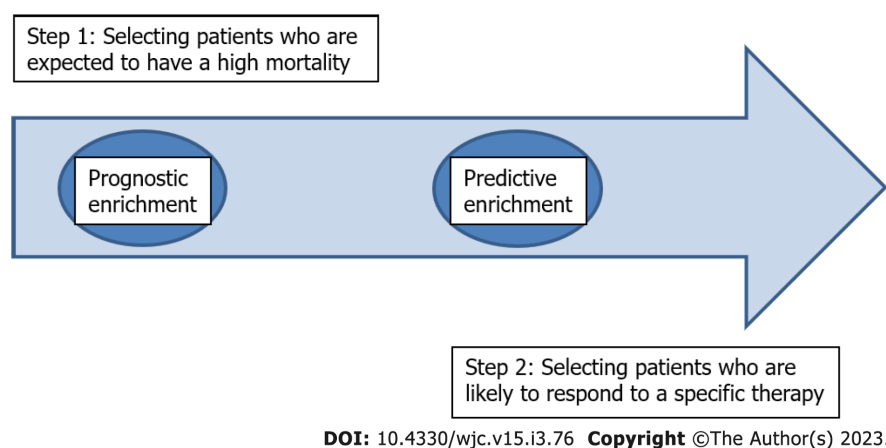


Figure 1 The path to precision medicine through patient phenotypes.

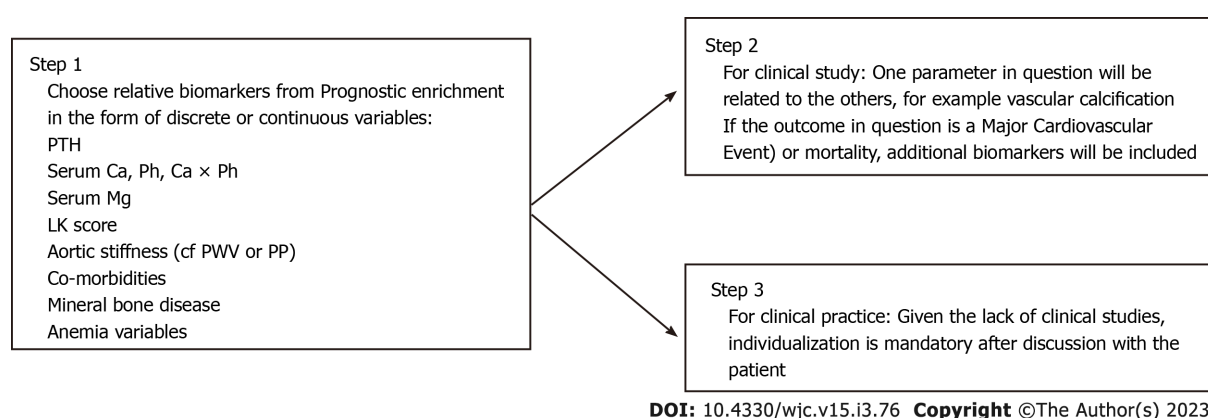


Figure 2 Predictive enrichment. Example for clinical study and clinical practice. Clinical question: Vascular disease management in CKD-5D. Bibliography: The calcification outcome in renal disease study[50] concluded that Leena Kauppila (LK) score > 4 and carotid femoral pulse wave velocity > 12 are predictors of mortality. In non-calcifiers (LK < 4) aortic stiffness plays a major role. CKD-5D: Chronic kidney disease stage 5 dialysis; PWV: Pulse wave velocity; LK: Leena Kauppila score; PTH: Parathormone; Ca: Calcium; Ph: Phosphorus; Mg: Magnesium; PP: Pulse pressure.

two strong independent predictors of CV mortality, as serum magnesium (sMg)[53] in combination with abdominal aortic calcification (AAC). We have shown that in peritoneal dialysis patients with AAC in the higher tertile of the baseline distribution, sMg levels were not predictive of outcome[54].

Erythropoietin stimulating agents have revolutionized the treatment of CKD related anemia in the last decades. Hypoxia inducible factor polyl-hydroxylase inhibitors (HIF-PHIs) promote erythropoietin transcription and synthesis in the liver/kidney. INNO2VATE trials have proven the non-inferiority of vadadustat compared with darbopoetin - alfa concerning the cardiovascular safety[55]. However there are long-term safety concerns related to HIF pathway interactions involving tumor growth, diabetic retinopathy, and or CKD progression. Till now no HIF-PHI is licensed for the treatment of CKD-anemia within the European Union.

Considering erythropoietin use in CKD population a U-shaped effect exists[56]. The optimal erythropoietin dose to achieve the desired level of hemoglobin (10-11.5 g/dL) for the individual patient is not known and is almost always a matter of individual assessment. Furthermore, assays detecting markers of inflammation (*e.g.*, hepcidin) which would predict clinical response in anemia lack in everyday clinical use.

CONCLUSION

In the stagnant era of effective treatment in the vulnerable population of CKD for CV morbidity and mortality, a paradigm shift seems mandatory. It is time to search for specific “biomarkers” to identify those at risk and even more those that would benefit from a targeted intervention. It is time to apply precision medicine through patient phenotypes.

FOOTNOTES

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Retrospective Study

Real-world five-year outcomes of FlexyRap® cobalt-chromium rapamycin-eluting stents with biodegradable polymer in patients with *de-novo* coronary artery disease

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Abstract

BACKGROUND

The use of biodegradable polymer drug-eluting stents (BP-DES) has been proven to minimize restenosis and stent thrombosis. The current post-marketing monitoring was observed at the 5-year clinical outcomes of individuals who had been treated with FlexyRap® DES in the real world.

AIM

To assess the safety and effectiveness of FlexyRap® DES at the 5-year follow-up in real-world settings.

METHODS

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of patients treated with FlexyRap® DES for *de novo* coronary artery disease (CAD) were reported. During the 12-mo follow-up, the primary endpoint was target lesion failure, which was defined as the composite of

cardiovascular death, target vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization.

RESULTS

The data of 500 patients received with FlexyRap® DES was obtained at the completion of the surveillance timeline of 5-year. After the implantation of FlexyRap® DES, the device success rate was 100%. Adverse events that led to major bleeding, permanent disability, or death were not experienced in the patients. The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

CONCLUSION

FlexyRap® DES was proved to be safe and efficacious in real-world patients with *de novo* CAD, indicating a lowered rate of cardiac events and stent thrombosis at 5-year follow-up.

Key Words: Coronary artery disease; Drug-eluting stents; Percutaneous coronary intervention; Rapamycin; Sirolimus

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Core Tip: Biodegradable polymer drug-eluting stents (BP-DES) have been proven to minimize restenosis and stent thrombosis. Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The study proved the feasibility, safety, and efficacy of the FlexyRap® rapamycin-eluting stent for the treatment of *de novo* coronary artery disease, indicating low rates of events and stent thrombosis at 5-year follow-up.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is a frequently conducted cardiac procedure aimed at enhancing the quality of life and reducing symptoms for individuals suffering from coronary artery disease (CAD)[1]. CAD is the leading cause of mortality across the globe[2]. Drug eluting stents, commonly referred to as DES, are considered as the primary method of percutaneous coronary revascularization for patients experiencing acute coronary syndromes and stable ischemic heart disease[3]. Recent advancements in the design of newer generation DES have centered on enhancing tissue biocompatibility and facilitating arterial healing. This has been achieved by incorporating innovative stent platform materials with thinner struts, utilizing biocompatible or biodegradable polymers with improved coatings, and implementing novel antiproliferative agents by lowering the content of drug and precisely controlling the rate of elution[4]. The advent of DES has decreased the rates of restenosis and become the preferred method of choice for most of the patients undergoing the procedure of PCI [1]. These stents have become widely used across a range of anatomic and clinical aspects due to their reduced rates of restenosis and the requirement for the repetition of the revascularization procedure[2]. The utilization of a polymer that is biodegradable has the possibility of lowering the chronic inflammatory response of the wall of blood vessels, facilitating the process of re-endothelialization and reducing the likelihood of blood clots and late restenosis[5]. Biodegradable polymers are being considered and analyzed to acquire and carry drugs. Polymers like poly lactic acid, polyglycolic acid, and their copolymer, poly lactic-co-glycolic acid, are most prevalent as they sight characteristics to get completely degraded and metabolized in the body[6]. It would have improved safety and performance of DES as they deliver controlled release of anti-restenosis agent and gradual degradation of coating[7].

FlexyRap® is one such novel biodegradable rapamycin-eluting coronary stent that has been developed by using a unique patented design of radial star, semi-opened, hybrid FlexyStar® platform, with a lower 60 µm thickness of strut and flexible link made of L605 cobalt-chromium metal. This design ensures the optimal delivery of the drug, radio-opacity, radial strength, biocompatibility, and vessel

conformability. The evidence supporting the effectiveness and safety of indigenously produced drug-eluting stents in patients with newly diagnosed coronary artery disease is limited[8]. This study aimed to assess post-market clinical follow-up of real-world safety and efficacy of the rapamycin-eluting FlexyRap® coronary stent system, made of biodegradable polymer, in patients with obstructive native coronary arteries over a 5-year period.

MATERIALS AND METHODS

The FlexyRap® DES study was conducted at 5 centers with the total of 500 patients included in this study. The study was a retrospective, single-arm, multi-center, observational, post-market clinical follow-up conducted in 500 patients who were eligible for PCI and coronary artery bypass grafting (CABG). The patients in whom the target lesion located within a native coronary vessel and the target lesion diameter stenosis $\geq 50\%$ were included in the study. Out of a total of 613 patients assessed for eligibility, 113 patients were excluded due to screen failure, and 500 patients were ultimately included in the study after meeting the predefined inclusion criteria as shown in Figure 1. The study was conducted in accordance with the declaration of Helsinki and ISO 14155:2020 GCP standards, ICH-GCP, MEDDEV 2.7.1 Appendix 1, MDR 2017/745 and applicable local regulatory requirements. The study was performed with the approval of an independent ethics committee. The PCI procedures were performed according to current standard guidelines. Clinical and angiographic data from all the patients who were treated with FlexyRap® DES were observed in this study. The clinical follow-up was performed at the time point of 12-mo, 3-year and 5-year after the discharge.

Device description

FlexyRap® cobalt chromium rapamycin-eluting coronary stent system consisting of a drug/polymer coated balloon expandable stent premounted on rapid exchange percutaneous transluminal coronary angioplasty (PTCA) balloon catheter. The stent is made from L605 cobalt chromium alloy (Co-Cr) which consists of cobalt, chromium, tungsten, iron and nickel with its strut thickness 60 μm . The stent is laser cut from the seamless tubing in hybrid design pattern and electro polished for ultra-smooth stent surface. The coating is comprised of biodegradable polymer matrix that contains an active pharmaceutical ingredient rapamycin (sirolimus). A conformal coating of a polymer carrier with approximately 1.0 $\mu\text{g}/\text{mm}^2$ of rapamycin of total stent surface area with minimal nominal drug content of 32 μg on the smallest stent (7 mm) to maximum nominal drug content of 213 μg on the largest stent (45 mm). Stent of 48 mm in length approved by the Central Drug Standard Control Organization was also implanted in the desired population. The stent delivery balloon catheter system is a semi-compliant polyamide balloon, which is nominally 0.5 mm longer than the stent. The two opaque platinum-iridium markers are nominally placed beyond the stent at each end which defines the stent location in length. Two proximal delivery system shaft markers (90 cm and 100 cm proximal to distal tip) indicate the relative position of delivery system to the end of appropriate guiding catheter. FlexyRap® DES is available in various lengths (7, 10, 13, 15, 17, 20, 24, 28, 33, 38, 42, 45 and 48 mm) and diameters (2.25, 2.5, 2.75, 3.0, 3.5, 4.0 and 4.5 mm).

Study procedure

Procedural anticoagulation was achieved using unfractionated heparin (at least 5000 IU or 70-100 IU/kg to maintain an activated clotting time of $> 250\text{s}$ during the procedure). Aspirin ($\geq 100\text{ mg}$) and clopidogrel (300-600 mg) or prasugrel (60 mg) were administered before or during the procedure at the investigator's discretion. Patients continued to take aspirin (100 mg QD) indefinitely clopidogrel (75 mg QD) or prasugrel (60 mg) was administered for at least 6-mo after stent implantation in all patients and for at least 12-mo in those who did not have a high risk of bleeding. In addition, glycoprotein IIB/IIIA inhibitors were administered in certain patients at the investigator's discretion. Biomarkers and electrocardiograms were recorded at different time points to assure the safety and well-being of patients.

Definitions and study endpoints

Target lesion failure (TLF) is defined as a composite of cardiovascular death, target-vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (CD-TLR)[9]. In the following study the primary endpoint was the TLF where the follow-up was taken at the interval of 12-mo and the secondary endpoints were cardiovascular death, TV-MI, clinically driven TLR, stent thrombosis (ST), target vessel failure, target vessel revascularization where the follow-up was taken at 12-mo, 3-year, and 5-year. The composite of cardiac death, target lesion-revascularization and myocardial infarction is defined as major adverse cardiac event (MACE). ST was also evaluated in this study which was classified according to the definitions of the academic research consortium[10]. Device success was defined as the successful delivery and deployment of the study stent at the intended target lesion, as well as the successful withdrawal of the delivery system, with final in-stent residual diameter stenosis of $< 30\%$ of all treated lesions, as determined by visual inspection or quantitative coronary angiography. Procedural success was defined as the delivery and deployment of the study stent at the intended target

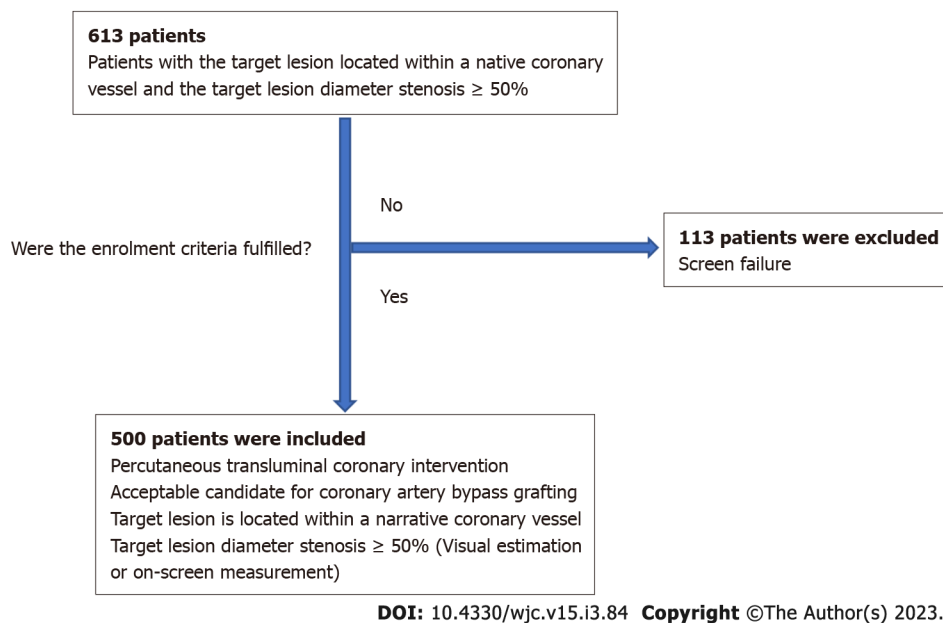


Figure 1 Patient selection criteria flowchart.

lesion, as well as the withdrawal of the delivery system, with a residual diameter stenosis of less than 30% as determined by visual inspection or quantitative coronary angiography, and no in-hospital major adverse cardiac event (death, MI, or repeat coronary revascularization of the target lesion)[11,12].

Sample size and statistical analysis

A sample size of 500 subjects was calculated based on the primary endpoint of the study. Categorical variables were summarized by frequency distribution for each categorical component (relative frequencies and percentage). All the analysis were done by using statistical package for the social sciences (SPSS) v.20. Results were reported as mean $\pm$ standard deviation for continuous variables and as number (%) for nominal variables. For changes in pre-post differences, Wilcoxon-test was used for ordinal variables and paired t-test for continuous variables. Other variables frequency was compared using the chi-square test or fisher's exact test. Result was significant at $P < 0.05$. For time-to-event variables, survival curves were represented using Kaplan Meier estimates.

RESULTS

Baseline demographics characteristics

Baseline demographics and clinical characteristics are summarized in Table 1. The data for 500 patients were collected retrospectively at 12-mo, 3-year, and 5-year. The average age of the study patients was 59.30 ± 11.27 years, with the majority being male (70.2%). The most frequently occurring comorbidities were hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), alcoholic (9.6%), and dyslipidemia (3.4%). History of myocardial infarction was found in 54.8% followed by CAD (4.8%), PCI (4.2%) and stroke (1.8%). Out of 500 patients, 299 (59.8%) were having stable angina and 201 (40.2%) patients with unstable angina.

Clinical outcomes

Lesion details are mentioned in the Table 2. Total 729 lesions were identified and 730 stents were deployed to treat the lesion. The average stent length and diameter was 26.03 ± 10.86 mm and 3.06 ± 0.41 mm. The device success rate were observed to be 100%.

The cardiac event rate associated with the use of FlexyRap® DES at the follow-up of 12-mo, 3-year, and 5-year is presented in Table 3. Total 2 (0.4%) patients experienced MACE during 5-year. The MACE rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at 12-mo follow-up, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up. The Kaplan-Meier method was used to conduct a time-to-event analysis, which showed a 98.8% result (Figure 2).

Table 1 Demographic baseline and clinical characteristics

Characteristics	FlexyRap [®] cobalt chromium rapamycin eluting coronary stent system; Number of patients, (n = 500)
Patient demographics	
Age, yr (mean ± SD)	59.30 ± 11.27
Male, n (%)	351 (70.2)
Female, n (%)	149 (29.8)
Heart rate (mean ± SD)	86.36 ± 11.34
Systolic blood pressure (mean ± SD)	133.57 ± 20.88
Diastolic blood pressure (mean ± SD)	83.36 ± 9.70
Haemoglobin (g/dL) (mean ± SD)	12.64 ± 2.45
Platelet count (mean ± SD)	205.85 ± 52.19
Baseline medical history, n (%)	
Hypertension	217 (43.4)
Smoking current	203 (40.6)
Diabetes mellitus	70 (14)
Alcohol current	48 (9.6)
Dyslipidemia	17 (3.4)
Previous MI	274 (54.8)
History of CAD	24 (4.8)
Previous PCI	21 (4.2)
Previous Stroke	9 (1.8)
Baseline cardiac history, n (%)	
Stable angina	299 (59.8)
Unstable angina	201 (40.2)
Angina class, n (%)	
Class I	12 (2.4)
Class II	30 (6)
Class IIA	1 (0.2)
Class IIB	12 (2.4)
Class IIC	6 (1.2)
Class III	198 (39.6)
Class IIIA	15 (3)
Class IIIB	51 (10.2)
Class IIIC	37 (7.4)
Class IV	138 (27.6)
Disease vessel, n (%)	
Single vessel	314 (62.8)
Double vessel	150 (30)
Triple vessel	27 (5.4)
Quadra vessel	9 (1.8)
LVEF (mean ± SD)	52.88 ± 15.46
Serum creatinine (mean ± SD)	1.47 ± 0.47

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

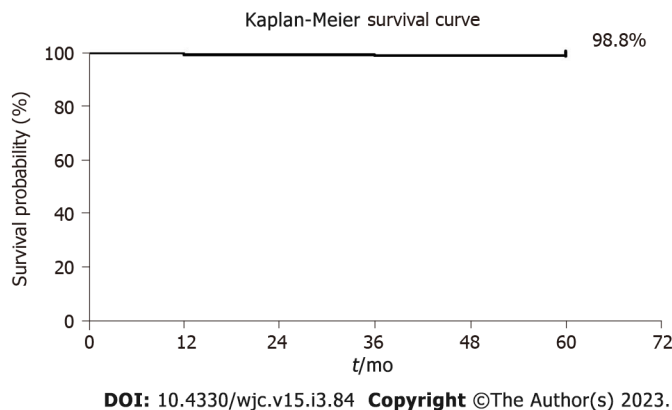


Figure 2 Time-to-event curve at up to 5-year follow-up by Kaplan-Meier method.

DISCUSSION

In the proposed retrospective study, the FlexyRap® DES has showed exceptional positive results in the patients with *de novo* obstructive native CAD including high procedural success and clinical performance. The patient population had hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), previous myocardial infarction (54.8%), alcoholism (9.6%), and dyslipidemia (3.4%).

As per the observed study, FlexyRap® cobalt-chromium rapamycin-eluting coronary stent system consisting of drug/polymer coated balloon expandable stent is premounted on rapid exchange PTCA balloon catheter. The polymers are biodegradable, biocompatible, and bioresorbable. Degradation of these materials has been thoroughly studied and has been shown to be safely resorbed by the body after implantation. Rapamycin belongs to a class of therapeutic agents known as macrocyclic lactone or macrolide. It's a cytostatic drug and an immunosuppressant. Rapamycin inhibits T cell activation and growth in response to antigenic stimuli and cytokines such as IL-3, IL-4, and IL-15 are inhibited through a unique mechanism that differs from other immunosuppressive agents. It has been noted that a variety of elements, including the design of the stent, thickness of its struts, antiproliferative agent used, release dynamics of the drug, the duration of drug release, and the type of polymer, can have an impact on the safety and effectiveness of coronary stent system[13]. The first-generation stent were constructed with bulky stent frameworks, making their delivery quite difficult[14]. However, the newest generation boasts thin struts and has demonstrated an 8% increase in its nominal pressure to rated burst pressure. These latest-generation FlexyRap® DES offer improved ease of delivery and vessel conformability, resulting in full deployment and proper placement against the vessel wall. Its design minimizes balloon overhang, reducing the likelihood of edge dissection or injury - a typical procedural issue in PCI. The results of the study, where procedural success was accomplished in all patients, support these claims. Compared to bare metal stent, the first-generation DES featuring a long-lasting polymer have been successful in lowering the rate of re-narrowing, but they have a higher incidence of late ST[15].

Also, the FlexyRap® has the advantage of not cracking, webbing, clumping, or adhering to the balloon surface, making it a promising option for coronary applications. The finding of 100% procedural success in this study can be attributed to these favorable product features.

Iglesias *et al*[16], compared the safety and effectiveness of ultrathin strut biodegradable polymer sirolimus-eluting stents (BP-SES) with thin strut durable polymer everolimus-eluting stents in patients experiencing acute ST-segment elevation myocardial infarction (STEMI). The results showed that 25 (4%) out of 649 patients who received (BP-SES) biodegradable polymer sirolimus-eluting stents and 36 (6%) out of 651 patients who received durable polymer everolimus-eluting stents (DP-EES) experienced TLF. Shetty *et al*[17], conducted a study illustrating the late-term clinical outcomes among patients treated with ultrathin strut BP-SES and thin-strut DP-EES where significant differences in target vessel MI and target lesion revascularization was observed. Out of 884 patients with BP-SES, target lesion failure was observed in 8.2% of patients, and 13.6% of patients shown up with TLF for DP-EES out of 450 patients[17]. Dani *et al*[8], assessed the comparative performance of a BP-SES compared with a DP-EES in the treatment of calcified or narrow vessel blockages. A total of 1553 patients were implanted with BP-SES and 784 patients with DP-EES with the validation of 12-mo follow-up. TLF and TV-MI were significantly lower in BP-SES than in DP-EES in non-small vessel lesions. In the patients with TLF, calcified lesions and cardiac death were numerically higher in DP-EES than in BP-SES. Similarly, the outcomes of the proposed study are comparable with the other studies where TLR was not observed in

Table 2 Procedural characteristics

Procedural characteristics (n = 500)	
Lesion details	
Total number of lesions treated with FlexyRap® (n)	730
Total number of stents deployed (n)	730
Total stent per lesion (n = 500 patients) (Total no. stent deployed (730)/Total lesion locations (729))	1.001
Total lesion per vessel (n = 500 patients); Total lesion locations (729)/(Sum of total No of diseased vessel (731))	0.997
Lesion locations (729) n (%)	
D1	6 (0.82)
Distal LAD	17 (2.33)
Distal LCx	4 (0.54)
Distal RCA	16 (2.19)
LAD	279 (38.27)
LCx	98 (13.44)
LM	1 (0.13)
MID LAD	19 (2.6)
MID LCx	9 (1.23)
MID RCA	15 (2.05)
O Mid	7 (0.96)
OM	4 (0.54)
OM1	8 (1.09)
OM2	6 (0.82)
OM3	1 (0.13)
OMI	1 (0.13)
Osteoproximal LAD	2 (0.27)
Osteoproximal RCA	4 (0.54)
PDA	7 (0.96)
PLV	3 (0.41)
Proximal LAD	23 (3.15)
Proximal RCA	15 (2.05)
Proximal LCx	7 (0.96)
PTCA	8 (1.09)
Ramus intermedius	8 (1.09)
RCA	156 (21.40)
RCX	2 (0.27)
PLB	2 (0.27)
POM	1 (0.13)
Stent length (mean ± SD)	26.03 ± 10.86
Stent diameter (mean ± SD)	3.06 ± 0.41
Type of stenosis, n (%)	
<i>de novo</i>	500 (100)

Thrombus load (<i>n</i> = 731), <i>n</i> (%)	
None	519 (71)
Mild	90 (12.31)
Moderate	59 (8.07)
Severe	63 (8.62)
Lesion type [ACC/AHA classification] (<i>n</i> = 731), <i>n</i> (%)	
Type A	20 (2.73)
Type B1	193 (26.40)
Type B2	302 (41.31)
Type C	216 (29.55)
Stent balloon inflation pressure (atm) (mean ± SD) (<i>n</i> = 500)	12.52 ± 1.75
TIMI FLOW <i>n</i> (%)	
II	9 (1.8)
III	491 (98.2)
% of occlusion (mean ± SD) (<i>n</i> = 500)	88.60 ± 8.79
All values are presented in <i>n</i> (%) or mean ± SD	

ACC/AHA: American college of cardiology/American heart association; LAD: Left anterior descending artery; LCx: Left circumflex; LM: Left main; OM: Obtuse marginal artery; PDA: Patent ductus arteriosus; PLV: Posterior left ventricular artery; PTCA: Percutaneous transluminal coronary angioplasty; PLB: Posterolateral branch; POM: Medial preoptic nucleus; RCAL Right coronary arterial ligation; RCX: Right Circumflex artery; SD: Standard deviation; TIMI: Thrombolysis in myocardial infarction.

Table 3 Cardiac event rate, *n* (%)

Clinical event	12-mo (<i>n</i> = 500)	3-yr (<i>n</i> = 500)	5-yr (<i>n</i> = 500)
TLF	0 (0)	0 (0)	0 (0)
Cardiovascular Death	0 (0)	0 (0)	0 (0)
TV-MI	1 (0.2)	0 (0)	1 (0.2)
Clinically-driven TLR	0 (0)	0 (0)	0 (0)
Late ST	2 (0.4)	0 (0)	0 (0)
TVF	0 (0)	0 (0)	0 (0)
TVR	0 (0)	0 (0)	0 (0)
Very late ST	0 (0)	2 (0.4)	0 (0)
Total MACE	1 (0.2)	0 (0)	1 (0.2)

MACE: Major adverse cardiac event; TLF: Target lesion failure; TV-MI: Target vessel myocardial infarction; TLR: Target lesion revascularization; ST: Stent thrombosis; TVF: Target vessel failure; TVR: Target vessel revascularization.

the patients and the TV-MI in 0.4% of the patients at the cumulative follow-up of 5-year demonstrating the successful clinical outcomes of the study device.

At the end of the 5-year analysis period, cumulative cardiac events presented with 0.4% of MACE where 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR was observed compositely, with 0.4% of late ST and 0.4% of very late ST. The unique configuration of the radial star segments and the minimal thickness of the struts ensure exceptional radial stability, facilitating the smooth navigational progress of the device through the circulatory system. Additionally, the decline in the occurrence of cardiac incidents is likely due to the biodegradable polymer's non-inflammatory properties and optimal drug release kinetics[17]. A decreased thickness of stent struts has been linked to a lower frequency of ST[8]. The main benefit of the study was that it was a 5-year follow-up thus the results were sustained in well- designed with longer follow-up duration. The positive outcomes seen in this study could be attributed to the unique design features of the product, such as the advanced stent design utilizing a

biodegradable polymer that offers strong radial strength, reduced overhang from the balloon, low recoil, and consistent support. The device and procedural success rate were 100% for the patients implanted with FlexyRap® DES. The survival probability of 98.8% was observed.

One significant drawback of this study was its observational design and examination of retrospective data. However, this approach provides a more accurate representation of a diverse patient population, unlike randomized trials with strict criteria for enrollment.

CONCLUSION

In conclusion, the present PMCF study offers evidence regarding the safety, and effectiveness of the FlexyRap® rapamycin-eluting stent for treatment of *de novo* CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

ARTICLE HIGHLIGHTS

Research background

Drug-eluting stents manufactured with biodegradable polymers (BP-DES) effectively reduce restenosis and the risk of stent thrombosis.

Research motivation

The motivation of the present study is focused on the safety and effectiveness from the stent eluting rapamycin for treating the *de novo* coronary artery disease (CAD).

Research objectives

Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The outcome of the study proved to be viable, safe, and efficacious results of the FlexyRap®, rapamycin-eluting stent for treating *de novo* CAD, indicating low rates of events and ST at 5-year follow-up.

Research methods

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of individuals treated with FlexyRap® DES for *de novo* CAD. During the 12-mo follow-up, the primary endpoint was to determine the rate of target lesion failure (TLF). TLF was established as the culmination of three events: Death caused by cardiovascular issues, a myocardial infarction in the target vessel, and the requirement for revascularization of the target lesion due to clinical findings.

Research results

The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%) and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

Research conclusions

In conclusion, this PMCF study investigated the preliminary indications of the feasibility, safety, and effectiveness of using the FlexyRap® rapamycin-eluting stent for treating *de novo* lesion in CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

Research perspectives

To improve the inner luminal diameter and decrease the likelihood of repeat blockages in the treatment of *de novo* lesions in the native coronary arteries.

FOOTNOTES

Author contributions: Vani P concept and study design, Neuss M, Garg N, Chawla R, Tandon V, Garg D, Parshottam N performed the research; All authors have reviewed and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the OM Institutional Ethics Committee.

Informed consent statement: As per ICH guidelines - E6 (R2/4.8), there is a need to obtain informed consent from subjects in the case of prospective/RCT/Observational clinical studies/investigations. However, in the case of Retrospective post-market clinical follow-up studies, where data collection is done from the hospital records, the permission for the patient (Anonymous) data collection shall be taken from the E/IRB/Head of the Institution from the medical records and not mandatorily requires Informed consent from the patient.

Conflict-of-interest statement: Ms. Preeti and Dr. Malte are employees of Sahajanand Laser Technology Ltd. (SLTL), India. All other authors have nothing to disclose.

Data sharing statement: No additional data are available.

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Retrospective Study

Prediction of permanent pacemaker implantation after transcatheter aortic valve replacement: The role of machine learning

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Abstract

BACKGROUND

Atrioventricular block requiring permanent pacemaker (PPM) implantation is an important complication of transcatheter aortic valve replacement (TAVR). Application of machine learning could potentially be used to predict pre-procedural risk for PPM.

AIM

To apply machine learning to be used to predict pre-procedural risk for PPM.

METHODS

A retrospective study of 1200 patients who underwent TAVR (January 2014-December 2017) was performed. 964 patients without prior PPM were included for a 30-d analysis and 657 patients without PPM requirement through 30 d were included for a 1-year analysis. After the exclusion of variables with near-zero variance or $\geq 50\%$ missing data, 167 variables were included in the random forest gradient boosting algorithm (GBM) optimized using 5-fold cross-validations repeated 10 times. The receiver operator curve (ROC) for the GBM model and PPM risk score models were calculated to predict the risk of PPM at 30 d and 1 year.

RESULTS

Of 964 patients included in the 30-d analysis without prior PPM, 19.6% required PPM post-TAVR. The mean age of patients was 80.9 ± 8.7 years. 42.1 % were female. Of 657 patients included in the 1-year analysis, the mean age of the patients was 80.7 ± 8.2 . Of those, 42.6% of patients were female and 26.7% required PPM at 1-year post-TAVR. The area under ROC to predict 30-d and 1-year risk of PPM for the GBM model (0.66 and 0.72) was superior to that of the PPM risk score (0.55 and 0.54) with a P value < 0.001 .

CONCLUSION

The GBM model has good discrimination and calibration in identifying patients at high risk of PPM post-TAVR.

Key Words: Transcatheter aortic valve replacement; Permanent pacemaker implantation; Machine learning

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Core Tip: Atrioventricular block requiring permanent pacemaker (PPM) implantation is an important complication of transcatheter aortic valve replacement. Application of machine learning could potentially be used to predict pre-procedural risk for PPM. Machine learning was used to predict patients who are at risk of developing conduction abnormalities requiring PPM at 30 d and 1 year. Our random forest machine learning model using machine learning outperforms PPM risk score model in its predictive value. Brachio-cephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation at both 30-d and 1-year, which has not been previously described in the literature.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly being used in preference to surgical aortic valve replacement (SAVR) in patients with aortic stenosis[1-3]. The most common complication of TAVR remains the development of atrioventricular conduction abnormalities, requiring permanent pacemaker (PPM) implantation, despite the use of improved implant performance and newer generation valves[4-12]. PPM is associated with increased length of hospital stay and mortality[13]. Additionally, advanced conduction defects requiring PPM implantation have been demonstrated to lead to worse functional capacity and clinical outcomes in patients with aortic stenosis[1-4]. The PPM requirement rate in TAVR is two to five-fold higher than in SAVR[15,16]. Certain baseline characteristics such as age, gender, pre-existing atrioventricular block, right bundle branch block, left bundle branch block[17,18], and size of the left ventricular outflow tract (LVOT), as well as procedure-related factors such as implantation depth have been shown to be associated with PPM requirement risk. Previous studies that evaluated risk factors associated with PPM requirement used data for older-generation valves and included only a limited number of variables, thus limiting their predictive potential[11,13,19, 20]. Consequently, it is very important to risk stratify patients for potential need of PPM implantation post-procedure. Artificial intelligence (AI) refers broadly to analytical algorithms that iteratively learn from data, enabling machines to find hidden insights without the need for explicit programming where to look[21-24]. Machine learning (ML) is a computer science sector that uses computer algorithms to identify patterns with a multitude of variables in large datasets and thereby anticipates various data-

based outcomes[25]. In this study, we used supervised ML with the gradient boosting machine learning model (GBM) to predict pre-procedural risk for PPM post-TAVR at 30 d and 1 year.

MATERIALS AND METHODS

We performed a retrospective study on all patients with severe symptomatic aortic stenosis who underwent TAVR at the Mayo Clinic hospitals in Rochester, MN, Phoenix, AZ, and Jacksonville, FL between January 1, 2012, and December 30, 2017. The Mayo Clinic Institutional Review Board (IRB) approved the study protocol and research authorization to utilize medical information for clinical research was provided by the patients. A retrospective chart review of the electronic health record was used to collect baseline data, and clinical coordinators were contacted for information on follow-up visits. We identified 285 clinical variables for potential inclusion into the ML algorithm.

Out of 1200 patients, 236 individuals with prior pacemakers were excluded. The remaining 964 patients were included in the 30-d PPM risk prediction analysis. We first eliminated all variables with $\geq 50\%$ missing and near-zero variance, where variables with near-zero variance have one unique value or the majority of the data is comprised within a single category. The GBM algorithm handles missing data internally by treating “missing” as its own category. This left 147 out of 285 variables to be included in the model. These variables were used to predict the risk of pacemakers 30 d post-TAVR using the GBM model. The model was optimized using 5-fold cross-validation repeated 10 times to get the highest prediction accuracy. Among the 964 patients without prior PPM who have undergone TAVR, 189 patients required PPM implantation by 30 d, 116 patients were deceased by 1 year, and 2 patients were lost to follow-up, leaving 657 patients who were included in the final analysis to predict the need for PPM at 1 year. There were 287 variables initially, but all variables with $\geq 50\%$ missing or near-zero variance were eliminated leaving a total of 163 variables. Patient recruitment is summarized in Figure 1.

Clinical variables, comorbidities, and procedural factors were obtained from chart review. Definitions conformed to those provided by the Transcatheter Valve Therapy (TVT) Registry[26]. Echocardiographic variables were collected using standard ultrasound scanners. Comprehensive Doppler and 2-Dimensional Transthoracic Echocardiogram (TTE) were performed prior to the procedure. TTE images were acquired and interpreted according to the European Association of Echocardiography and American Society of Echocardiography guidelines. Multi-detector computed tomography (MDCT) was performed a month before the treatment. The size of the aortic annulus was determined pre-procedure.

Statistical analysis

The study population data set ($n = 964$ and $n = 657$) for 30 d and 1 year, respectively, had low event rates. Due to a small percentage of events, the entire data set was used in the modeling phase and was not broken into a test and train cohort. The *caret* R package was used to fit a GBM model from the *gbm*³ R package using 5-fold cross-validation repeated 10 times. Model hyperparameters, specified prior to fitting the model, are tunable variables that control the chosen model’s learning process. The hyperparameters tuned were the interaction depth, number of trees, and shrinkage. The minimum number of observations required at each node was fixed at 20. Figures 2 and 4 include the top 20 variables that indicate which have the highest predictive power in classifying those with events and those without events. The study population for PPM risk was limited to those that had a trans-femoral or trans-apical approach. The PPM risk score developed by Vejpongsa *et al*[20] uses 6 factors. Each factor had points associated that collapsed into a three-group score (low, moderate, or high risk). Tuning of hyperparameters optimizes the target metric, that metric being the area under the receiver operating characteristic curve (AUC). AUC is a numeric metric that measures how well the model can distinguish between patients with PPM and those without PPM.

The predicted probabilities that were generated on each fold were stacked, which was repeated 10 times for each patient. The model took the average of the predicted probabilities of all 10 repeats; the average predicted probabilities for each patient were then used to compute the final AUC. The *pROC* R package was used to produce the ROC curves along with the 95%CI for the AUC (Figures 3 and 5). Variable importance is determined by calculating the relative influence of each variable included in the model. The variable importance plot provides a ranked list of the most significant variables in descending order.

The *caret* R package was used to fit a logistic regression using 5-fold cross-validation repeated 10 times. Similar to the GBM model, this process also used 5-fold cross-validation repeated 10 times, where the predicted probabilities for each fold were stacked and then averaged over all 10 repeats for each patient. The average predicted probabilities of PPM risk for each patient were used to produce the final AUC. Categorical and ordinal variables were compared either with the chi-square or Fisher exact tests and are expressed as numbers and percentages. Continuous variables were compared with the *t*-test and expressed as mean $\pm$ SD. Pearson’s χ^2 test and Analysis of Variance were used to assess the baseline differences. A $P < 0.05$ was considered significant. R software version 3.4.1 (Foundation of Statistical Computing, Vienna, Austria) was used to run the analysis. Baseline characteristics, echocardiographic variables, EKG variables, and MDCT variables for 30 d and 1-year analysis are shown in the [Supple-](#)

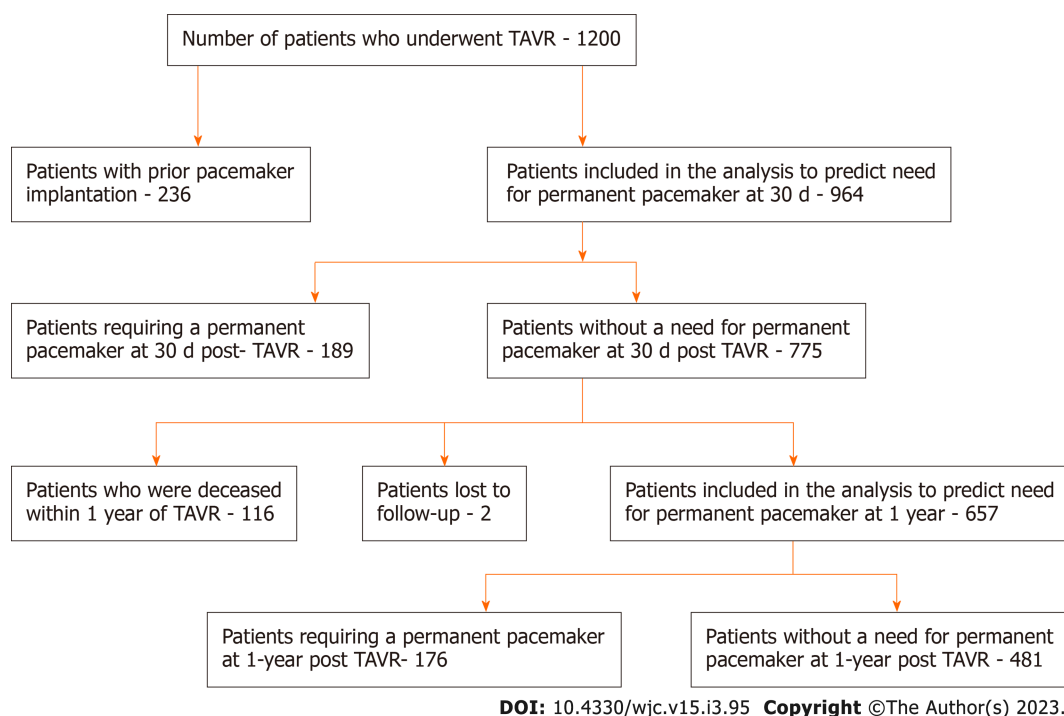


Figure 1 Flowchart depicting patient recruitment for the analysis transcatheter aortic valve replacement-transcatheter aortic valve replacement. TAVR: Transcatheter aortic valve replacement.

mentary material. Marlene Girardo and Matthew Buras are the statisticians who ran the analysis and are also authors of the paper.

RESULTS

30-d analysis

The mean age of the patients was 80.9 ± 8.7 . 42.1% of patients were female and 19.6% ($n = 189$) required PPM at 30 d post-TAVR. 68.8% of the entire patient cohort had a balloon-expandable valve. Patients requiring PPM post-TAVR had higher proportions of prior percutaneous coronary interventions, aspirin use, trans-femoral access, self-expandable valve use, and New York Heart Association heart failure class III/IV as compared to those who did not require PPM post-TAVR. Other baseline differences between the two groups can be seen in the **Supplementary material**. Using our GBM machine learning algorithm, a scoring model using the 20 highest weighted predictors of PPM requirement post-TAVR was generated. The highest weighted characteristic was a higher brachiocephalic artery to annulus distance to patient height ratio, followed by right bundle branch block (RBBB), higher brachiocephalic to aortic annulus distance, high pre-operative risk, and the use of self-expanding valves (as opposed to balloon expandable valves). **Figure 2** shows the full list with the relative weights of the twenty variables. The area under ROC to predict the need for PPM at 30 d for the GBM model was 0.66 (95%CI: 0.61-0.70) *vs* 0.55 (95%CI: 0.49-0.60) for the PPM risk score model ($P < 0.001$). The comparison of the ROC curves of both models is shown in **Figure 3**.

1-year analysis

The mean age of the patients was 80.7 ± 8.2 . 42.6% of patients were female and 26.7% ($n = 176$) required PPM at 1-year post-TAVR. 67.6% of the entire patient cohort had a balloon-expandable valve. Patients requiring PPM at 1-year post-TAVR had higher proportions of prior aortic valve intervention, aspirin use, severe mitral stenosis, elevated filling pressures, and percutaneous transfemoral access compared to those who did not require PPM at 1 year. Other baseline differences can be seen in the **Supplementary material**. Based on the GBM machine learning algorithm, a scoring model using the 20 highest weighted predictors of PPM dependency at 1-year post-TAVR was generated. The five highest weighted predictors were higher brachiocephalic artery to annulus distance to height ratio, higher mitral valve diastolic mean gradient, RBBB, higher LVOT diameter, and higher distance of right coronary artery to basal ring (mm). **Figure 4** shows all twenty variables with the highest weightage. The area under ROC to predict the need for PPM at 1 year for the GBM model was 0.72 (95%CI: 0.67-0.76) *vs* 0.54 (95%CI: 0.49-0.60) for the PPM risk score model (P value < 0.001). The comparison of the ROC curves of both models

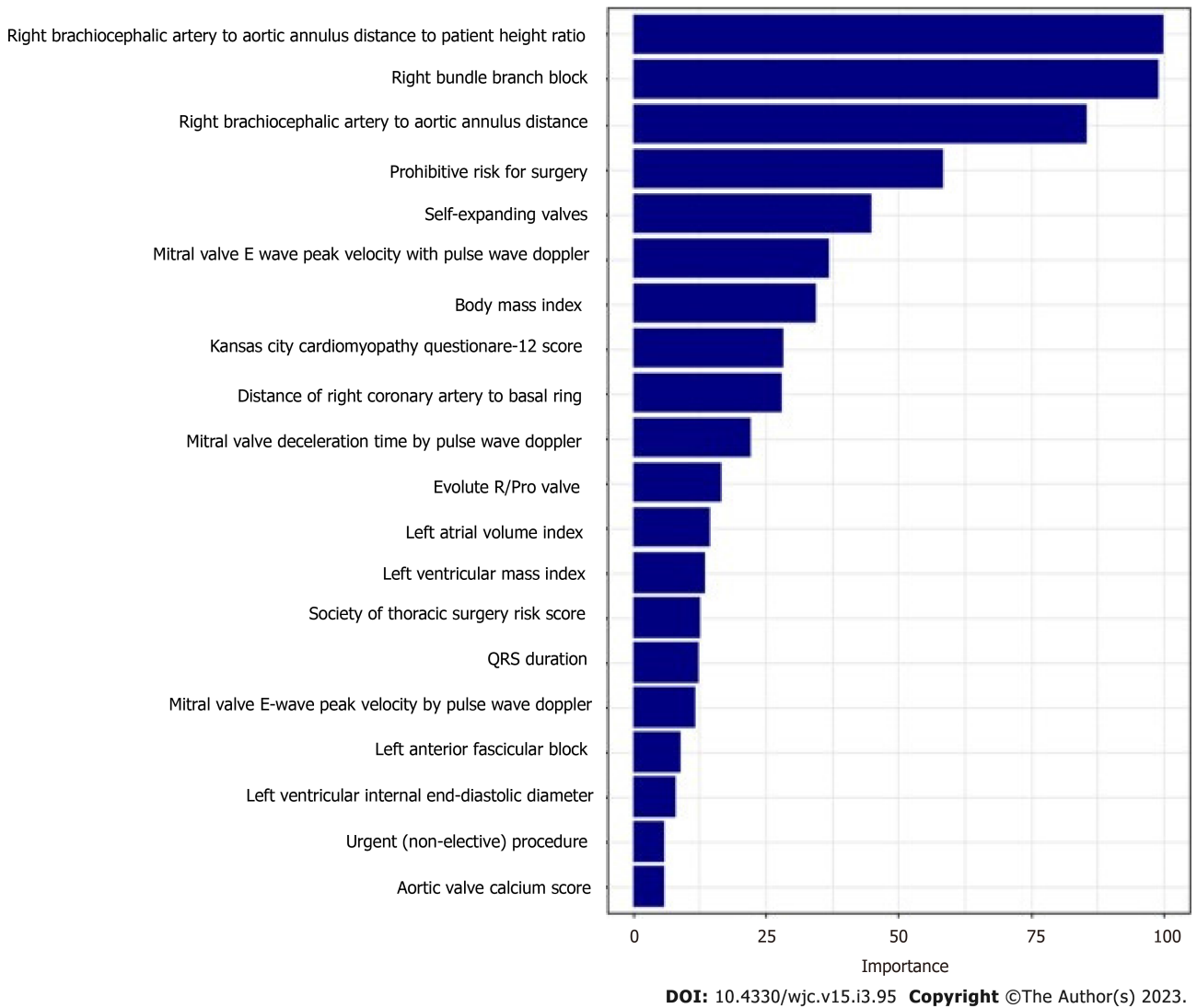


Figure 2 Variables with the highest importance in a gradient boosting model to predict the need for a permanent pacemaker at 30 d.

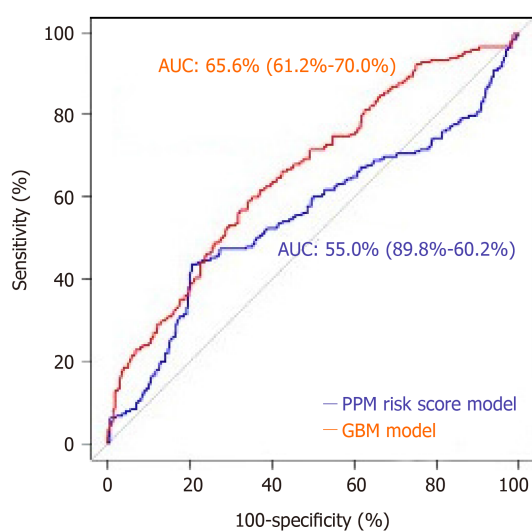
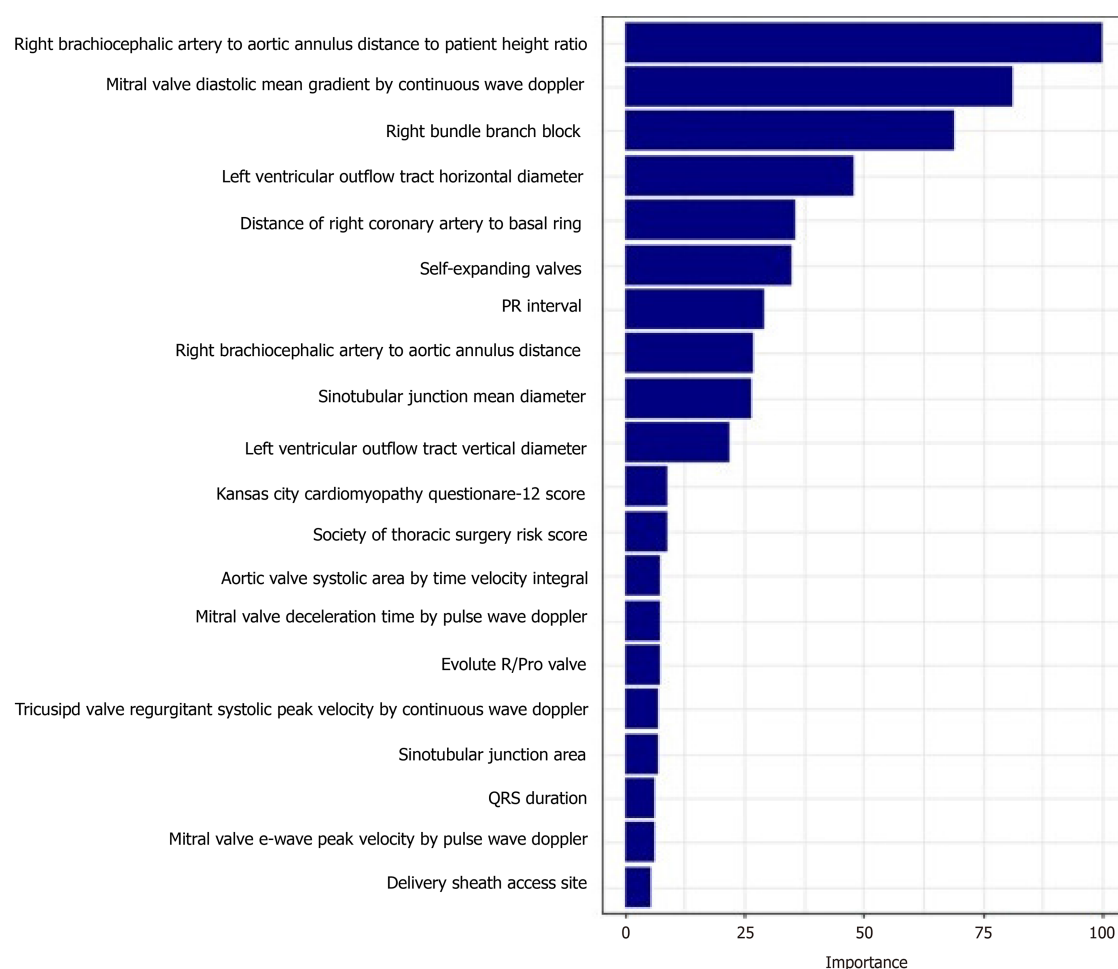


Figure 3 Receiver operator curves of the gradient boosting model and permanent pacemaker risk score model to predict the need for a permanent pacemaker at 30 d. GBM: Gradient boosting model; PPM: Permanent pacemaker model.



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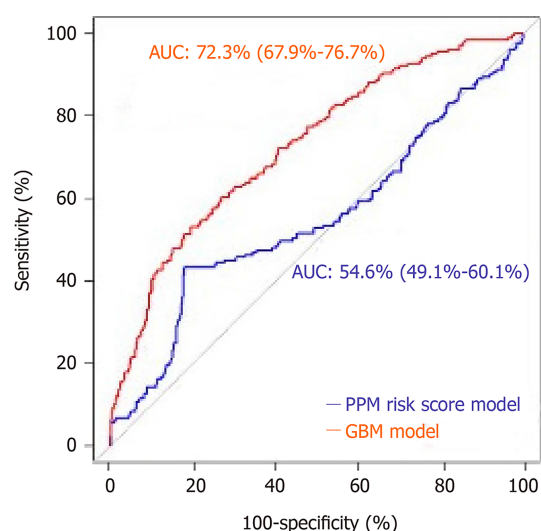
Figure 4 Variables with the highest importance in the gradient boosting model to predict the need for a permanent pacemaker at 1 year.

is shown in [Figure 5](#).

DISCUSSION

Given the clinical relevance of conduction abnormalities necessitating PPM, we sought to develop a risk assessment tool to predict PPM implantation in patients post-TAVR using machine learning (ML). ML seeks to mimic the thought process, learning capacity, and storage of knowledge of humans[28]. Its techniques have been in use in cardiovascular medicine, but our study is the first to predict the risk of PPM implantation in patients post-TAVR. This study demonstrates that ML could be used to accurately predict the requirement of PPM at 1-year post-TAVR with a high level of discriminatory ability. The GBM model had a modest level of discriminatory ability to predict the requirement of PPM at 30 d. Arteriovenous conduction disturbances are well-known post-TAVR. The most common conduction abnormalities post-TAVR are left bundle branch block (LBBB) and complete heart block[30,31]. Multiple mechanistic reasons for these abnormalities have been theorized, and the most popular one is that the spatial proximity of the cardiac conduction system to the calcified aortic valve[32,33], as well as the underlying conduction disease prevalence in this elderly group[34], predisposes it to damage during the TAVR procedure. Many patients require placement of PPM post-TAVR, with an incidence of 10%-15% commonly cited in the literature, with substantial variability based on the specific TAVR valve used[4]. Conduction abnormalities are clinically relevant as these patients have a higher incidence of subsequent hospitalizations, less improvement in LV function and functional status after TAVR, and possibly even higher mortality, though there is conflicting evidence regarding the latter and long-term prognosis[11, 13,30,35].

The rate of PPM implantation post-TAVR in our study was 19.6% at 30 d and 26.7% at 1 year, which is similar to previous trials[8,36-39]. Pre-existing conduction abnormalities such as RBBB, LBBB, and 1st-degree AV block were significantly associated with post-TAVR PPM implantation, and these are consistent with the previous studies[12,13]. Trans-femoral access was also significantly correlated with the PPM rate, which has also been described as a risk factor in a prior registry[13]. Another variable that



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Figure 5 Receiver operator curves curves of gradient boosting model and permanent pacemaker risk score model predicting the need for a permanent pacemaker at 1 year. GBM: Gradient boosting model; PPM: Permanent pacemaker model.

strongly associates with the PPM rate was self-expanding valves which are also known through prior studies[12,13]. High rates (13.3%-17%) of implantation with the Edwards Sapien 3 valve have previously been demonstrated which was also consistent with our study[19,36,40]. Brachiocephalic artery to aortic valve annulus distance to height ratio was the highest weighted predictor for PPM implantation post-TAVR at both one month and one year. As far as we are aware, we are the first to describe this variable as a predictor for PPM requirement, let alone as the highest weight predictor. It is not clear why it is associated with conduction abnormalities requiring PPM. We suspect that the longer distance of the ascending aorta proximal to the origin of the brachiocephalic artery allows for the TAVR valve to hug the outer curve of the aorta more, thus exerting more force on the right/non-cusp side where the conduction system lies. This needs to be confirmed in other studies.

Overall, the model used for the 30-d and 1-year predictors yielded a very similar set of variables. The main difference was the presence of mitral valve diastolic mean gradient on echo which was the second highest weighted predictor for PPM at 1 year but was not present in the 30-d predictive model. Whether it is the gradient itself that is associated with conduction abnormalities or the mitral annular calcification that is presumably associated with such gradients and would be expected in such populations with calcific aortic stenosis is unclear. The mitral valve and annular calcification were not one of our echocardiographic parameters that were included in the study, so further studies need to be completed. The subsequent evaluation of whether mitral valve or annular calcification is associated with conduction abnormalities independent of AS and TAVR is an obvious corollary. The comparison of our predictive model with the PPM risk score developed by Vejpongsa *et al*[20] which uses 6 variables for scoring, demonstrates the enhanced prognostic capability of our model (Figures 3 and 5). Other risk score models for PPM requirement post-TAVR that have been described are the Emory Risk Score developed by Kiani *et al*[19] and the risk score developed by Maeno *et al*[41]. We were unable to compare our model with these risk score models due to a lack of complete variables, including the history of syncope in the Emory risk score, and membranous septum (MS) length in the risk score. Some of the limitations of this study need to be noted. Firstly, the model is complex, and therefore its use may be limited in clinical practice. Additionally, given the large number of demographic information and clinical variables included in this model, these variables may not always be present. Nevertheless, we feel that the prognosticating ability of the model overcomes this limitation and that with the increasing use of electronic medical records, most data is available. Secondly, this was primarily a feasibility study and is retrospective in nature, which restricts our ability for defining causal associations. There is a need for prospective validation with an external cohort. Thirdly, we did not include a few variables in our model that have been included in other risk scores for PPM implantation, such as a history of syncope or distal landing zone calcium burden, as these variables were not present in enough of our cohort to include. Thus, there is a potential for change in the analysis with the inclusion of such variables. Lastly, the study included primarily referred patients in three high-volume tertiary care centers, and thus are likely higher risk and more complex than the average TAVR patient.

CONCLUSION

Machine learning was used to predict patients who are at risk of developing conduction abnormalities requiring PPM at 30 d and 1 year. Our GBM model using machine learning outperforms the PPM risk score model in its predictive value. Brachiocephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation at both 30 d and 1 year, which has not been previously described in the literature.

ARTICLE HIGHLIGHTS

Research background

For aortic stenosis, it is a fact that transcatheter aortic valve replacement use has greatly increased relative to surgical replacement with the most common complications of the procedure including atrioventricular conduction abnormalities development and permanent pacemaker requirement (PPM). Hence, it is essential to risk stratify patients for potential need of PPM implantation post-procedure. We used artificial intelligence to predict pre-procedural risk for pacemaker placement post-transcatheter aortic valve replacement at 30 d and 1 year.

Research motivation

Previous studies that evaluated risk factors associated with permanent pacemaker requirement used data for older-generation valves and also included only a limited number of variables and hence, limiting their predictive potential. Artificial intelligence does a remarkable job of predicting variables *via* machine learning and the same has been used in our study.

Research objectives

To predict pre-procedural risk for permanent pacemaker post-transcatheter aortic valve replacement (TAVR) at 30 d and 1 year.

Research methods

We performed a retrospective study on patients with severe symptomatic aortic stenosis who underwent transcatheter aortic valve replacement (TAVR). Gradient boosting machine learning model has been used for predicting probabilities.

Research results

For 30-d analysis, higher brachiocephalic artery to annulus distance to patient height ratio was the highest weighted characteristic that predicted PPM placement post-TAVR. Also for 1-year analysis, higher brachiocephalic artery to annulus distance to patient height ratio was the highest weighted characteristic that predicted PPM placement post-TAVR.

Research conclusions

Brachiocephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation in the study both at 30 d and 1 year and it was not been previously described in the literature.

Research perspectives

We sought to develop and have developed a risk assessment tool to predict PPM implantation post-TAVR using machine learning.

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FOOTNOTES

Author contributions: Agasthi P conceptualized, did methodology, project administration, review, and editing; Ashraf H methodology and writing the manuscript; Pujari SH did the data curation, visualization, and writing; Girardo M did the formal analysis, methodology, review, and editing; Tseng A writing, review, and editing the manuscript; Mookadam F did the methodology, project administration, review, and editing; Venepally N did the writing and data curation; Buras MR did the methodology and writing; Allam M did the data curation, visualization,

and writing; Abraham B, Khetarpal BK, MD SKM, Eleid MF, Greason KL, Beohar N, Sweeney J, and Fortuin D writing, review and editing the manuscript; Holmes DRJ and Arsanjani R did the methodology, project administration, review, and editing.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available.

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Observational Study

Effect of reperfusion strategy on QT dispersion in patients with acute myocardial infarction: Impact on in-hospital arrhythmia

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Abstract**BACKGROUND**

Myocardial ischemia and ST-elevation myocardial infarction (STEMI) increase QT dispersion (QTD) and corrected QT dispersion (QTcD), and are also associated with ventricular arrhythmia.

AIM

To evaluate the effects of reperfusion strategy [primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy] on QTD and QTcD in STEMI patients and assess the impact of the chosen strategy on the occurrence of in-hospital arrhythmia.

METHODS

This prospective, observational, multicenter study included 240 patients admitted with STEMI who were treated with either PPCI (group I) or fibrinolytic therapy (group II). QTD and QTcD were measured on admission and 24 hr after reperfusion, and patients were observed to detect in-hospital arrhythmia.

RESULTS

There were significant reductions in QTD and QTcD from admission to 24 hr in both group I and group II patients. QTD and QTcD were found to be shorter in group I patients at 24 hr than those in group II (53 ± 19 msec vs 60 ± 18 msec, $P =$

0.005 and 60 ± 21 msec *vs* 69 ± 22 msec, $P = 0.003$, respectively). The occurrence of in-hospital arrhythmia was significantly more frequent in group II than in group I (25 patients, 20.8% *vs* 8 patients, 6.7%, $P = 0.001$). Furthermore, QTD and QTcD were higher in patients with in-hospital arrhythmia than those without ($P = 0.001$ and $P = 0.02$, respectively).

CONCLUSION

In STEMI patients, PPCI and fibrinolytic therapy effectively reduced QTD and QTcD, with a higher observed reduction using PPCI. PPCI was associated with a lower incidence of in-hospital arrhythmia than fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients not experiencing in-hospital arrhythmia than those with arrhythmia.

Key Words: Arrhythmia; QT dispersion; ST-segment elevation myocardial infarction; Reperfusion; Primary percutaneous coronary intervention; Fibrinolytic therapy

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Core Tip: We evaluated the effect of a reperfusion strategy on QT dispersion (QTD) and corrected QT dispersion (QTcD) in patients with ST-segment elevation myocardial infarction. Primary percutaneous coronary intervention was found to be superior in the reduction of QTD and QTcD and associated with a lower incidence of in-hospital arrhythmias when compared to fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients not experiencing in-hospital arrhythmia than those with arrhythmia.

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INTRODUCTION

Arrhythmia is a major cause of death in ST-elevation myocardial infarction (STEMI) patients, especially in the early in-hospital period[1]. Many studies have shown that dispersion of repolarization is the most common trigger and the main substrate for the occurrence of lethal arrhythmia in patients with STEMI [1-3]. QT dispersion (QTD), the difference between maximal and minimal QT interval calculated on a standard 12-lead electrocardiogram (ECG), measures the heterogeneity of myocardial repolarization[4]. It has previously been discovered that QT interval and QTD are increased in cases of acute ischemia and STEMI[5]. These variations may reflect the changing patterns of underlying recovery of ventricular excitability, which is profoundly disturbed at the earliest phase of acute myocardial infarction (MI)[6]. Moreover, QTD prolongation has been reported as a predictor of arrhythmia in patients with STEMI[7].

Although primary percutaneous coronary intervention (PPCI) is the treatment of choice when managing STEMI patients, fibrinolytic therapy is still an important reperfusion strategy in settings where primary PCI cannot be offered at the appropriate time[8]. Reperfusion of the infarct-related artery, either by fibrinolytic therapy or PPCI, could homogenize the duration of the ventricular action potential, thereby reducing the QTD. However, there are conflicting data about the effects of both reperfusion therapy modes with respect to their abilities to reduce QTD in patients with STEMI. Moreover, there are inadequate data relating to the effects of these reperfusion strategies on incidence of in-hospital arrhythmias.

Here, we evaluate the QTD and corrected QT dispersion (QTcD) in patients presenting with STEMI by comparing those treated with PPCI with those receiving fibrinolytic therapy. In addition, the impacts of these treatment modalities on in-hospital incidence of arrhythmia are compared.

MATERIALS AND METHODS

Study population

This was a prospective, observational, multicenter study that included 240 consecutive patients with first acute STEMI who were treated with either fibrinolytic therapy or PPCI. Patients with STEMI who received either fibrinolytic therapy with successful fibrinolysis or PPCI with final thrombolysis in myocardial infarction (TIMI) flow grade III were included. This study was conducted at 4 centers. PPCI-

treated patients were recruited and treated at Assiut University Heart Hospital (a center with resources to perform this procedure at any time), and the fibrinolytic therapy-treated patients were recruited and treated at Sohag Heart & GIT Center, Assiut Police Hospital, and Qena General Hospital.

The STEMI diagnosis in each case was made using the 4th universal definition of MI, which is based on typical electrocardiographic changes alongside clinical symptoms associated with elevation of cardiac biomarkers[9]. Patients were included if they had chest pain for more than 30 min, ST-segment elevation in at least 2 contiguous ECG leads, and hospital admission within 12 hr of onset of chest pain. Successful fibrinolysis was defined as the presence of at least 2 of the following criteria: (1) Disappearance of chest pain within 90 min of starting the fibrinolytic infusion; (2) resolution of ST-segment elevation (in the ECG lead with maximum ST-elevation at baseline) by more than 50% after starting fibrinolytic infusion; or (3) abrupt initial increase in cardiac enzyme levels within the first 24 hr following onset of symptoms[10].

Exclusion criteria were non-ST elevation myocardial infarction, prior history of MI or surgical revascularization, absence of sinus rhythm, presence of bundle branch block or any other inter-ventricular conduction abnormality, ventricular pacing rhythm, pre-excitation on ECG, electrolyte abnormalities, use of medications that affect the QT interval (*e.g.*, antiarrhythmic, antidepressant, and antipsychotic drugs), and cases in which the QT interval could not be measured in at least 8 ECG leads. Patients with unsuccessful reperfusion after thrombolytic therapy and those not achieving TIMI-III flow within the infarct-related artery during PPCI were also excluded.

Study design

Patients were classified into 2 groups based on the reperfusion strategy used. Group I (120 patients) were treated with PPCI and group II (120 patients) received fibrinolytic therapy (1.5 million units of streptokinase given intravenously over 30-60 min).

The 12-lead ECG was recorded at a paper speed of 25 mm/sec. and 10 mm/mV gain standardization. ECG measurements were taken on admission and 24 hr after the reperfusion with either of the two strategies using an ECG machine (EC3T 01 RD/1, MONITOR, Russia). Heart rate, QT interval, and corrected QT (QTc) interval for each ECG lead were calculated automatically using built-in software (ArMaSoft-12-Cardio software, MONITOR, Russia) using Bazett's formula[11]. QT and QTc dispersions were defined as the differences between the maximum and minimum QT and QTc intervals, respectively, in a given ECG lead. Delta (Δ) was defined as the difference in ECG measurement parameters before treatment and 24 hr after reperfusion. For example, Δ QT interval was defined as the QT interval before treatment minus the QT interval 24 hr after reperfusion. ECG data were included where there were adequate measurements using at least 8 leads total with at least 4 precordial leads. All ECGs were in sinus rhythm.

The study endpoint was designated as the occurrence of arrhythmia during admission. Examples of arrhythmias considered included frequent premature ventricular ectopic beat, non-sustained ventricular tachycardia, sustained ventricular tachycardia, ventricular fibrillation, and atrial fibrillation. The study population was further classified into 2 more groups according to the incidence of in-hospital arrhythmia. These groups comprised an in-hospital arrhythmia group whose arrhythmias were recorded and a group who did not experience arrhythmia during admission (and therefore had no recorded arrhythmia events).

Sample size calculation

Sample size calculation was carried out using G Power 3 software. The calculated minimum sample of adult patients presenting with STEMI was 238. This calculation was made based on a 2-group 1:1 design [Group I ($n = 119$): treated with PPCI and Group II ($n = 119$): treated with fibrinolytic therapy] and would have 85% power to detect an absolute difference of 35% in the mean QTD, at a 1-sided significance level of 0.05.

Ethical considerations

This study was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB No. 17101454), and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants. The authors are accountable for all aspects of the work, including full data access, integrity of the data, and the accuracy of the data analysis. They ensure that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

Statistical analysis

Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation (SD) and those without normal distribution as median (interquartile range). Normality of the continuous variables was checked with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequency and percentage (%). Continuous variables were compared using an unpaired student's *t*-test for normally distributed data and Mann-Whitney test for non-normally distributed data. Comparisons of ECG data before and after reperfusion therapy were conducted using paired *t*-tests. Chi-Square tests

or Fisher exact tests were used when appropriate to compare categorical variables. A *P* value of < 0.05 was considered statistically significant, with all reported *P* values being 2-tailed. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Table 1 shows similar baseline clinical characteristics of both groups of the study population. Moreover, there were no significant differences between the groups with respect to the location of MI and the time from chest pain onset to the start of the reperfusion (**Table 1**).

Regardless of the chosen perfusion strategy, there was a significant reduction in QTD and QTcD from admission to 24 hr after reperfusion. This reduction in both QTD and QTcD was due to a significant increase in the minimum QT interval ($\Delta = -15.9 \pm 42.4$ msec) with a concomitant decrease in maximum QT interval ($\Delta = 8.5 \pm 47.8$ msec) for the QTD and an increase in the minimum QTc interval ($\Delta = -22.4 \pm 44.5$ msec) alongside a concomitant decrease in QTc interval ($\Delta = 5.1 \pm 47.8$ msec) for the latter measurement (**Table 2**).

From admission to 24 hr, both QTD and QTcD decreased significantly in both groups I and II (**Table 3**). Following reperfusion (24 hr later), the QTD and QTcD of patients in group I were significantly shorter than those in group II ($P = 0.005$ and $P = 0.003$, respectively). Moreover, Δ changes in both QTD and QTcD were significantly higher in group I compared with group II (37.6 ± 17.1 msec *vs* 11.3 ± 7.9 msec, $P < 0.001$ for the former and 43.6 ± 13.6 msec *vs* 11.4 ± 8.0 msec, $P < 0.001$ for the latter) (**Table 3**).

The incidence of in-hospital arrhythmia was significantly lower in group I (8 patients, 6.7%) than in group II (25 patients, 20.8%), $P = 0.001$. Different types of recorded arrhythmia observed in both groups are illustrated in **Figure 1**. Patients who did not experience in-hospital arrhythmia had significantly reduced QTD and QTcD values compared to those who did experience in-hospital arrhythmia regardless of the perfusion strategy used (**Table 4**). Furthermore, the Δ changes of both QTD and QTcD were significantly higher in patients who did not experience in-hospital arrhythmia (25.9 ± 18.3 msec and 28.7 ± 20.1 msec, respectively; $P = 0.003$) than patients who experienced in-hospital arrhythmias (14.8 ± 18.9 msec and 19.8 ± 14.5 msec, respectively; $P = 0.016$) (**Table 4**).

DISCUSSION

It is well known that QTd has a prognostic role for stratifying MI patients who are at higher risk of arrhythmic events. In a recent large meta-analysis of 22 trials, an improved QTd after acute MI was associated with lower risk of associated serious arrhythmia. However, no prognostic role was found with respect to all-cause mortality or sudden cardiac death in such a patient population[12].

The current study provides further evidence supporting the beneficial impact of reperfusion therapy on decreasing both QTD and QTcD in the setting of STEMI. Moreover, to our knowledge, our study is the first to calculate QT and QTc intervals automatically using a software program that eliminates human bias of manual measurement. We showed that reperfusion therapy decreases QTD and QTcD in patients with STEMI regardless of reperfusion strategy. Also, our study demonstrated that PPCI had a more favorable effect on reducing QTD and QTcD (measured 24 hr after treatment) when compared to fibrinolytic therapy. Moreover, we showed that restoration of coronary reperfusion using PPCI had a greater impact in reducing the incidence of in-hospital arrhythmias than fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients without in-hospital arrhythmia than in those with arrhythmia recorded during admission.

In the setting of acute coronary syndrome, evidence suggests that there are electrophysiological alterations in action potentials, causing repolarization dispersion between normal and ischemic fibers and between the epicardium and endocardium. This leads to repolarization delays in regions influenced by acute ischemia, thus causing QT and QTc prolongation[5,13-15]. The present study included STEMI patients with achievement of TIMI flow grade III in group I and successful fibrinolysis in group II. Establishing the patency of the infarct-related artery, either by fibrinolytic therapy or PPCI, could reduce regional myocardial ischemia and homogenize the ventricular action potential, thereby reducing the QTD and QTcD. This theory is supported by studies finding that TIMI flow grades II and III were associated with far lower QTD and QTcD values as compared to TIMI flow grades 0 and I[16,17]. Thus, the degree of QTD and QTcD reduction depends on the reperfusion status of the infarcted artery. The results of PPCI in STEMI patients are superior to fibrinolytic therapy with respect to reestablishing infarct-related artery patency. The present study supports this assumption, as our results revealed that PPCI more significantly reduced QTD and QTcD intervals than fibrinolytic therapy in STEMI patients.

The mechanism of QT prolongation and QTD in the setting of MI is attributed to the elevation in extracellular potassium level, acidosis, and anoxia. These conditions also cause reductions in membrane excitability, shortening of action potential duration, and prolongation of recovery of excitability

Table 1 Patient characteristics

Characteristic	Group I, n = 120 patients	Group II, n = 120 patients	P value
Age in yr	57.9 ± 9.6	59.1 ± 10.7	0.38
Male sex	96 (80)	93 (77.5)	0.64
Smoking	49 (40.8)	58 (48.3)	0.24
Hypertension	35 (29.2)	43 (35.8)	0.27
Diabetes mellitus	38 (31.7)	40 (33.3)	0.78
CKD	4 (3.3)	7 (5.8)	0.35
Family history of CAD	15 (12.5)	21 (17.5)	0.28
Dyslipidemia	61 (50.8)	49 (40.8)	0.12
Location of MI: Anterior MI non-anterior MI	72 (60) 48 (40)	61 (50.8) 59 (49.2)	0.15
Time from chest pain onset to reperfusion in hr	4.04 ± 1.96	4.39 ± 2.79	0.29

Data are expressed in form of mean ± SD or frequency (%). CAD: Coronary artery disease; CKD: Chronic kidney disease; MI: Myocardial infarction; SD: Standard deviation.

Table 2 Heart rate and QT interval before and after reperfusion, all patients

Parameter	Before reperfusion, n = 240 patients	After reperfusion, n = 240 patients	Δ	P value
Heart rate in beat/min	78.6 ± 16.2	80.5 ± 15.7	-1.8 ± 16.9	0.09
Maximum QT in msec	407.1 ± 43.0	398.7 ± 45.2	8.5 ± 47.8	0.007
Minimum QT in msec	325.4 ± 41.7	341.3 ± 43.7	-15.9 ± 42.4	< 0.001
QTD in msec	81.8 ± 21.9	57.3 ± 18.9	24.4 ± 18.7	< 0.001
Maximum QTc in msec	461.2 ± 42.5	456.1 ± 38.9	5.1 ± 47.8	0.10
Minimum QTc in msec	368.5 ± 37.6	390.0 ± 36.4	-22.4 ± 44.5	< 0.001
QTcD in msec	92.7 ± 26.1	65.2 ± 22.6	27.5 ± 19.6	< 0.001

Data are expressed in form of mean ± SD. QTc: Corrected QT; QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Delta is change in variables before and 24 hr after the reperfusion strategy.

following an action potential[18]. The prolonged QT and QTD have been linked to the occurrence of arrhythmia in patients with congenital long QT syndrome and with drug-induced torsades des pointes [19,20]. Therefore, MI associated with increased dispersion of cardiac repolarization could lead to the occurrence of arrhythmia[7]. Opening of the infarct-related artery results in perfusion of the infarcted area and consequently washing off of the excess extracellular potassium leading to correction of tissue anoxia and acidosis. This leads to improvement in membrane excitability and recovery of excitability following an action potential, ameliorating repolarization abnormalities and decreasing QTD. Consequently, the occurrence of arrhythmia is less likely. Our results support this mechanism, as the data presented here revealed that patients without in-hospital arrhythmia had shorter QTD and QTcD intervals with higher Δ than those with arrhythmia.

Lopes *et al*[21] studied the effect of thrombolytic therapy on QTD in patients with STEMI, and showed that QTD was significantly shorter in patients with STEMI who underwent successful thrombolysis (Table 5). On the other hand, they found that QTD did not correlate with ventricular arrhythmia; however, QTD was higher in patients with ventricular arrhythmia than those without. This conclusion is undermined by the study design (retrospective) and the inclusion of patients with unsuccessful thrombolysis who had high post-procedure QTD. Furthermore, this study measured QT values manually, which introduces the possibility of measurement bias. In line with the present study, Ornek *et al*[22] and Mulay *et al*[23] not only found that thrombolytic therapy reduces QTD significantly in STEMI patients in the 1st wk of admission, but also that patients with ventricular arrhythmia had higher QTcD values than patients without arrhythmia (Table 5).

In concurrence with our study, Pan *et al*[24] demonstrated that QTcD measured before PPCI was significantly longer than 24 hr after PPCI administration. Furthermore, they showed that the absolute QTcD change after PPCI was an independent predictor of the development of major cardiovascular

Table 3 Heart rate and QT interval before and after reperfusion, group I vs group II

Parameter	Group I, n = 120 patients			Group II, n = 120 patients			P value				
	Before	After	Δ	Before	After	Δ	P1	P2	P3	P4	P5
Heart rate in beat/min	81.0 ± 15.7	82.7 ± 16.4	-1.7 ± 18.9	76.2 ± 16.3	78.2 ± 14.8	-2.0 ± 14.9	0.34	0.14	0.02	0.02	0.87
Maximum QT in msec	411.7 ± 38.4	392.0 ± 44.1	19.7 ± 48.8	402.6 ± 46.9	405.3 ± 45.6	-2.8 ± 44.3	< 0.001	0.49	0.10	0.02	< 0.001
Minimum QT in msec	320.2 ± 34.6	338.1 ± 39.0	- 17.9 ± 34.4	330.6 ± 47.4	344.6 ± 48.0	-14.0 ± 41.3	< 0.001	0.001	0.06	0.25	0.48
QTD in msec	91.5 ± 20.6	53.9 ± 19.1	37.6 ± 17.1	72.0 ± 18.5	60.7 ± 18.1	11.3 ± 7.9	< 0.001	< 0.001	< 0.001	0.005	< 0.001
Maximum QTc in msec	474.3 ± 45.9	453.8 ± 38.1	20.6 ± 53.1	448.1 ± 34.1	458.4 ± 39.7	-10.4 ± 35.8	< 0.001	0.002	< 0.001	0.35	< 0.001
Minimum QTc in msec	369.9 ± 43.2	393.0 ± 32.1	- 23.1 ± 51.7	367.1 ± 31.1	388.9 ± 40.3	-21.8 ± 36.2	< 0.001	< 0.001	0.56	0.38	0.82
QTcD in msec	104.4 ± 22.1	60.8 ± 21.6	43.6 ± 13.6	80.9 ± 24.4	69.6 ± 22.8	11.4 ± 8.0	< 0.001	< 0.001	< 0.001	0.003	< 0.001

Data are expressed in form of mean ± SD. P1: P value comparing before and after PPCI in group I. P2: P value comparing before and after thrombolytic therapy in group II. P3: P value comparing group I and group II before reperfusion strategy. P4: P value comparing group I and group II after reperfusion strategy. P5: P value comparing group I and group II regarding delta change. QTc: Corrected QT; QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Change in variables before and 24 hr after reperfusion; SD: Standard deviation.

Table 4 QT and corrected QT dispersion before and after reperfusion in patients with or without in-hospital arrhythmia

Parameter	In-hospital arrhythmia group, n = 33 patients			No in-hospital arrhythmia group, n = 207 patients			P value				
	Before	After	Δ	Before	After	Δ	P1	P2	P3	P4	P5
QTD in msec	82.1 ± 19.3	67.3 ± 22.7	14.8 ± 18.9	81.7 ± 22.3	55.8 ± 17.7	25.9 ± 18.3	< 0.001	< 0.001	0.91	0.001	0.003
QTcD in msec	94.0 ± 25.3	74.2 ± 24.9	19.8 ± 14.5	92.5 ± 26.2	63.7 ± 21.9	28.7 ± 20.1	< 0.001	< 0.001	0.75	0.03	0.02

Data are expressed in form of mean ± SD. P1: P value comparing before and after reperfusion strategy in in-hospital arrhythmia group. P2: P value comparing before and after reperfusion strategy in no in-hospital arrhythmia group. P3: P value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group before reperfusion strategy. P4: P value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group after reperfusion strategy. P5: P value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group regarding delta change. QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Change in variables before and 24 hr after reperfusion; SD: Standard deviation.

events at 1 year (Table 5). Hamza *et al*[25] reported that PPCI was effective in reducing QTc and QTD after 24 h, although the study showed no effect on these arrhythmogenic indices 90 min after successful revascularization with PPCI (Table 5). However, it should be emphasized that they did not monitor patients for the occurrence of arrhythmia.

In contrast to our results, other studies have shown that thrombolytic therapy decreased QTD over time, but without statistical significance. Studies have also shown a decrease in QTD 24 hr after PPCI treatment; however, this decline was also not significant[26,27] (Table 5). Oni Heris *et al*[26]'s study included patients with successful or unsuccessful thrombolysis who had high QTD following treatment, which would have affected the results of the QTD measured. Additionally, this study compared time points at 1 hr before thrombolytic therapy and 4 d later. Babapour *et al*[27]'s study was retrospective in design and included all patients with PPCI, irrespective of the final TIMI results. In this study, TIMI 0 and I had a higher value of QTD and QTcD than TIMI II and III, affecting the final results. Our prospective study included patients with successful fibrinolysis or PPCI with final TIMI flow grade III [17]. Moreover, our ECG parameters were computed automatically, thus reducing potential bias and variability.

Few studies have compared the effects of PPCI and fibrinolytic therapy on ventricular repolarization ECG parameters. However, previous attempts to explore the impact of these treatments on the incidence of in-hospital arrhythmia have been deficient. In agreement with our findings, Cavusoglu *et al*[28] showed that PPCI was associated with more significant decreases in QTD and QTcD as compared to

Table 5 Studies addressing repolarization changes following reperfusion in ST-segment elevation myocardial infarction

Ref.	Study type	Study population	Time to evaluation	Reduction of QTD and QTcD	In-hospital arrhythmia	Remarks
Lopes <i>et al</i> [21], 2006	Retrospective	Thrombolytic (<i>n</i> = 154)	4 d	Sig. after 4 d	QTD not correlated with arrhythmia	CA after 48 h; Reduction in QTD is a predictor of coronary reperfusion
Ornek <i>et al</i> [22], 2014	Prospective	Thrombolytic (<i>n</i> = 20)	7 d	Sig. after 7 d	QTD correlated with arrhythmia	Use 24-h Holter monitor
Mulay <i>et al</i> [23], 2004	Prospective	STEMI (<i>n</i> = 100) Normal (<i>n</i> = 100)	24 hr On discharge	NA	Sig. high QTD in patients with ventricular arrhythmias compared to those without	Sig. higher QTD on admission, at 24 h, and at discharge than normal subjects
Pan <i>et al</i> [24], 2011	Prospective	PPCI (<i>n</i> = 81)	24 h	Sig. after 24 h	NA	QTcD change was an independent predictor of MACE at 1 yr
Hamza <i>et al</i> [25], 2014	Retrospective	PPCI (<i>n</i> = 54)	90 min 24 hr	Not sig after 90 min Sig. after 24 h	NA	
Oni Heris <i>et al</i> [26], 2014	Prospective	Thrombolytic (<i>n</i> = 160)	1 hr 4 d	Not sig. after 1 hr Not sig. after 4 d	NA	
Babapour <i>et al</i> [27], 2018	Retrospective	PPCI (<i>n</i> = 77)	24 h	Not sig. after 24 hr	NA	
Cavusoglu <i>et al</i> [28], 2001	Prospective	PPCI (<i>n</i> = 21) Thrombolytic (<i>n</i> = 21)	24 h	Sig. in PPCI group Sig. in thrombolytic group Sig. in PPCI compared with thrombolytic	NA	
George <i>et al</i> [29], 2015	Prospective	PPCI (<i>n</i> = 25) Thrombolytic (<i>n</i> = 25)	24 h	Sig. in PPCI group Not sig. in thrombolytic group Sig. in PPCI compared with thrombolytic	NA	
Valizadeh <i>et al</i> [30], 2020	Prospective	PPCI (<i>n</i> = 70) Thrombolytic (<i>n</i> = 115)	24 h	Sig. in PPCI group Not sig. in thrombolytic group Not sig. in PPCI compared with thrombolytic	QTD mean in patients with arrhythmia was reduced before and after treatment with a significant reduction after PPCI as compared to thrombolysis	

CA: Coronary angiogram; MACE: Major adverse cardiovascular event; NA: Not applicable; PPCI: Primary percutaneous coronary intervention; Ref.: Reference; Sig.: Significant; STEMI: ST-elevation myocardial infarction.

thrombolytic therapy (Table 5). Similarly, George *et al* [29] found that PPCI was superior in reducing QTD and QTcD in patients with STEMI as compared to thrombolytic therapy. However, these reports included only a small number of patients, were single-center studies, measured ECG parameters manually, and did not observe patients for arrhythmia. On the other hand, Valizadeh *et al* [30] observed that no significant decreases were seen in QTD and QTcD values in the PPCI group compared to the thrombolytic group, but QTD values in the PPCI group showed a greater reduction after treatment (Table 5). Unlike ours, this was a single-center study and used PPCI or fibrinolytic drugs based on the patient's clinical status. This also raises the possibility of bias in patient assignment to either group, and obviously, PPCI improves survival and decreases complications whatever the patient clinical status. Moreover, this study included all patients who received thrombolysis whether successful or not, and who underwent PPCI regardless of the final TIMI flow. Furthermore, QT values were manually measured, again raising the possibility of bias and error, which the authors themselves stated as a limitation. Nonetheless, they found that mean QTD values in patients with arrhythmia were lower before and after treatment, with a significant reduction after PPCI group as compared to the thrombolytic group, similar to our results.

The present study indeed also has some limitations. Our sample size was relatively small, even though it was powered sufficiently to identify the pre-specified endpoints. Still, the findings need to be endorsed by further studies in larger cohorts. Additionally, various medications can affect the QT interval; however, these could not be standardized at the time of patient enrolment. Finally, long-term observation for arrhythmia development in these patients was not performed, and therefore our findings are only applicable to the acute phase of STEMI.

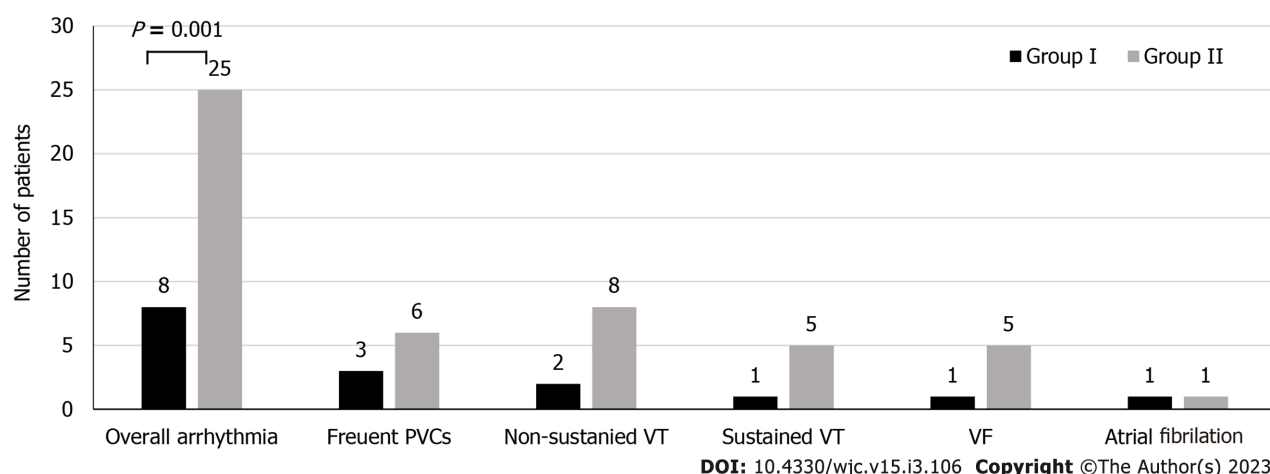


Figure 1 Types of arrhythmia in group I and group II. Overall incidence of in-hospital arrhythmia was significantly lower in group I than in group II. PVC: PolyVinyl chloride; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

CONCLUSION

We demonstrated that reperfusion with PPCI or fibrinolytic therapy was effective in reducing QTD and QTcD in STEMI patients. Reperfusion with PPCI was associated with shorter QTD and QTcD than thrombolytic therapy 24 hr after reperfusion. Moreover, PPCI was associated with a lower incidence of in-hospital arrhythmia than fibrinolytic therapy. Additionally, patients with in-hospital arrhythmia had a higher QTD and QTcD than patients without arrhythmia. Therefore, QTD and QTcD measurements in STEMI patients are important arrhythmogenic parameters that respond to reperfusion therapy.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) increases QT dispersion (QTD) and corrected QT dispersion (QTcD), and is also associated with ventricular arrhythmia. Fibrinolytic therapy or primary percutaneous coronary intervention (PPCI) was used as the reperfusion strategy in acute STEMI patients.

Research motivation

Cardiac arrhythmia in the setting of acute myocardial infarction (MI) has serious impact on patient morbidity and mortality. Every effort should be made to prevent post-MI arrhythmia and to predict its occurrence as early as possible.

Research objectives

To compare the impact of revascularization with fibrinolysis or PPCI in STEMI patients on cardiac electrical stability, as indicated by QTD and QTcD measurements.

Research methods

Two groups of patients were treated for acute STEMI; 1 group of patients were treated with fibrinolysis, and the other group of patients were treated with PPCI. QTD and QTcD were measured at baseline and at 24 hr following successful reperfusion. We compared these measures between the two groups and observed all patients for incidence of arrhythmia during hospital admission.

Research results

There were significant reductions in QTD and QTcD at 24 hr in both study groups. QTD and QTcD were found to be shorter in group I at 24 hr than in group II. Moreover, the incidence of in-hospital arrhythmia was significantly higher in group II as compared to group I.

Research conclusions

In STEMI patients, both PPCI and fibrinolytic therapy effectively reduced QTD and QTcD, with a more significant reduction observed after PPCI. Furthermore, PPCI was associated with a lower incidence of in-hospital arrhythmia.

Research perspectives

PPCI was superior to fibrinolytic therapy with respect to the electrical stability of the heart.

FOOTNOTES

Author contributions: Abdelmegid MAF conceived and designed the study; Bakr M collected and analyzed the data; Shams-eddin H drafted the manuscript and performed statistical analysis; Youssef A critically revised and assisted in writing the manuscript; Abdel-Galeel A critically revised and coordinated the submission of the manuscript.

Institutional review board statement: This study was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB No: 17101454), and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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

Conflict-of-interest statement: All authors declare having no conflicts of interest.

Data sharing statement: All supplementary data related to the current research work are available and ready to be shared upon request.

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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Role of artificial intelligence in cardiology

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Abstract

Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence by mimicking human thought processes. AI is a rapidly evolving transdisciplinary field which integrates many elements to develop algorithms that aim to simulate human intuition, decision-making, and object recognition. The overarching aims of AI in cardiovascular medicine are threefold: To optimize patient care, improve efficiency, and improve clinical outcomes. In cardiology, there has been a growth in the potential sources of new patient data, as well as advances in investigations and therapies, which position the field well to uniquely benefit from AI. In this editorial, we highlight some of the main research priorities currently and where the next steps are heading us.

Key Words: Artificial intelligence; Machine learning; Deep learning; Electrocardiography; Cardiac imaging

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Core Tip: The main aims of artificial intelligence (AI) in cardiovascular medicine are triple: To improve patient care, increase efficiency, and enhance clinical outcomes. In cardiology, there has been a progress in the potential sources of new patient data, along with advances in diagnostic tests and therapies, which position this specialty well to uniquely gain from AI. For the prediction of the future probably, we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come.

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INTRODUCTION

Artificial intelligence (AI) is the process of having a computational program that can execute tasks of human intelligence (*e.g.*, pattern recognition) by mirroring human thought processes[1]. AI is a transdisciplinary fast evolving field which puts together statistics, computer science, material science, neuroscience, psychology, computer hardware design, and mechanical engineering to create algorithms that aim to simulate human intuition, object recognition, and decision-making[2].

AI IN CARDIOLOGY

The main aims of AI in cardiovascular medicine are triple: To improve patient care, increase efficiency, and enhance clinical outcomes. In cardiology, there has been a progress in the potential sources of new data from patients, along with innovations in diagnostic tests and therapies, which position this specialty well to distinctively gain from AI[3].

The AI applications in cardiology are showing for instance that uncomplicated instruments like electrocardiography (ECG) might provide us a plenty of useful data, and AI converts the ECG data in a robust tool for prediction[4]. On the same side with more complexity, the use of AI tools in cardiovascular imaging into daily decision-making will improve care provision. AI has influenced every area of cardiovascular imaging in all stages from acquisition to reporting[5-7].

In cardiovascular medicine, the pioneer uses of AI were the creation of self-learning neural networks applied to ECG[8,9]. The next step on research has been the use of enormous sets of digital ECGs connected to detailed clinical data to create AI algorithms for the detection of silent (previously asymptomatic and undocumented) atrial fibrillation, left ventricular dysfunction, and hypertrophic cardiomyopathy, in addition to the ability to determinate a person's age, race, and sex, amongst other phenotypes. The population-level and daily clinical implications of AI-based ECG phenotyping keep up to arise, especially with the fast rise in the disposal of wearable and mobile ECG technologies[4]. These deep learning algorithms, once created, could be used in low-end machines like smartphones or wearables like smartwatches, providing great access to population. The first example has been recently published[10], applying an algorithm that detects the potential presence of left ventricular dysfunction through the ECG signal. This approach for sure is the future to spread this technology.

In the field of imaging, the progress of AI has been enormous in the last years, affecting all the phases of the diagnostic process. The advances have been bigger in the field of computed tomography imaging or magnetic resonance imaging[11], but the next step is echocardiography to generalize the value of AI in imaging[12], as shown in the review of Barry *et al*[11].

For the prediction of the future probably, we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come. Currently, nearly all studies of AI in echocardiography for example are constructed with retrospective data and concentrated largely on the performance of AI in concrete diagnostic tasks, and these studies range from small and simple exploratory studies[13] to larger studies[14,15]. There is a need on prospective studies to show the feasibility of the AI algorithms in the cardiovascular field[15]. One more preoccupation is what to make when machine and man differ. The value of outstanding validation of the algorithms must, consequently, be emphasised. Clinical judgment by the physician will be crucial, with a dose of humbleness additionally, to guarantee that AI will be employed to assist and not substitute clinical decision-making.

CONCLUSION

A possible future lies in having this AI software implemented in low-end machines, and it would certainly help in the early detection and prevention of some cardiovascular diseases. We could affirm that for sure it will be essential that cardiovascular medicine specialists should keep the final step in the handling of the system, take care for the decisions, and have the power to modify algorithms in the situations that get mistaken.

FOOTNOTES

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Arrhythmic syncope: From diagnosis to management

Jaume Francisco Pascual, Pablo Jordan Marchite, Jesús Rodríguez Silva, Nuria Rivas Gándara

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Abstract

Syncope is a concerning symptom that affects a large proportion of patients. It can be related to a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. However, benign causes are the most frequent, and identifying high-risk patients with potentially severe etiologies is crucial to establish an accurate diagnosis, initiate effective therapy, and alter the prognosis. The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope is cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope. Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output and produce syncope. In this review, we summarized the main guidelines in the management of patients with syncope of presumed arrhythmic origin. Therefore, we presented a thorough approach to syncope work-up through different tests depending on the clinical characteristics of the patients, risk stratification, and the management of syncope in different scenarios such as structural heart disease and channelopathies.

Key Words: Syncope; Arrhythmia; Electrophysiological study; Loop recorder; Myocardial diopathy; Atrioventricular conduction block

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Core Tip: In this review, we summarized the most important and novel data on arrhythmic syncope, the value of the different diagnostic tests, the management, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. The review emphasized the importance of an appropriate stepwise approach work-up and intervention.

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INTRODUCTION

Definition and causes

Syncope is a total loss of consciousness (T-LOC) secondary to cerebral hypoperfusion, characterized by rapid onset, short duration, and complete spontaneous recovery[1]. It must be differentiated from other T-LOC that do not meet these characteristics, such as T-LOC of traumatic origin, some types of epilepsy, or certain psychiatric disorders. It should be noted that syncope is a symptom that encompasses a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. Therefore, it should not constitute a final diagnosis. It is of great importance to stratify the risk and try to determine the cause.

The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope refers to cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope (Table 1). Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output, causing the syncope. Non-arrhythmic causes of cardiac syncope are usually related to structural heart diseases with obstruction of outflow and/or inflow of blood. These obstructions can restrict increases in cardiac output on exercise rendering this insufficient to maintain the circulation. Severe aortic stenosis (AoS), hypertrophic cardiomyopathy (HCM), mitral stenosis, atrial myxoma, or severe pulmonary hypertension are some examples of conditions that can cause cardiac syncope *via* this mechanism.

Furthermore, myocardial ischemia and acute ischemic syndromes may also precipitate syncope through multiple mechanisms. It is important to highlight that most of these heart diseases can also be associated with arrhythmias or reflex syncope, and therefore it is often challenging to determine the main cause of syncope in structural cardiac syncope[1-5]. In other words, the mere presence of structural heart disease associated with obstruction does not allow us to conclude that the syncope is due to this mechanism. In many cases, it will be necessary to rule out other possible causes, especially arrhythmic ones.

Epidemiology

It is estimated that almost one in two people will suffer at least one syncopal episode in their lifetime[1, 6]. It is a front-line health problem with a high impact on the health system, even though it is known that only a small proportion of patients with syncope seek medical attention. An epidemiological study carried out in the United States showed that the prevalence of patients with syncope in the community requiring medical attention is 9.5 per 100 inhabitants, and that 1 in 10 required hospital admission[7].

The incidence of the first syncopal episode is distributed with a bimodal curve, with a first peak in youth (between 10-30 years of age) and a second peak over 65 years of age. Cardiac syncope is the third most common cause of syncope after reflex and orthostatic hypotension (OH)[1,8,9]. In the emergency department (ED), cardiac syncope accounts for 5%-21% of syncope. In the Framingham cohort, the prevalence of syncope and long-term prognosis were analyzed[10]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Reflex or vasovagal syncope is the most common cause in the general population. In the Framingham cohort it represented 21.0% of the cases, while cardiac syncope made up only 9.5%[10]. It is remarkable that the prevalence of cardiac syncope increases with advancing age[1,9-11]. Cardiac syncope causes less than 1% of syncope in youth (< 40 years)[12] and up to one-third in those over 60 years of age[10,12].

Prognosis

The prognosis of syncope is mostly related to the underlying cause and the presence of structural heart disease. While reflex syncope has an excellent prognosis in terms of survival, cardiac syncope is associated with an increased risk of mortality, especially if it is not identified and treated properly. Patients with reflex syncope have similar survival to patients without syncope[10], with a mortality rate between 4%-12% after 1 year (depending on the patient's age and comorbidities)[10,13-15]. By contrast, the 1-year mortality rate for cardiac syncope rises to 20%-30%[10,13-15]. In the Framingham cohort,

Table 1 Main cardiac causes of syncope

Cardiac syncope			
Arrhythmic causes	Bradyarrhythmia	Sick sinus syndrome/sinus node dysfunction	
		Atrioventricular block	
	Tachyarrhythmia	Supraventricular tachycardia (AVNRT, AVRT, AT, fast AF, <i>etc.</i>)	
		Ventricular arrhythmias	Related to structural heart disease
		Channelopathies and inherited arrhythmia syndromes	
Non-arrhythmic causes	Mechanical causes	Valvulopathies (aortic stenosis, mitral stenosis, <i>etc.</i>)	
		HCM	
		Atrial myxoma	
		Pulmonary emboli	
		Tamponade	
		Severe pulmonary hypertension	
		Acute coronary syndrome	

AVNRT: Atrioventricular nodal re-entrant tachycardia; AVRT: Atrioventricular re-entrant tachycardia; HCM: Hypertrophic cardiomyopathy; AF: Atrial fibrillation; AT: Atrial tachycardia.

cardiac syncope was associated with a two-fold increase in the risk of death compared with those without a history of syncope, with an approximately 50% 5-year survival[10]. In this study, patients with syncope of unknown origin also had an increased risk of all-cause mortality compared with the general population [hazard ratio = 1.32, 95% confidence interval (CI): 1.09-1.60]. This observation was also made in other studies focused on specific populations[5]. This may be due to the fact that there are potentially serious causes for syncope left untreated due to a lack of diagnosis.

Importantly, in patients with syncope of unknown origin, the mere presence of structural cardiac abnormalities or the evidence of a conduction system disorder is associated with a poor prognosis, increasing the risk of death by a factor of more than five[1,9,16-19]. On the other hand, a structurally normal heart with a normal electrocardiogram (ECG) is usually associated with a benign etiology for syncope and a favorable prognosis[1,20-22].

DIAGNOSTIC APPROACH AND TEST

Initial evaluation, clinical history, physical examination, and ECG

T-LOC is a relatively common cause of presentation to the ED, and half of these episodes can be attributed to syncope[23]. However, it is important to distinguish it from other causes of T-LOC, to avoid unnecessary investigations in patients with benign causes, and to correctly detect and treat patients with cardiac syncope, which can lead to serious outcomes. The most common condition that can be confused with syncope is probably epilepsy. This confusion is an important phenomenon leading to misdiagnosis with rates ranging from 6%-67%[24]. This misdiagnosis contributes significantly to the numbers of patients with a questionable diagnosis of epilepsy and to those with apparently drug-resistant epilepsy. Syncope can be accompanied with urinary incontinence and/or muscular contractions that can resemble epileptic seizures, making it difficult to differentiate between the diagnoses. While in epilepsy muscular movements are generalized and appear from the beginning of the T-LOC and continue for a few minutes, syncope can also be associated with muscular contractions, which often tend to appear a few seconds after the collapse. They tend to be pleiomorphic and last only a short period of time. Some clinical findings have been suggested to differentiate seizures from convulsive syncope. Tongue biting and confusion on awakening are the most useful in predicting an epileptic origin[25]. In addition, clinical clues that should raise the suspicion for psychogenic pseudo-syncope include prolonged duration, eye closure during the episode, unusual triggers, no recognizable prodromes, and a high frequency of attacks[26].

Another common source of confusion in the ED is represented by falls, especially in the elderly population with non-witnessed T-LOC. On the one hand, elderly people with cognitive impairment and muscular weakness can present with falls as a manifestation of another illness, such as infections or

metabolic disorders[27]. On the other hand, these populations are usually treated with medications that can lower blood pressure (BP) and heart rate (HR) and tend to be dehydrated due to reduced water consumption. This combination of factors can promote orthostatic syncope. Additionally, in the elderly, there is a high prevalence of sinus node dysfunction, conduction disturbances, and structural heart disease, putting these patients at high risk of presenting with cardiac syncope[2]. For all these reasons, current guidelines recommend that repeated falls in elderly people without a reasonable explanation should be approached like unexplained syncope[1].

Once the syncope diagnosis has been established, special attention should be paid to determining the underlying cause. Syncope can be caused by three main different etiologies: Reflex mechanism (also known as neural-mediated syncope); OH; or cardiac syncope, which can be due to arrhythmia or structural heart disease. The diagnostic approach should focus on detecting potential cardiac syncope, as it could be clinical manifestation of a primary cardiac disease with high risk of events.

Initial evaluation of any patient presenting with syncope should include three basic elements: (1) Careful history taking regarding the current and previous episodes (including eyewitness accounts); (2) Physical examination; and (3) ECG. Clinical history is probably the most important one, and it should be focused on past medical history, especially previous cardiac conditions, and symptoms related to the episode. Syncope during exertion or in a supine position accompanied by chest pain or palpitations have been described as high-risk factors and should raise the suspicion of cardiac syncope[28,29]. In addition, a family history of sudden cardiac death (SCD) at a young age or personal history of structural heart disease or coronary artery disease (CAD) have been considered high-risk factors. Physical examination does not usually show relevant findings, but it could reveal signs of heart failure or a systolic murmur suggesting structural heart disease. Performing an ECG is crucial, as it can show conduction disturbances, pathological Q waves, or repolarization abnormalities reflecting an underlying cardiac disease[15,30-32] (Figure 1). It is important to mention that every patient with syncope should have an ECG even if there is clear evidence that is a reflex syncope since there are some channelopathies such as long QT syndrome (LQTS) that can present with ventricular arrhythmias after emotional stimulus that can be confused with reflex syncope. Additionally, it has been described that patients with Brugada syndrome (BrS) are more prone to vasovagal syncope[33].

There are several scores developed for risk stratification according to clinical and ECG findings[34]. However, some of them have been tested with external validation cohorts showing poor sensitivity and specificity for detecting cardiac syncope, and they perform no better than clinician judgement at predicting short-term serious outcomes. Therefore, current guidelines do not recommend using them alone to make decisions in the ED. Most items included on these scales are those suggesting cardiac syncope, such as ECG abnormalities or signs or symptoms of structural heart disease.

Carotid sinus massage

Carotid sinus massage (CSM) consists of applying external pressure to the area of the neck where the carotid sinus is located and is indicated in patients over 40 with syncope. According to current clinical guidelines, carotid sinus hypersensitivity is defined by a sinus pause longer than 3 s or a drop in systolic BP (SBP) higher than 50 mmHg[1,9]. However, this condition is very common among older individuals with cardiovascular disease, even in the absence of syncope. To avoid misdiagnoses, it has been proposed that the diagnosis of carotid sinus syndrome requires reproduction of patient's symptoms and a sinus pause longer than 6 s or more or a drop in mean arterial pressure of 60 mmHg or more[35]. Patients fulfilling these criteria have been shown to have recurrent long pauses on monitoring and to respond well to cardiac pacing[36,37]. The worst complication of CSM is stroke, which is extremely uncommon.

Orthostatic challenge

Orthostatic challenge consists of measuring HR and BP changes between supine and upright positions. It is recommended to measure them during the first 3 min, but it can be extended to the first 10 min if there is a high suspicion of OH since retarded responses have been described[38]. OH is defined by a drop of more than 20 mmHg in SBP, or a drop of more than 10 mmHg of diastolic BP, or if SBP becomes lower than 90 mmHg, and always accompanied by symptoms[39]. OH is very common among elderly people, especially in patients taking anti-hypertensive medications and/or with autonomous nervous system diseases like Parkinson's disease or diabetes, and it represents an important cause of syncope in this population[2,40].

Tilt testing

Tilt testing is recommended in patients with suspected reflex syncope or autonomic failure, including delayed forms of OH or postural orthostatic tachycardia syndrome. The most frequently used protocol is the so called "Italian protocol," which includes a 20-min stabilization phase, followed by administration of sublingual nitroglycerin[41]. It is useful in patients with true reflex syncope, as it has been demonstrated that a positive cardioinhibitory response is highly predictive of asystolic spontaneous syncope[42]. However, it can also be positive in a high percentage of patients with unexplained syncope and even in patients with cardiac arrhythmic syncope. Therefore, it offers little diagnostic value in these

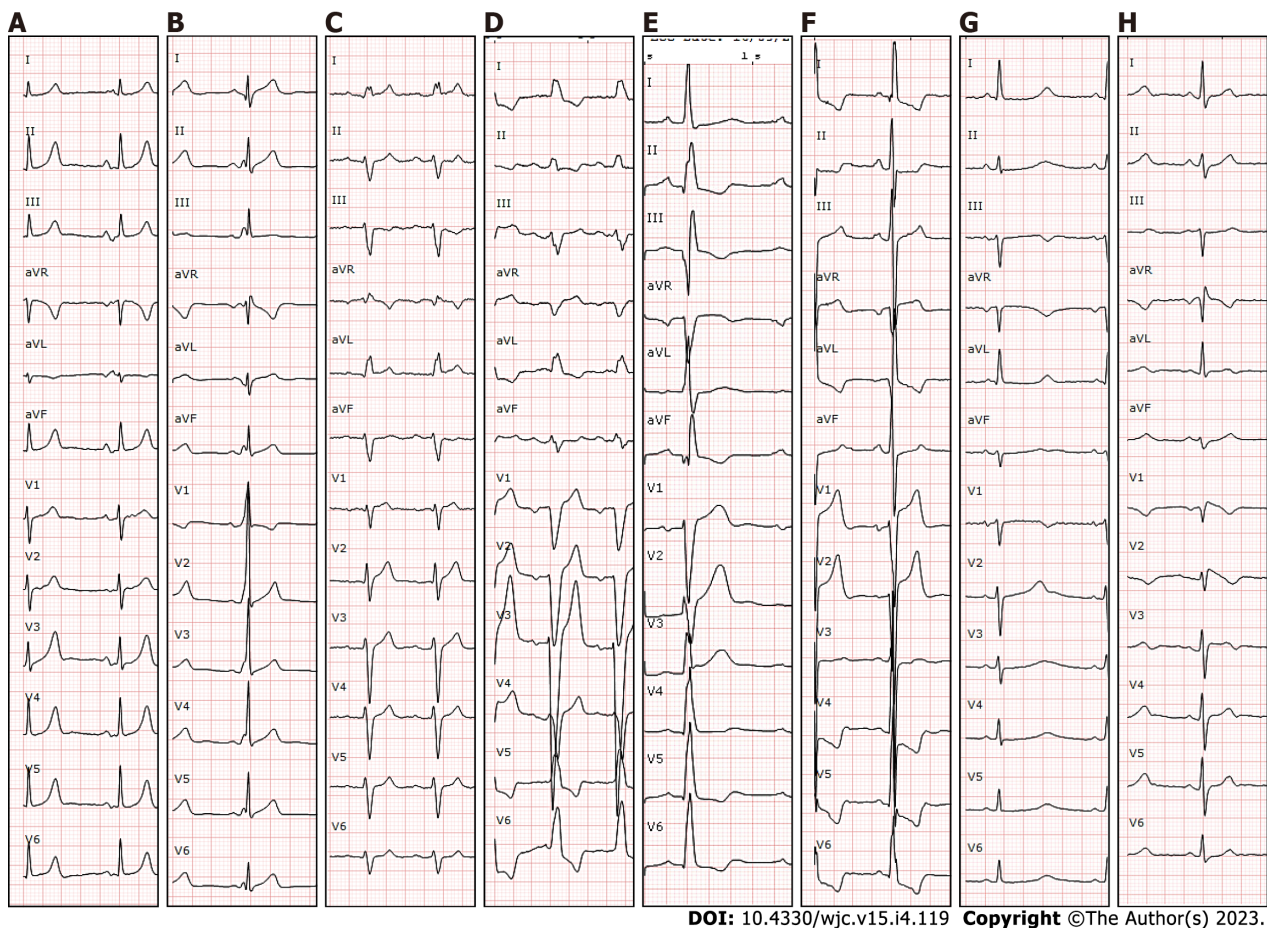


Figure 1 Examples of pathological electrocardiogram that should lead to suspicion of an arrhythmic origin of the syncope. A: Bayes Syndrome (biphasic p wave in inferior leads compatible with interatrial block, which is related with atrial arrhythmias); B: Pre-excitation syndrome; C: Long PR interval and left anterior fascicular hemiblock; D: Left bundle branch block; E: Inferior necrosis (Q waves); F: Hypertrophic cardiomyopathy; G: Long QT syndrome; H: Brugada syndrome. Suspected supraventricular tachycardia (A and B), suspected atrioventricular block (C and D), suspected ventricular tachycardia (E and F), and suspected polymorphic ventricular tachycardia (G and H).

populations and should not be performed routinely[1]. It has also been tested to evaluate treatment effectiveness, showing little value in this aspect. Finally, in recent years it has been demonstrated that cardiac denervation of parasympathetic ganglia can be highly effective in reducing cardioinhibitory reflex syncope, a technique known as cardioneuroablation[43]. Tilt test might play a crucial role in detecting suitable patients for this promising procedure[44].

Electrophysiological study

According to current European Guidelines[1], electrophysiological study (EPS) is indicated in patients with syncope and bifascicular block (BFB) or previous myocardial infarction or other scar-related conditions, when the etiology remains unexplained after non-invasive evaluation. It could also be considered when syncope is preceded by palpitations or in patients with sinus bradycardia, when the rest of the study has been negative. However, in patients with normal ECG and no structural heart disease, EPS is of poor diagnostic value, and other options like home monitoring are more appropriate. Additionally, a positive EPS is strongly predictive of the origin of the previous syncope, but a negative result cannot exclude arrhythmic events in the future. Therefore, it has a low negative predictive value [45,46].

Sick sinus syndrome is a heterogenous disease where sinus node does not function normally and includes some different kinds of bradycardia such as sinus pauses or junctional rhythm. However, these conditions are relatively common in elderly people, and it is crucial to correlate the bradycardia episodes with the patient's symptoms. A sinus node recovery time (SNRT) longer than 1600 ms is considered abnormal [or corrected SNRT (cSNRT) longer than 525 ms] and has been correlated with sick sinus syndrome[45], but its prognostic value remains unclear. There are few data supporting the benefit of pacing in patients with an abnormal SNRT.

Patients with intraventricular conduction disturbances like BFB or nonspecific conduction disturbance with a QRS greater than 120 ms are at higher risk of arrhythmic events due to His-Purkinje system disease, and in this population paroxysmal atrioventricular block (AVB) is the most common

cause of syncope[46-48]. In these patients with syncope suspected to be related to bradycardia, an HV interval longer than 70 ms or the development of second or third-degree AVB during incremental atrial pacing or pharmacological stress identifies a group with a high risk of developing AVB in the future [49], and pacing is recommended. In addition, some studies have evaluated the relationship between ECG conduction disturbance and the results of EPS, showing that PR interval prolongation and/or BFB patterns make a positive result in EPS more likely rather than a right bundle branch block (RBBB) pattern alone[50] (Figure 2).

Another important part of the EPS in the syncope work-up is programmed ventricular stimulation. In patients with previous myocardial infarction and syncope, the induction of monomorphic sustained ventricular tachycardia (MSVT) is strongly predictive of the cause of syncope and should be managed as spontaneous MSVT[51,52]. In contrast, the induction of polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) is considered a less specific finding, especially with aggressive stimulation protocols[53]. However, induction of PVT or VF may play a role in risk stratification of specific populations such as patients with repaired tetralogy of fallot[19,54-56] or BrS[57,58].

Electrocardiographic cardiac monitoring

ECG cardiac monitoring is one of the cornerstones of the etiological diagnosis of arrhythmic syncope. In addition, there are several areas of interest other than unexplained syncope in which monitoring devices have been investigated[54,59-72]. The objective of ECG monitoring is to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis. For this reason, the diagnostic yield of ECG monitoring is primarily related to the duration of monitoring and the frequency of symptoms. Since syncope is often an infrequent event, a long-term monitoring device is usually needed to have a chance of recording a syncopal episode. Moreover, the identification of significant asymptomatic arrhythmias (such as advanced AV block) can be important for the diagnosis. Therefore, as a general rule, ECG monitoring is indicated when there is a high pre-test probability of identifying an arrhythmia associated with syncope and after appropriate risk stratification. The choice of monitoring modality depends on the frequency of events.

In recent years, ECG monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-hr Holter monitor. This evolution of the ECG recording systems include, among other aspects, smaller devices, greater memory capacity for long-term monitoring, better quality of records, or remote monitoring capacity[70] (Table 2).

The main current ECG monitoring devices available are the following:

(1) In-hospital telemetry. In-hospital monitoring should be mandatory in patients with high-risk clinical features, especially if the monitoring is applied immediately after syncope. A recent study that evaluates the optimal ECG monitoring duration of ED patients with syncope found that a serious underlying arrhythmia was often identified within the first 2 h of ED arrival for low-risk patients and within 6 h for medium-risk and high-risk patients[73]. The diagnostic yield of ECG monitoring varies from 2%-20% depending on the patients' characteristics[1,9,69,73-75].

(2) 24/48-hr Holter monitoring. Despite likely being the most frequently used device, the diagnostic yield is as low as 1%-2% in unselected patients due to its short monitoring time[69,70]. Even the newest devices with a longer recording capacity (7-14 d) offer a very limited diagnostic yield. In the opinion of the authors of this review, at the present time, the 24/48-hr Holter should only be considered in patients with daily or very frequent symptoms[69,70]. In different circumstances, other modalities offer not only a greater diagnostic yield but also better cost efficiency per diagnosis.

(3) Loop recorders. These allow for more prolonged monitoring since they do not store a continuous recording. Even though they continuously monitor the ECG, the device just stores a few minutes, which is subsequently overwritten with a newer recording. Only when the device is activated (be it *via* manual activation or through an automatic arrhythmia detection algorithm), it stores from a few minutes before the start of the event until its end in another part of the memory. These stored episodes are protected from overwriting and available for review. In this way, several minutes before activation are stored in the device memory, and the likelihood of recording the trace at the time of the syncope episode is relatively high. Within this category, we have differentiated between external and implantable devices.

External loop recorders. The device uses cutaneous electrodes to record, like the 24 hr Holter monitor. The patients themselves position the electrodes daily. Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3-4 wk, although there are reports of more prolonged periods of time[70,76]). For this reason, in the setting of syncope, the diagnostic yield is no greater than 10%. They are especially useful for the investigation of symptoms that occur every 2-3 wk. Significantly, it has been found in various studies that early recorder use increased the likelihood of diagnostic events during external ECG monitoring[73,77].

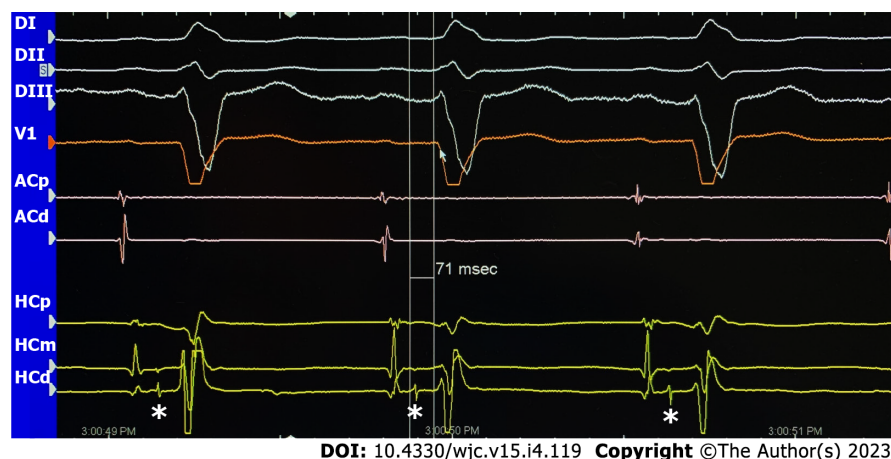
Implantable loop recorders (ILR). These are small devices that are implanted subcutaneously, usually in the left parasternal region. They have the disadvantage of being minimally invasive since the latest models have been made significantly smaller. However, these devices allow for a more prolonged continuous monitoring of up to 3 to 4 years, making them especially useful in patients with syncope. Numerous studies have evaluated the diagnostic value and the usefulness of ILRs for the work-up and the diagnostic yield increases up to 30%-50%[5,48,59,62,78-82]. In a meta-analysis of five randomized controlled trials, it was found that initial implantation of an ILR in the work-up provided a 3.7-fold

Table 2 Main advantages, limitations, and indications of the most commonly used devices for electrocardiogram cardiac monitoring in patients with syncope

	Advantages	Disadvantages	Main indications
24-hr holter	Continuous recording; 12 leads with good correlation with surface ECG; low economic cost per study	Discomfort for the patient; artifacts; maximum recording of 24-48 h (low diagnostic yield); high economic cost per diagnosis	Very frequent (daily) symptoms; in-hospital monitoring (if ECG-telemetry not available)
Skin patches	Continuous recording of 7-14 d; good tolerability for patients	Single-use and greater economic cost; only one lead ¹ ; low diagnostic yield	Frequent (weekly) symptoms
External loop recorders	Loop recording (includes beginning and end of arrhythmic event); monitoring for 4 wk; low economic cost per study	Patient discomfort; requires education from healthcare professional on how to correctly place the electrodes; relatively low diagnostic yield	Frequent (weekly-monthly) symptoms
Implantable loop recorders	Loop recording; up to 3-yr monitoring (good diagnostic yield); patient does not have to do anything; remote monitoring	Invasiveness and associated complications (infection, bleeding, <i>etc.</i>); individual economic cost; single lead	Infrequent symptoms; most useful in syncope

¹There are devices with more leads.

ECG: Electrocardiogram.



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Figure 2 Electrophysiological study of a patient with syncope and left bundle branch blocked. Surface electrocardiogram (DI, DII, DIII, V1) (top) and intracardiac electrograms at 100 mm/seg of an electrophysiological study to evaluate infra-Hisian conduction. A diagnostic catheter was placed in the right atrium (pink register: ACp and ACd) and in the His bundle zone (yellow register: HCp, HCM and HCD). *Indicates the His deflection. HV interval, from the onset of the His deflection to the onset of the QRS, is measured with the caliper (71 milliseconds in this case).

(95%CI: 2.7-5.0) increase in the relative probability of a diagnosis compared with the conventional strategy[1,71,83,84]. Different studies have also demonstrated that ILR was more cost-effective than the conventional strategy[69,81,83-85].

(4) Skin patches. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads that allow for a continuous ECG recording for 7-30 d of monitoring. Diagnostic yield and limitations are similar to external loop recorders. It should be noted that some new wearable devices like intelligent watches or other ECG prospective intermittent event recorders, which are quite popular nowadays, are generally not useful for syncope workup. These devices start recording only when the patient activates them. They have the limitation of not allowing for the recording of the onset of the episodes, which is often important for diagnosis. Furthermore, if the patient activates the device after recovering from the syncopal episode, in most cases the possible rhythm disorder would have resolved.

Other tests

Autonomic function tests like the Valsalva maneuver or deep breathing test can be considered to diagnose autonomic dysfunction, but there is weak evidence that these tests may be useful in patients with syncope. Echocardiography should be performed in all patients with suspected valvular or structural heart disease, as it can detect some conditions that could present with cardiac obstructive syncope (*i.e.*, AoS or cardiac tamponade). Exercise testing is especially useful in patients that have experienced syncope during or shortly after exertion. The main purpose of these tests is to rule out ventricular arrhythmias related to CAD or exercise-induced advanced AVB, which is usually located distally to the AV node. Cardiac biomarkers such as high sensitivity troponin and natriuretic peptides

can be elevated in patients with syncope and have been associated with worse outcomes in some case series[86,87]. However, such determinations are highly non-specific and rarely contribute to a certain diagnosis, and they may indicate serious illness rather than myocardial ischemia or heart failure. Therefore, it remains unclear whether they should be determined on a routine basis[88].

RISK STRATIFICATION

Cardiac syncope is a life-threatening condition. By consequence, the main goal of risk stratification is to identify those low-risk patients with benign causes that can be discharged home and only require medical education from those high-risk patients with syncope likely related with cardiac arrhythmias or structural heart disease who require hospital admission for further investigation. This initial evaluation is especially necessary in the ED, where most patients with syncope first consult (Table 3).

For this purpose, several risk scores have been developed. In 2016, the Canadian Syncope Risk Score [34] was published. They included 4030 patients who presented to EDs of three centers in Canada for syncope and analyzed the occurrence of serious events including death, myocardial infarction, arrhythmia, structural heart disease, pulmonary embolism, serious bleeding, and procedural intervention within 30 d from admission. Finally, they included nine predictors: (1) Predisposition to vasovagal syncope; (2) Heart disease; (3) Any systolic pressure reading in the ED < 90 or > 180 mmHg; (4) Troponin level above 99th percentile for the normal population; (5) Abnormal QRS axis (< -30° or > 100°); (6) QRS duration longer than 130 ms; (7) QTc interval longer than 480 ms; (8) ED diagnosis of cardiac syncope; and (9) ED diagnosis of vasovagal syncope. Those items suggesting reflex syncope conferred negative points, and those suggesting cardiac syncope conferred positive points. Each patient obtained a final score, with higher scores representing a greater risk of serious events (-3-0 points are considered low risk, while 0-3 points and 4-11 points are considered high and very high risk, respectively).

Recently, the same authors have validated this risk score in another large cohort of 3819 patients, showing very good correlation. Setting a threshold score of -1 point, they achieved very good sensitivity (97.8%) but poor specificity (44.3%) for serious events[89]. In addition, another group of researchers validated the same score in a cohort of 2283 patients from three continents also showing good correlation and better performance when compared with another European risk score[90]. However, they also observed that a simplified model including only the clinical classification (vasovagal, cardiac, or other), also achieved a similar degree of discrimination with regard to the primary outcome, showing that some of the predictors included may have a secondary role.

There are some other scales previously developed, such as the San Francisco Syncope Rule[91] or the EGSY score[29]. Both have shown similar results with good sensitivity but poor specificity. However, lack of reproducibility and remarkable heterogeneity in study design, variables, and outcome definitions of primary studies have prevented widespread use of these tools in clinical practice[92]. Moreover, recently some authors compared the EGSY score with clinical judgement, both alone and in addition to cardiac biomarkers, showing that clinical judgement has the highest diagnostic accuracy[93].

In summary, multiple risk scores have shown good sensitivity but poor specificity for predicting short-term serious outcomes, and they performed no better than clinical judgement. Therefore, they should not be used in isolation for the purposes of decision-making. It is also worth mentioning that, apart from risk scores, some other tests such as EPS, cardiac magnetic resonance (CMR), or stress test may be useful for risk stratification in selected groups of patients, as is discussed above in other sections of this article.

ARRHYTHMIC SYNCOPE IN SPECIFIC POPULATIONS

As previously mentioned, syncope could be the presenting symptom of an impending sudden cardiac arrest or can be related to more benign conditions such as neuro-mediated syncope or OH. Thus, it is important to correctly stratify the risk of each patient. For this reason, we need to understand the clinical scenario in which syncope takes place. Patients without overt structural heart diseases are at a lower risk of subsequent cardiac complications. Nonetheless, we must also consider some inherited heart diseases, which are primarily electrical, known as channelopathies and that can take place themselves in the absence of structural heart disease. In the following paragraphs we summarized some of those heart conditions that are associated with a higher risk of ventricular arrhythmias and sudden cardiac arrest.

Structural heart disease

Ischemic heart disease: Patients with ischemic heart disease (IHD) are at a higher risk of ventricular arrhythmias. It is necessary to differentiate between three stages in the ischemic evolution: (1) Acute ongoing ischemia. A patient suffering from an acute myocardial infarction might have VF and ventricular tachycardia related to the ischemic myocardium[1,19,94,95]. The acute ischemia induces a dispersion of the repolarization that may produce polymorphic ventricular arrhythmias and VF in the

Table 3 High-risk features suggesting cardiac syncope

High-risk features
Past medical history
Previous myocardial infarction
Previous cardiovascular condition (<i>i.e.</i> , BrS, hypertrophic cardiomyopathy, Long QT syndrome, <i>etc.</i>)
Syncopal event
Syncope during exertion or in supine position
Syncope associated with chest pain, palpitations, breathless, or abdominal pain
Physical examination
Signs of heart failure
Cardiac murmur suggesting specific condition (<i>i.e.</i> , aortic stenosis)
Signs of shock
Electrocardiogram
Conduction disturbance (AV block, bundle branch block)
Pathological Q waves
Long QT interval
Pre-excitation syndrome
Negative T waves

BrS: Brugada syndrome; AV: Atrio-ventricular.

acute setting. In the same way, some patients might present with monomorphic ventricular arrhythmias during acute myocardial infarction, in which a macro re-entrant circuit involving the ischemic tissue is a more probable mechanism. This latter mechanism is much less frequent than the former[94]; (2) In the subacute phase of ischemia, comprising hours to days after the ischemic event, Purkinje-related ectopia is a frequent mechanism for VF and acute cardiac arrest. The premature ventricular complexes are characterized by their very short coupling intervals and by the presence of a normal QT interval. It is believed that the ischemia induces an abnormal calcium release to the cytosol of Purkinje cells, which causes such early post depolarization[94]; and (3) In the chronic setting, which accounts for most patients with syncope and IHD, a frequent mechanism is a ventricular arrhythmia due to macro re-entry in well-established ventricular scars[1,19]. The risk of ventricular arrhythmias is much higher among those patients with IHD with low ventricular ejection fraction[1,19,96].

Ventricular arrhythmias should be suspected in patients with syncope and IHD[1,6,9,97]. If the patient has a left ventricle ejection fraction (LVEF) of < 35% despite optimal medical treatment, an implantable cardiac defibrillator (ICD) is indicated[18,19,98]. These patients have solid evidence of high arrhythmic risk independently of the invasive risk stratification, and an ICD implantation is strongly indicated even if the etiology of the syncope is treated subsequently. This recommendation is strongly supported by large randomized clinical trials (SCD-HeFT, MADIT-II)[99,100] and class 1A recommendation in the 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[101], and the 2019 Guidelines on Chronic Coronary Syndromes[102].

When the cause of the syncope remains unknown after an initial evaluation, and there is no apparent direct indication for ICD, an EPS with programmed ventricular stimulation should be performed. If MSVT are induced, the implantation of an ICD should be considered. The induction of polymorphic ventricular arrhythmias or VF has not been consistently related with ventricular arrhythmias or sudden cardiac arrest and no recommendation about ICD implantation can be made in this scenario. Despite the absence of solid evidence, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] recommends performing an EPS in patients with syncope and previous ST elevation myocardial infarction with a class IC recommendation. It is not clear if this recommendation is applicable to patients with a history of coronary revascularization without infarction or in the absence of late gadolinium enhancement in the CMR, and further studies are needed.

As we previously mentioned, the induction of a monomorphic VT in a patient with previous myocardial infarction presenting with syncope is an indication for an ICD implantation. On the other hand, the induction of VF has been traditionally considered as a non-specific result as these patients

appear to have a similar prognosis as patients without any ventricular arrhythmia induction. Brugada *et al*[103] demonstrated that non-sustained PVT and VF are nonspecific responses to an aggressive stimulation protocol including three to four extra stimuli. Brodsky *et al*[104], presenting the results of the AVID trial, were not able to demonstrate that the induction of VF or fast VT (rate > 200 bpm) is related with death or ventricular arrhythmia recurrence ($P = 0.07$), but the induction of slow VTs (HR < 200 bpm) was independently related with recurrences as monomorphic VT.

Mittal *et al*[53] also evaluated the prognosis of ventricular arrhythmia induction in a cohort of 118 consecutive patients with CAD presenting with syncope. The mean LVEF of their cohort was $42\% \pm 13\%$. VF was the only arrhythmia induced in 20 patients (17% of the cohort). There was a survival rate of 89% and 81% at 1 year and 2 years consecutively in the entire cohort, and there were no differences between patients with VF induction or no induced arrhythmia ($P = 0.39$). By contrast, Link *et al*[105] found contradictory results in their cohort where they followed 274 consecutive patients with CAD and syncope or presyncope. The risk of arrhythmia occurrence was evaluated at the time of presentation with syncope by an EPS. VF was induced in 23 patients (8%) and ventricular flutter (monomorphic tachycardia with CL < 230 ms) in 24 patients (9%). Overall, 41 patients (15% of the cohort) were inducible for monomorphic ventricular tachycardias. After a follow-up of 37 ± 25 mo, 34 patients had ventricular arrhythmias. VF was induced in the initial EPS in 3 out of 23 patients (13% of this group) and in ventricular flutter in 7 out of 24 patients (30% of this group). Considering these results together, the induction of VF/ventricular flutter was predictive of ventricular arrhythmias during follow-up ($P \leq 0.001$ vs non-inducible patients)[105].

Nonetheless, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] only have clear recommendations for the induction of sustained monomorphic ventricular tachycardia. Thus, an ICD is recommended in patients with CAD and unexplained syncope with MSVT induced during EPS with a IIa B level of recommendation. The induction of polymorphic VT, VF, or non-sustained ventricular arrhythmias are considered non-specific responses, and considering the absence of solid evidence, no specific recommendations can be made.

Despite the fact that VT should be ruled out in patients with IHD, many other causes may be present in this set of patients[3,9,106,107]. In fact, VT is not the most common cause of syncope. Patients with IHD have some factors that predispose them to other causes. For example, they are often on different hypotensive drugs that predispose to OH or reflex syncope[2]. Also, some conduction disturbances are more frequent in patients with IHD[30,48,50]. In the presence of conduction disturbances on the ECG, advanced AV block is a common cause of syncope[46,50,108]. Importantly, if the EPS is negative, VT is unlikely to be the cause of syncope, with reflex and OH syncope being the most probable etiologies[3, 107].

Mid-range left ventricular dysfunction

Patients with left ventricular dysfunction are at high risk of cardiac and arrhythmic syncope[6]. In observational studies, unexplained syncope in this population has been associated with an increased risk of sudden death[1,9,79,109,110], although the evidence for the benefit of an ICD is limited. In general, the direct implantation of an ICD is indicated in those patients who fulfil the primary prevention criteria (NYHA class II-III heart failure, with LVEF < 35% on optimized pharmacological therapy). The evidence regarding the management of syncope in patients with mid-range LVEF is even more scant. Current ESC syncope clinical practice guidelines[1], which are similar to ACC/AHA/HRS [9] guidelines, suggest a work-up in line with general recommendations and state that the implantation of an ICD should be considered in patients with systolic dysfunction and unexplained syncope. The implantation of a cardiac monitor (ICM) is an alternative that may be considered in patients with recurrent episodes. Newly published ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] suggest a conservative strategy based on risk stratification and ICM implantation in patients with no other direct indication for an ICD.

Our group has recently investigated a similar strategy based on a stepwise protocol[79]. In summary, the diagnostic work-up for syncope in this population is based on three steps. Step 1 consists of the initial assessment in the ED. In a systematic manner, a clinical history and physical examination are performed, including testing for OH and CSM (if not contraindicated), general bloodwork, chest x-ray, and 12-lead ECG, as well as 12-24-h telemetry monitoring and a transthoracic echocardiogram. In cases where no certain or highly probable diagnosis is reached, it is considered unexplained syncope, and the patient is admitted to the hospital. Step 2 involves the hospital admission with continuous ECG monitoring and carrying out an invasive EPS if the following criteria are fulfilled: (1) Presence of conduction disorder on baseline ECG [1st degree AV block, Mobitz type 1 s degree AV block, complete RBBB or left bundle branch block (LBBB), BFB, left anterior or posterior fascicular block]; (2) Clinical, electrocardiographic, and/or imaging evidence of myocardial scar (history of myocardial infarction, presence of Q waves on surface ECG, presence of late enhancement on cardiac magnetic resonance imaging, and/or presence of necrosis on myocardial perfusion single-photon emission computed tomography scan); and (3) History of palpitations prior to the syncopal episode. If these criteria are not fulfilled, the EPS is not carried out, and the patient moves on to Step 3. Step 3 involves implanting an implantable cardiac monitor with subsequent clinical monitoring (Figure 3).

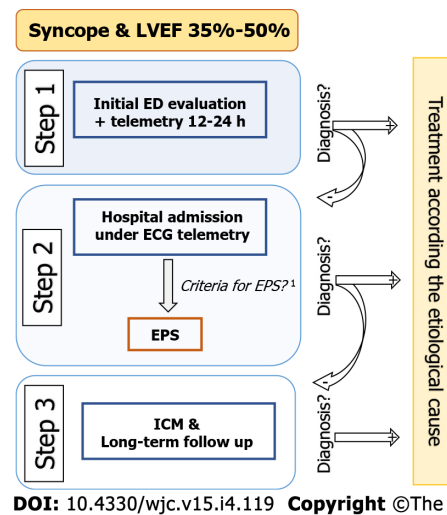


Figure 3 Proposed algorithm for the management of syncope in patients with mid-range left ventricular dysfunction. ¹Criteria for electrophysiological study: (1) Presence of conduction disorder on baseline electrocardiogram (1st degree atrioventricular block or Mobitz 1 s degree block, complete right or left bundle branch block, left anterior or posterior hemiblock); (2) Evidence of myocardial scar; and (3) Palpitations prior to the syncopal episode. ECG: Electrocardiogram; ED: Emergency department; LVEF: Left ventricle ejection fraction; EPS: Electrophysiological study; ICM: Implantable cardiac monitor.

In a recent published study that evaluated patients with unexplained syncope (excluding patients diagnosed in step 1), it was found that the application of this systematic protocol had a high diagnostic yield with a low rate of sudden death[79]. The overall diagnostic yield with both steps was 68.3%. Of note, the most common cause was arrhythmia. In 60 patients (57.7% of the total patients and 84.5% of the total diagnoses), a rhythm disorder was identified as the cause of the syncopal episode, with a high proportion of bradycardias, mostly due to AV block (47 patients, 45.2%). VT was the second most frequent cause, although it was significantly less common (9.6%). Most of the arrhythmias, be they AV block or VT, were able to be diagnosed in step 2. Another key finding of the study was that the diagnoses reached allowed treatment to be effectively guided. The sudden or unknown cause mortality rate of 0.9 per 100 person-years was comparable with general mortality rates published in the literature in patients with mid-range left ventricular dysfunction without syncope[106,111-113]. The findings of this study, in line with others on patients with structural heart disease[3,107,114], suggest that a stepwise diagnostic strategy and prolonged monitoring may be a safe and effective management alternative, reducing the number of patients requiring an ICD.

HCM

The hallmark of HCM is the abnormal increase of left ventricular wall thickness unrelated to abnormal loading conditions such as high BP, valvular heart diseases, or congenital heart disease. At the histopathological level, HCM is characterized by an increase in the size of myocardial cells and disordered myocardial cell organization with interstitial fibrosis that may predispose patients to suffer from ventricular arrhythmias. HCM carries a mortality rate that ranges from 1%-2%. New data from cohorts of patients with ICDs suggest that the mortality rate might be even lower (about 0.8%) and that it is related with several risk factors summarized in the HCM-SCD score[115]. The eight variables included in the risk score are: Age, LV wall thickness, left atrial size, left ventricular outflow tract (LVOT) gradient, nonsustained ventricular tachycardia, unexplained syncope, and family history of SCD.

HCM patients may have different syncope etiologies such as: Hypovolemia, conduction system disorders, sustained ventricular tachycardia, LVOT obstruction, and abnormal vascular reflexes, *etc*[116-118]. After ruling out non-cardiogenic and neural-mediated causes, arrhythmic syncope is one of the more worrisome causes for syncope in those patients. Patients with unexplained syncope should be tested with at least 24-hr Holter recording and exercise time-to-exhaustion to rule out LVOT obstruction on exertion. After an extensive evaluation of causes of syncope in those patients without clear diagnosis, an ILR should be implanted[1,117]. Routine tilt table testing in patients with HCM may be associated with an unacceptable number of false positives, and its use should be limited to selected cases[117].

Syncope of unknown origin is included in the risk score with an independent hazard ratio of 2.05 (1.48, 2.82; $P < 0.001$)[115]. Patients with intermediate-risk and low-risk clinical profiles should be evaluated for additional risk factors not included in the score, following 2022 ESC guidelines[19]. LV systolic dysfunction, apical aneurysm, > 15% of LV mass with late gadolinium enhancement on CMR, and several sarcomeric mutations have demonstrated a higher risk of ventricular arrhythmias in different studies and should be considered when evaluating the risk profile of a given patient[117,118]. The risk of ventricular arrhythmias is nonetheless dynamic and needs to be reassessed at every clinical

visit. Those patients with syncope and a high-risk clinical profile (SCD HCM risk score > 6%) or intermediate risk and other risk factors should be considered for ICD implantation (IIa B level of recommendation)[116], and those with intermediate risk (SCD HCM risk score 4%-6%) may be considered for ICD implantation (IIb B level of recommendation)[19].

Valvulopathies

A hemodynamic origin of syncope should be suspected in patients with valvular heart disease. However, other causes are possible[1,5,9,119-123]. The valvular heart disease with the highest risk of syncope is AoS[5,124,125]. Syncope is more frequent in severe stages of AoS but can occur in patients with moderate severity when suffering from other hemodynamic disturbances. Pharmacologic hypotension and atrial arrhythmias are also a frequent cause of syncope in patients with moderate and severe AoS[5,72,121,126]. In a recent study performed by our group in a cohort of patients with severe AoS and syncope, we observed that in 65% of the patients, the stenosis per se was initially identified as the likely cause of syncope, but later only 17.5% of the total cohort of patients was confirmed as having AoS as their final diagnosis. Conduction system disease and vasovagal etiologies were a more frequent cause of syncope in this population[5]. Importantly, syncope in the setting of a severe AoS has been suggested as having prognostic implications.

In a study published in 2019, these patients had a greater risk of mortality after aortic valve replacement in both the short-term (hazard ratio = 2.27; 95% CI: 1.04-4.95) and the long-term (hazard ratio = 2.11; 95% CI: 1.39-3.21) compared with patients who did not have syncope[127]. Although patients with syncope had somewhat different characteristics on echocardiography (smaller aortic valve area, smaller cardiac chambers, and lower ejection volumes), we believe that this rise in mortality was also partially due to the presence of other causes for the syncope such as underdiagnosed arrhythmias. In the cohort studied by Francisco-Pascual *et al*[5], those patients in whom it was not possible to precisely determine the cause of the syncope had more than triple short-term and medium-term mortality.

Furthermore, several studies have observed a high incidence of syncope and SCD after transcatheter aortic valve replacement (TAVR)[66,67,72,126,128]. It is theorized that induced conduction system delays after TAVR may predispose patients to suffer from electrical re-entry within the His-Purkinje system favoring a rare type of cardiac arrhythmia called bundle-branch re-entry in which the electrical impulse circulates between both branches of the conduction system with a slight delay often happening in the left bundle in the retrograde arm of the tachycardia. This arrhythmia is very rapid and frequently compromises the patient hemodynamically producing syncope or sudden cardiac arrest. The real incidence of this problem is unknown, but it needs to be kept in mind when evaluating a patient after a TAVR with some degree of conduction system delay.

Another significant but infrequent cause of syncope in patients with valvular heart disease is the presence of VF in patients with mitral valve prolapse, which has been named “the malignant mitral valve prolapse syndrome”. In a recent meta-analysis carried out by Nalliah *et al*[129], they reported the population prevalence of mitral valve prolapse (MVP) of 1.2% and the prevalence of MVP in SCD autopsies of 11.7%. Nonetheless an incidence of 0.14 SCD events per 100 patient-years in the community MVP cohort, deserves an in-depth investigation of other risk factors for ventricular arrhythmias such as the presence of myocardial fibrosis or frequent complex ventricular ectopy, as has been proposed.

Conduction disturbances

In patients with conduction disturbances and syncope, the presence of bradyarrhythmia is always a concern although other causes may also be present. For example, in a recent cohort of 503 patients with unexplained syncope and BBB, arrhythmic syncope was identified in 57.9% patients, mostly secondary to AV block (51.3%). However, 12% were due to reflex syncope or an OH mechanism, 1.4% were due to ventricular tachycardia, and 10% were secondary to other causes[108].

The optimal management of patients with unexplained syncope and BBB is still controversial[1,9,46-48,130,131]. In fact, the 2017 ACC/AHA Guidelines[9] suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies, while ESC guidelines[1] recommend opting for a stepwise approach. The systematic stepwise approach (that includes an EPS and long-term follow-up with an ICM) was initially evaluated in the B4 study[47]. This study found that the diagnostic approach is safe and achieves a high rate of etiological diagnosis allowing for the selection of specific treatment and avoiding the implantation of unnecessary pacemakers. The results of the B4 study have been confirmed by several subsequent studies, some of them with a relatively high number of patients and long-term follow-up[80,108,132-134].

On the other hand, the strategy of direct pacemaker implantation was recently evaluated in the SPRITELY trial. This study randomized 105 patients older than 50 years with BFB (41 LBBB and 74 RBBB plus left fascicular block) and at least one syncope in the previous year to receive ICM or empirical pacemaker implantation. In the 33-mo follow-up period, the 57 patients randomized to the pacemaker arm showed a lower primary composite endpoint (cardiovascular death, syncope, bradycardia resulting in an intervention, and device complications) than the ILC arm; [20 (35%) vs 44 (76%); $P < 0.0001$]. However, the presence of syncope during follow-up was similar in both groups (29% vs 26%; $P = 0.95$)[135].

It must be highlighted that in the SPRITELY trial, EPS was not systematically carried out before ICM implantation, and therefore it cannot be considered as a direct comparison with the stepwise approach. Similar findings were previously found in the PRESS study[136], where patients were randomized to pacemaker in pacing mode (DDD at 60 bpm) or backup pacing mode (drug-drug interaction at 30 bpm). The primary endpoint of this study was a composite endpoint of syncope, presyncope with device intervention, or documented bradycardia and AVB, and patients allocated to active pacing had a significant reduction of this composite endpoint. However, when only syncope recurrences were analyzed separately, there were no differences between the two groups. Furthermore, there are some studies that have analyzed the recurrence rate in patients with syncope and BBB, in whom a pacemaker has been implanted, showing that syncope recurrence is higher in those patients in whom a pacemaker was implanted empirically than in those in whom a pacemaker was implanted after a positive EPS or a documented AVB[137,138].

With the available evidence, the authors of this review continue to support the stepwise approach to manage these patients. Nevertheless, direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment (Figure 4). According to the newest 2021 ESC guidelines for cardiac pacing and resynchronization[18], in patients with sinus bradycardia and syncope of unclear origin after a thorough work-up, an exercise test to evaluate chronotropic competence and an EPS to evaluate for sinus node overdrive suppression pathologic responses might be indicated. cSNRT (basal cycle length; normal value 525 ms) has demonstrated good predictive value in patients with sinus bradycardia despite the presence of symptoms (overall accuracy of cSNRT in predicting serious sinus node disease regardless of the presence of symptoms: 90%, 100% in the presence of symptoms; sensitivity of the test: 66%). Patients presenting with a ventricular rate below 40 bpm have a 70% probability of having an abnormal cSNRT. In patients with a basal HR of 50 to 55 bpm, the probability of finding an abnormal response in cSNRT test is 24%[139]. However, it should be noted that pacing patients with sinus node dysfunction has not demonstrated improved survival so far[18,131].

EPS diagnostic yield is higher in patients with sinus bradycardia or BFB and structural heart disease and is lower in patients with a normal ECG and no structural heart disease[46,50]. Thus, it is preferable to perform EPS in patients with higher pretest probability and implant a loop recorder in those with lower pretest probability. Patients with first degree AV block and second degree type I (Wenckebach) block presenting with syncope without a firm diagnosis after extensive study should be offered an EPS. The presence of second degree type II block or third degree AVB constitutes a clear indication for cardiac pacing. Patients with 2:1 AV block can be evaluated by increasing the sinus node rate (atropine 1 mg or exercise test). If the degree of block increases by increasing of the sinus rate, an infra-Hisian origin must be suspected, and pacemaker implantation should be considered. Patients with syncope and BFB represent a group whose risk of syncope is especially difficult to stratify. Therefore, in patients with BFB and syncope of unknown origin an EPS should be performed.

In the presence of an HV interval longer than 70 ms (basal) or > 100 ms after infusion of 2 mg/kg of flecainide (or other Vaughan Williams class I antiarrhythmic drugs), cardiac pacing should be considered[140]. The absence of high-risk characteristics in the EPS of patients with syncope and BBB or BFB does not preclude the development of paroxysmal AV block, and an ILR needs to be considered. Roca-Luque *et al*[50] demonstrated that the most predictive combination of conduction disorders were LBBB or RBBB + long PR interval + left fascicular block [odds ratio = 4.5 (1.06-20.01); $P < 0.042$], LBBB + prolonged PR interval [5.2 (1.52-17.74); $P < 0.001$], and RBBB + prolonged PR interval [3.8 (1.7-8.7); $P < 0.001$] in their 271 patient cohort in 2018.

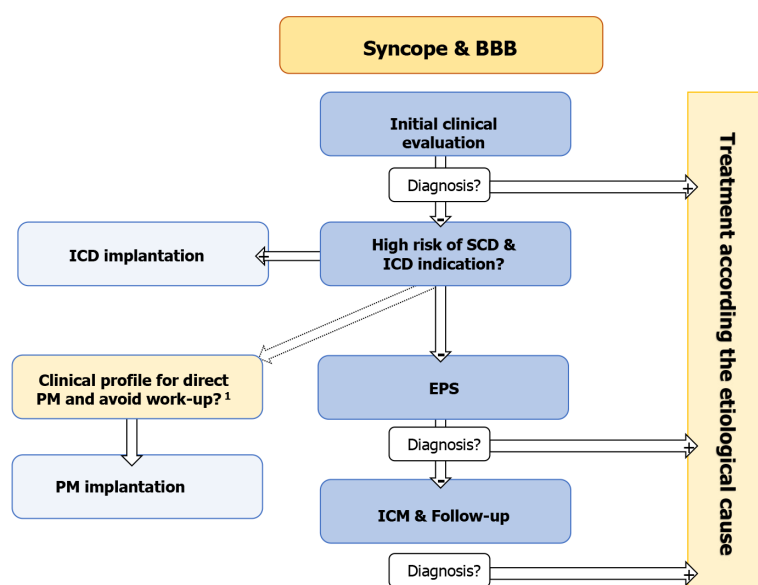
Channelopathies and inherited arrhythmia syndromes

Cardiac channelopathies are a group of diseases in which a mutation of different regulatory proteins of the action potential may predispose a patient to suffer from ventricular arrhythmias and SCD. Syncopal episodes in these patients might be due to non-sustained polymorphic VT or VF. In this section, we discussed the implications of the presence of syncope in patients with BrS, LQTS, and catecholaminergic PVT.

BrS

BrS was first described by the Brugada *et al*[141] in their elegant paper published in JACC in 1992. In their first publication of this syndrome, they described a cohort of 8 patients with RBBB and ST elevation in leads V1-V2-3 that suffered from aborted episodes of SCD[142].

Even though the mechanism of the electrical dysfunction leading to VF is not completely understood, it is believed that an increase in early repolarizing currents (Ito current) or a reduction in depolarizing currents (INaT) may lead to a phase II dispersion of repolarization and early post-depolarizations, which might generate phase II re-entries, possibly triggering VF. This electrical disorder seems to be more accentuated in the anterior part of the right ventricular outflow tract obstruction, where Ito current has been shown to be higher than in other heart sites. This latter observation might explain the isolated ST elevation in precordial leads and the effectiveness of ablation on the right ventricular outflow tract in patients with BrS and arrhythmic storm[143].



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Figure 4 Proposed algorithm for the management of syncope in patients with bundle branch block. ¹Direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment. SCD: Sudden cardiac death; BBB: Bundle branch block; EPS: Electrophysiological study; ICD: Implantable cardiac defibrillator; PM: Pacemaker; ICM: Implantable cardiac monitor.

Patients with BrS pattern on ECG and syncope have a four-fold risk of sudden cardiac arrest, representing a 1.5% annual risk of sudden cardiac arrest. When the syncope cannot be classified as neuro-mediated or a cardiac origin is a possibility, ICD implantation should be considered[19]. Therefore, it is usually not necessary to perform an EPS to stratify the risk in the presence of unexplained syncope, as it is assumed to be high risk.

However, patients with sodium channel dysfunction may exhibit conduction system dysfunction as well. It is not infrequent for patients with those specific mutations to exhibit sinus bradycardia and/or BBB. Furthermore, reflex syncope is also frequent in young patients with BrS[144]. For these reasons, some authors have also suggested a more conservative approach, where implantation of a loop recorder can be considered in BrS patients with an unexplained syncope (not clearly cardiac) and without other indications for an ICD[19,145].

LQTS

The hallmark of the LQTS is an inadequately prolonged corrected QT interval, measured from the beginning of the QRS complex to the point at which the descending limb of the T wave crosses the isoelectric baseline of the ECG. The measure is frequently performed in leads II or V5-6 where the T wave and the isoelectric baseline are often well demarcated. The diagnosis of LQTS is made in the presence of a cQT interval of ≥ 480 ms or a Schwartz score (including several clinical and electrocardiographic parameters) of > 3 . In the presence of a cardiogenic syncope, the presence of a cQT ≥ 460 ms is sufficient to reach the diagnosis.

The mechanism of arrhythmogenicity in patients with LQTS seems to be related with dispersion of the repolarization. The prolongation of the repolarization is not homogeneous among the different layers of myocardium. Therefore, early post depolarization occurring over the T wave may generate functional re-entry patterns of conduction ultimately generating fibrillatory conduction.

Up to 17 different mutations leading to LQTS have been described. The majority of them are produced by three specific mutations. LQTS1 is produced by mutation in the α subunit of the delayed rectifier potassium channel with slow opening kinetics. This mutation comprises 40%-55% of cases. LQTS1 patients are prone to suffering from ventricular arrhythmias during sports or physical activity (especially during swimming). LQTS2 is caused by a mutation in the α subunit of the delayed rectifier potassium channel with rapid opening kinetics. This mutation is present in up to 30%-45% of cases, and ventricular arrhythmias are frequent during loud noises and in the postpartum period in females. The activating mutation in the α subunit of the sodium channel (INaT) keeps the channel opened beyond phase 0, increasing late sodium currents (INaL), thus prolonging repolarization and therefore the QT interval. This mutation is present in 5%-10% of patients and is related to fatal events during rest or sleep [146].

It has been observed that LQTS patients respond favorably to beta-blockers; thus every patient with a diagnosis of LQTS should be treated with beta-blockers. Apparently, non-specific beta-blockers, such as propranolol or nadolol, have shown better results with a lower incidence of ventricular arrhythmias. If patients suffer from syncope despite the use of beta-blockers, an ICD must be implanted for the

prevention of SCD[147].

Catecholaminergic PVT

Catecholaminergic PVT (CPVT) is an inherited channelopathy in which several mutations may affect the intracellular handling of calcium release-uptake. The overload of cytoplasmatic calcium leads to cell membrane voltage instability leading to delayed depolarizations that lead to the characteristic arrhythmia of this disorder, bidirectional ventricular tachycardia (also seen in digitalis toxicity), or VF.

The mutation in the ryanodine receptor gene, inherited in an autosomal dominant manner, is the cause of 50%-55% of cases. A new mutation in the calsequestrin gene has been described and has an autosomal recessive inheritance pattern. The ryanodine receptor gene mutation generates an aberrant ryanodine channel that permeabilizes the channel to calcium release. The calsequestrin proteins work close to the ryanodine channel, regulating its function.

Patients with CPVT are prone to ventricular arrhythmias related to exercise. Ventricular arrhythmias usually occur with HR over 130 bpm. With increasing levels of exercise, patients may exhibit monomorphic ectopy, polymorphic ectopy, non-sustained VT, bidirectional VT, and finally, if the exercise continues, VF. CPVT is a highly arrhythmogenic condition with a cardiac event rate of up to 80% at 40 years. Therefore, a low threshold for ICD implantation is advised. The use of non-selective beta-blockers has been shown to reduce the incidence of ventricular arrhythmias from 25% to 11% at 8 years[148].

Probably due to small cohorts, no single risk factor has demonstrated sufficient prognostic value to be used routinely. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend implantation in patients with CPVT who have survived a cardiac arrest (class I C) and should be considered in patients with CPVT and either arrhythmic syncope or presence of polymorphic VT or bidirectional VT on maximal tolerated doses of beta-blockers (class IIa C)[19].

CONCLUSION

Syncope is a symptom that involves a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. The highest mortality and SCD risk occur when syncope is associated with underlying cardiac disease, in particular when the main cause of syncope is not well established and treated properly. Arrhythmia is the most common cause of cardiac syncope. Appropriate risk stratification and work-up to determine the main cause of the event is warranted to improve the prognosis of patients. This review provided an update on the important and novel data about arrhythmic syncope, the value of the different diagnostic tests, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. This review emphasized the importance of an appropriate stepwise approach work-up and interventions.

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Optimization of the pharmacological therapy in patients with poly-vascular disease: A multidisciplinary approach

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Abstract

The recent shift of the concept of cardiovascular disease as a chronic progressive condition, potentially involving multiple districts, has driven attention to the optimal management of patients with concomitant coronary and peripheral artery disease, representing a subset of patients with an increased risk of events and impaired survival. Recent pharmacological achievements in terms of antithrombotic therapy and lipid-lowering drugs allow multiple therapeutical combinations, thus requiring optimizing the treatment in a tailored fashion according to patients' risk profiles. Nevertheless, data dedicated to this specific subset of patients are still modest. We summarize currently available strategies and indications for the management of antithrombotic and lipid-lowering drugs in patients with the poly-vascular disease.

Key Words: Poly-vascular disease; Coronary artery disease; Atherosclerosis; Antithrombotic therapy; Cholesterol; Statins; PCSK9

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Core Tip: Patients with concomitant coronary and peripheral artery disease, *i.e.* poly-vascular disease, represent a subset of patients with higher risk and worse prognosis. In these patients antithrombotic and antilipidemic drugs should be tailored in order to achieve the most aggressive combination tolerated for each patient. Multidisciplinary approach, involving both a cardiologist and vascular surgeon, combining different therapeutic goals and perspectives, could provide additional benefits in the correct management of poly-vascular patients.

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INTRODUCTION

The large efforts dedicated in the last decades to reducing the burden of cardiovascular disease (CVD) worldwide have allowed a better identification of causal risk factors and pathophysiological mechanisms, thus leading to progressive shift in the concept of CVD as a chronic progressive condition [1].

In the 2019 European Society of Cardiology (ESC) guidelines[2], the term stable coronary artery disease (CAD) has been replaced with “chronic coronary syndrome”, focusing on CAD as a dynamic evolutive process, resulting from a myriad of interactions, both environmental and genetic.

A subsequent development has led to consider CAD as part of a wider spectrum of disease, sharing the same atherosclerotic pathogenesis, thus leading to the most recent concept of “cardio-cerebro-vascular continuum”[3,4], representing a condition with a high potential of progression to death or major acute ischemic events, in absence of interventions interrupting this pathological loop.

Recent advances in terms of more potent antithrombotic and lipid-lowering therapies, allowing prevention of a large proportion of acute ischemic events and the progression of the disease[5,6], have significantly modified the prognosis of these patients, therefore promoting attentive research of multidistrict involvement.

However, despite the rising attention, and especially in secondary prevention, among patients with an established diagnosis of CAD or peripheral arterial disease (PAD), still the indications for systematic pan-vascular screening and the appropriate management of the newly available therapies is debated, leading to the risk of underestimation of the risk and undertreatment[7].

Moreover, increasing evidence has emerged on the advantages of an earlier establishment of pharmacological anti-atherosclerotic measures, remarking the importance to identify the instruments for adequate assessment of the cardiovascular risk profile. The present review will aim to provide an overview of the management of patients with poly-vascular disease, with a particular focus on recent updates in the management of antithrombotic and lipid-lowering therapies.

DEFINITION AND RISK STRATIFICATION OF PATIENTS WITH POLY-VASCULAR DISEASE

PAD is defined, according to the European Society of Cardiology guidelines[8], as a blood circulation disorder of the arteries that supply all the districts excluding coronary circulation and aorta.

However, CAD and PAD or multidistrict PAD often tend to co-exist, representing different presentations of the same pathogenetic process, atherosclerosis, an inflammatory disease leading to the progressive occlusion of the vessel lumen[9]. Atherosclerosis within 2 or more arterial beds has been termed a poly-vascular disease and recent studies have documented that its prevalence could be even more common than previously considered[10].

In the Reduction of Atherothrombosis for Continued Health Registry (REACH)[11], an international registry including patients ≥ 45 years of age with established CAD, CVD, PAD, or ≥ 3 risk factors for atherosclerotic disease; 24.7% of patients with CAD and up to 61.5% of patients with PAD had the concomitant disease in other vascular beds, being associated with a severely worsened prognosis. In fact, in the same study, the strongest predictor for future ischemic events was a poly-vascular disease, which was associated with a 99% increased risk of major cardiovascular ischemic events (MACE) at 4-year follow-up, an almost doubled mortality (4.6% *vs* 2.4%) and markedly increased morbidity. A similar negative prognostic impact was also confirmed in several registries and trials[12,13]. However, routine screening for poly-vascular involvement in patients with disease in one arterial bed has not been recommended, so far, in guidelines, in consideration of multiple factors.

Indeed, the modest awareness of patients and physicians, being generally more focused on the prognostic weight of CAD, rather than PAD, and the more delayed presentation of the latter, remaining often symptomatic until the occurrence of critical or acute ischemia, certainly have represented a limitation for many years[14].

Moreover, whereas an early establishment of lifestyle counseling and medications was able to reduce the risk of cardiovascular events in primary prevention, no differential pharmacological management was advised, so far, among patients with CAD, PAD or both, due to the lack of evidence of potential additional benefits with more aggressive therapy[1,8].

Nevertheless, the recently introduced antithrombotic and antilipidemic drugs have provided greater benefits among patients with more severe multidistrict vascular disease, thus raising the need to better define risk models and shared protocols.

In particular, the role of indirect indexes of vascular disease, which are widely validated in primary prevention, still needs to be defined among patients with an established diagnosis of CAD or PAD.

Among them, the ankle-brachial index (ABI) represents an easy-to-measure and widely available tool for objectifying CAD. Several studies have shown that patients with an ABI < 0.9 have more severe coronary artery disease[15].

Moreover, among patients with PAD, ABI has emerged as a strong predictor of mortality and major acute cardiovascular and limb-related ischemic events (MACE and MALE)[16].

A similar prognostic role of ABI, however, was also confirmed among asymptomatic patients undergoing screening for PAD, where an ABI < 0.85 increased the relative risk for total mortality to 2.36 (95%CI: 1.60, 3.48), being even enhanced with decreasing ABI ($P < 0.0001$). Specific causes of death, directly related to the magnitude of ABI were mainly due to myocardial infarctions, further reinforcing the importance of poly-vascular disease identification[17].

Similarly, pulse wave velocity (PWV), the most widely used measure of arterial stiffness, has emerged as a useful tool for risk stratification in CVD. Various studies and meta-analyses have shown the association between PWV and PAD or CAD. Moreover, PWV emerged as an independent risk factor for future cardiovascular events[18].

Other indirect markers of an ongoing atherosclerotic process, such as carotid intima-media thickness, as well as vasculogenic erectile dysfunction or coronary calcium score, have been addressed for the estimation of cardiovascular risk, although their exact predictive role and prognostic impact is still under debate. Recent studies suggested that carotid intima-media thickness (cIMT) evolution, and in particular cIMT reduction, rather than the baseline value, could predict the degree of CVD risk reduction[19].

Indeed, future dedicated studies are certainly deserved to define the most appropriate tools and criteria for the assessment of cardiovascular risk and for establishing the most appropriate preventive measures for the management of higher-risk patients.

ANTITHROMBOTIC THERAPY IN POLY-VASCULAR DISEASE

The cardiological approach in acute and chronic coronary syndromes

Antiplatelet therapy is the cornerstone of the treatment of patients with acute and chronic coronary syndrome. Dual antiplatelet therapy (DAPT) consisting of aspirin (ASA) and an adenosine diphosphate inhibitor, such as clopidogrel, prasugrel or ticagrelor is currently indicated for the prevention of cardiovascular events in patients presenting with the acute coronary syndrome (ACS), after percutaneous coronary intervention for any indication and in particular subsets of higher-risk stable CAD patients.

Clinical practical guidelines in the United States and Europe recommend more potent P2Y12 inhibitors in ACS, such as ticagrelor and prasugrel, given that head-to-head comparison clinical trials have shown the superiority of these inhibitors over clopidogrel in reducing ischemic events[20,21].

In the acute setting, clopidogrel should be used only if these potent inhibitors are contraindicated or unavailable, while still representing the first choice in patients undergoing elective percutaneous coronary interventions[1].

The recommended duration of DAPT is 12 mo after an acute coronary syndrome, unless there are contraindications, and 6 mo in CCS. In specific clinical scenarios, DAPT duration can be shortened (< 12 mo), extended (> 12 mo) or modified (switching DAPT, DAPT de-escalation) and these decisions depend on individual clinical judgment being driven by the patient's ischemic and bleeding risk[1,22].

Patients are defined as having "high ischemic risk" if presenting multivessel CAD and at least one additional risk factor, including diabetes, recurrent acute myocardial infarction (AMI), renal failure or PAD. On the other hand, patients with at least one criterion between multivessel CAD, diabetes, recurrent AMI, PAD, renal failure or heart failure are considered to be at "moderate" risk[23].

In these patients, the potential advantage of extending DAPT duration beyond the routine period of 6-12 mo was first suggested in the DAPT trial[24]. In this study dual antiplatelet therapy beyond 1 year and up to 30 mo after placement of a drug-eluting stent, as compared with aspirin alone, significantly reduced the risk of stent thrombosis and major adverse cardiovascular and cerebral events, but was associated with an increased rate of bleeding.

Subsequently, the PEGASUS-TIMI 54 trial documented the reduction of MACE with ASA+ ticagrelor 60 mg × 2 among moderate-high risk patients with a previous AMI who had tolerated DAPT for 1 year, with no difference in severe bleedings[25].

Among the patients at higher risk included in the study, patients with PAD are at heightened risk of MACE, including myocardial infarction (MI) and stroke. In a sub-analysis of the PEGASUS-TIMI 54 trial dedicated to this specific setting, it was observed that the benefit of ticagrelor for relative risk reduction of MACE was consistent, regardless of the presence or absence of known PAD; however, patients with

PAD had a particularly robust risk reduction, due to the higher rate of events, furthermore, producing advantages on MALE. However, the low number of patients (only 5% of the overall study population) and the lack of any impact on mortality did not translate into a particular indication for ticagrelor in patients with previous MI and PAD[26].

More recently the COMPASS Trial compared rivaroxaban (2.5 mg bid) plus ASA 100 mg/d or rivaroxaban 5 mg bid alone *vs* ASA 100 mg/die in patients with stable CAD and/ or PAD. Rivaroxaban 2.5 mg bid plus ASA showed a significant reduction of stroke, total and cardiovascular mortality, in addition to reducing MACE and MALE[27]. This regimen was associated with an increase in major bleeding events primarily from gastrointestinal sites, but there was no increase in critical organ bleeding, non-fatal intracranial bleeding or fatal bleeding. The net clinical benefit analysis (inclusive of MACE, MALE and severe bleeding events) maintained significant benefits in favor of the rivaroxaban plus aspirin arm[28,29].

Therefore, given this evidence, the cardiological approach to antiplatelet therapy, should be to pursue the extension of antithrombotic therapy for the longest tolerated period (> 1 year after ACS; > 6 mo after CCS), balancing with the hemorrhagic risk and tailoring the different strategies according to the patient's characteristics. Our proposed strategy is depicted in Figure 1. In patients with poly-vascular disease in whom the ischemic risk outweighs the risk of bleeding, the combination of antiplatelet therapy and low-dose anticoagulation currently appears supported by the most robust evidence and by the larger prescribing criteria, being allowed both in ACS and CCS patients and even in those who have discontinued DAPT at distance from an event.

Surgical approach in a patient with and without revascularization

Peripheral artery disease (PAD) is one of the manifestations of atherosclerosis, which is known to involve many different vascular districts. Indeed, PAD shares with CAD a common etiology and therefore therapeutical approaches are often similar. In this context, the management of antithrombotic therapy is the milestone of pharmacological strategy in vascular surgery, both in primary and secondary prevention after revascularization. Historically, PAD patients have often represented a subgroup in large RCTs assessing generic antithrombotic therapies in poly-vascular populations. These trials then led to more specific studies dedicated to vascular patients in the last years, both in the chronic and postoperative settings. MACE is often the pivotal outcome of these studies; however, in PAD patients, also MALE becomes a crucial parameter to assess the efficacy of antithrombotic therapy. Therefore, in all RCTs and metanalysis these two outcomes are usually evaluated, balanced with the bleeding risk of different antithrombotic approaches.

The benefit of aspirin in atherosclerotic disease is well established. In 2002, the Antithrombotic Trialists' Collaboration established a general benefit of aspirin in terms of prevention of death and different cardiovascular events, but many antiplatelet drugs and regimens were tested[30]. However, use of aspirin was afterward re-assessed in asymptomatic diabetic patients with ABI < 0.9[31].

Clopidogrel, a second-generation thienopyridine, showed better results in terms of MACE *vs* aspirin in the CAPRIE trial, mostly in a subgroup of patients with PAD; however, no benefit for MALE was found.

Ticagrelor is another thienopyridine often used in CAD. The EUCLID trial[13] compared clopidogrel with ticagrelor in PAD patients and showed no difference in MACE or bleeding events.

Nevertheless, the use of these two antiplatelet agents in monotherapy for PAD patients is limited, with only clopidogrel often being considered as an alternative in case of aspirin intolerance.

Aspirin has also been evaluated in combination with both clopidogrel and ticagrelor. The CHARISMA trial[32] compared a heterogeneous population with different cardiovascular diseases receiving aspirin *vs* aspirin plus clopidogrel. In the PAD subgroup no difference in MACE was found between the two groups, with a slightly higher risk of moderate/severe bleeding with the dual antiplatelet regimen.

The PEGASUS-TIMI 54 trial[25] was similar, but ticagrelor was used instead of clopidogrel. The study found a higher benefit of the dual therapy in patients with PAD, both for MACE and MALE.

In the past decades, the combination of antiplatelets and anticoagulants did not show favorable outcomes in PAD patients[33]. The advent of NOACs recently changed the scenario also in vascular surgery. In 2017 the COMPASS trial highlighted the effectiveness of low dose of rivaroxaban (*i.e.* 2.5 mg bid) in a large population of atherosclerotic patients[27]. This benefit was found to be even clearer in PAD patients. In a COMPASS subgroup analysis of PAD patients[28], both MACE and MALE were significantly lower in those assigned to rivaroxaban plus aspirin *vs* aspirin alone and this evidence was directly proportional to the Rutherford class and cardiovascular risk profile at baseline. Furthermore, critical bleedings were not significantly higher in patients with combined therapy.

The role of antithrombotic therapies is even more important after lower extremity revascularization [34]. While single antiplatelet therapy is essential after any kind of bypass, it is unclear whether the addition of warfarin is useful in venous grafts, due to a higher risk of bleeding.

Similarly, there is strong evidence to support single antiplatelet therapy after prosthetic bypass, while the role of DAPT is less clear. Indeed, the CASPAR trial[35] evidenced a benefit of aspirin plus clopidogrel only in a subgroup of patients after below-the-knee prosthetic bypasses (typically at risk of low patency), without significant increasing major bleeding.

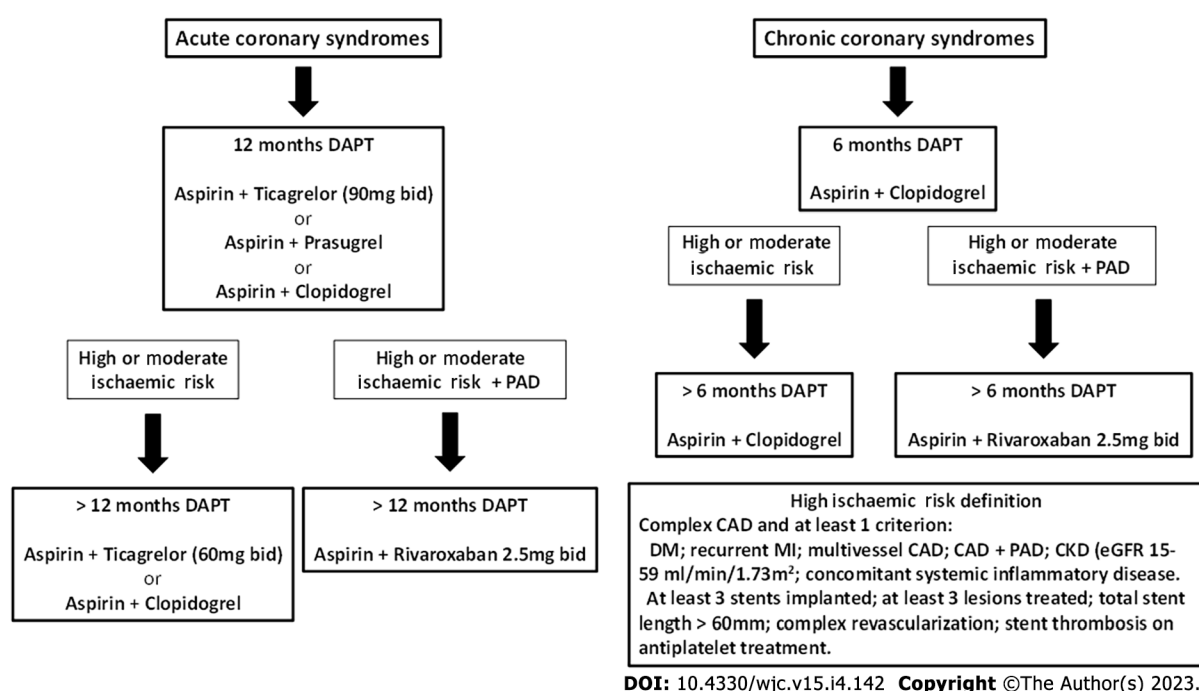


Figure 1 Flow-chart for the management of antithrombotic therapy in patients with coronary artery disease. CAD: Coronary artery disease; DAPT: Dual antiplatelet therapy; DM: Disease management; eGFR: Glomerular Filtration Rate; PAD: Peripheral arterial disease; MI: Myocardial infarction.

More recently, based on the COMPASS trial findings[28], a randomized controlled trial was designed to assess the efficacy of aspirin plus a low dose of rivaroxaban in patients who underwent lower extremity revascularization[36]. Those assigned to the dual therapy had better outcomes in terms of both MACE and MALE, balanced by an acceptable risk of bleeding. A subgroup analysis that referred to only open-surgical patients confirmed these findings[37]. Recently, Bonaca *et al*[38] tried to compare a “CASPAR-like” population derived from a post hoc analysis of the VOYAGER PAD trial to assess whether aspirin plus rivaroxaban performed better than aspirin plus clopidogrel after LER. No trials so far directly compared these two postoperative antithrombotic regimens. Their findings confirmed that aspirin combined with rivaroxaban led to better postoperative outcomes compared with clopidogrel as adjunctive therapy. Furthermore, Hiatt *et al*[34] found that the addition of rivaroxaban to aspirin after LER was effective and safe even if concomitant clopidogrel was prescribed, suggesting the potential role of a triple antithrombotic therapy, which however should be further evaluated in a dedicated trial.

In the wake of all the aforementioned trials[28,34,36-38], four major guidelines have been published in the last years regarding PAD[8,39-41].

In 2016 the ACC/AHA reported their recommendations for PAD[39]. Single antiplatelet therapy was strongly recommended in symptomatic PAD patients and after revascularization, while its routine use in asymptomatic patients was uncertain, as well as the role of DAPT. Indeed, these guidelines were released before the COMPASS trial, therefore not considering anticoagulant drugs.

The European guidelines[8] were published one year later by the ESC in collaboration with the European Society for Vascular and endovascular Surgery. They recommended antiplatelet therapy for asymptomatic patients, while a single drug is mandatory for symptomatic patients. Of note, deferring from the American guidelines, the latter suggested clopidogrel as the preferred molecule over aspirin [40]. Regarding postoperative schemes, DAPT was recommended after percutaneous procedures for 1 mo (or longer if concomitant CAD), while single antiplatelet was deemed adequate after open surgery. According to these guidelines, standard anticoagulants (*i.e.* warfarin) could be associated with antiplatelet therapy only after endovascular procedures and in patients at low risk of bleeding who were preoperatively on this regimen for other reasons (*i.e.* atrial fibrillation, mechanical heart valve, *etc.*). The European guidelines only cited the COMPASS trial as a potential landmark for future updates, as no published data were available yet.

The Global vascular guidelines on critical limb ischemia (CLI)[41] have been published in 2019. They gave weak recommendations for DAPT after infrainguinal bypasses for a period of 6 to 24 mo postoperatively and at least 1 mo after endovascular procedures (or a longer period in case of multiple reinterventions). Of note, these are the first guidelines that recommend the association between aspirin and a low dose of rivaroxaban to reduce MACE and MALE in patients with CLI (having the COMPASS trial been published 1 year before, while the VOYAGER PAD trial was ongoing at the time of publication).

The Canadian guidelines[42] are the most recently published guidelines for PAD. They confirm most of the recommendations given by the previous ones, except for more precise indications for rivaroxaban

associated with aspirin. Indeed, this represents the preferred antithrombotic strategy in symptomatic patients with high-risk comorbidities and higher stages of limb ischemia (“high-risk patients” and “high-risk limb”). Furthermore, they suggest the same approach after both open and endovascular interventions, with a restricted indication for DAPT only in patients unable to receive rivaroxaban. These conclusions, which are outlined in [Figure 2](#), may represent a paradigm shift in the treatment of PAD patients, regardless of the need for surgical procedures. Of course, these statements have to be confirmed by further trials, but we can affirm that this new antithrombotic strategy represents one of the most interesting fields of research in vascular surgery for the next years.

ANTILIPIDEMIC THERAPY IN POLY-VASCULAR DISEASE

Cardiological perspectives

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease, as evidenced by epidemiological and Mendelian randomization studies. LDL-C lowering is associated with a reduction of MACE in a linear way, without any plateau for lower LDL-C levels[43].

Therefore, a progressive lowering of the target of LDL-C has been observed in guidelines and consensus documents. The 2018 AHA/ACC/multisociety cholesterol guidelines[44], are more conservative in the definition of the LDL-C threshold to < 70 mg/dL and in the identification of very-high risk patients (not enclosing patients without established atherosclerotic cardiovascular disease, as those with diabetes or chronic kidney disease). On the contrary 2019 ESC/EAS Guidelines on the management of dyslipidemias[45] recommend, for very-high-risk patients, LDL-C target to be lower than 1.4 mmol/L (55 mg/dL), in addition to the goal of achieving a 50% reduction from baseline. Patients with any documented atherosclerotic cardiovascular disease, involving one or more districts are already considered at “very high” risk, whereas patients with repeated acute coronary syndrome events within 2 years should be considered at “extremely” high risk and pursue a lower threshold of 1.03 mmol/L. Patients with post-acute coronary syndrome and presence of peripheral artery disease or poly-vascular disease; post-acute coronary syndrome and coexistent multivessel coronary artery disease; and post-acute coronary syndrome and familial hypercholesterolemia have been recently paired in the latter category, according to certain European cardiological societies[46].

Lipid-lowering therapies modify the risk in patients with atherosclerosis and have been shown to exert larger absolute risk reductions in patients with the poly-vascular disease[47].

New evidence has raised the opportunity to start with a combination of statin therapy plus ezetimibe for very high-risk patients. If patients do not achieve the 2019 Guideline-recommend LDL-C goal, a third lipid-lowering therapy, such as bempedoic acid or proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9-i) targeted therapies should be added. Furthermore, in extremely high-risk patients triple therapy (statin plus ezetimibe plus PCSK9-inhibitors) could be administered at the beginning[48].

As observed in a sub-analysis of the FOURIER Trial, Evolocumab significantly reduced the risk of MACE in symptomatic PAD, including those without prior MI or stroke. Furthermore, LDL-C lowering with evolocumab reduced the risk of MALE including acute limb ischemia and major amputation. Akin to what has been observed for MACE, there was a consistently lower risk of MALE with lower levels of achieved LDL-C, down to 10 mg/dL[49].

Similar results were found in an analysis of the ODISEY-OUTCOME trial. In patients with recent ACS and dyslipidemia, the poly-vascular disease is associated with a high risk of MACE and death. The large absolute benefit of PCSK9 inhibition with alirocumab, when added to high-intensity statin therapy, is a potential benefit for this group of patients[50].

A new therapeutic weapon is represented by inclisiran, a small interfering RNA (siRNA) therapeutic agent which reduces hepatic synthesis of PCSK9. Inclisiran was approved in the European Union in 2020 for use in adults with primary hypercholesterolemia or mixed dyslipidemia based on the results of the ORION Trials. Inclisiran, administered subcutaneously every 6 mo, reduces LDL-C levels by approximately 50%[51].

In a post-hoc analysis of the Orion Trials, focused on patients with the polyvascular disease (PVD), two-yearly dosing with inclisiran provided an effective and sustained LDL-C lowering, irrespective of PVD status, with no relevant side effect[52].

Targets and objectives in peripheral artery disease

The relationship between statins and PAD has been seldom investigated. As well as for antithrombotic therapies, the literature focused more on pleiotropic effects rather than limb-related benefits of statins in PAD patients. Moreover, PAD patients often represented a subgroup in large RCTs of atherosclerotic patients, with few dedicated studies published so far. In a meta-analysis by Antoniou[53], statins proved to significantly reduce mortality and stroke in symptomatic PAD patients when compared to placebo. These trends have been recently confirmed by Kokkinidis[54] in another meta-analysis, which summarized some observational studies regarding the impact of statin therapy in CLI patients. Of note, this study investigated almost 27000 patients with CLI, but only half of them were statin users; these patients had better patency rates and a lower risk of amputations after revascularization, besides better

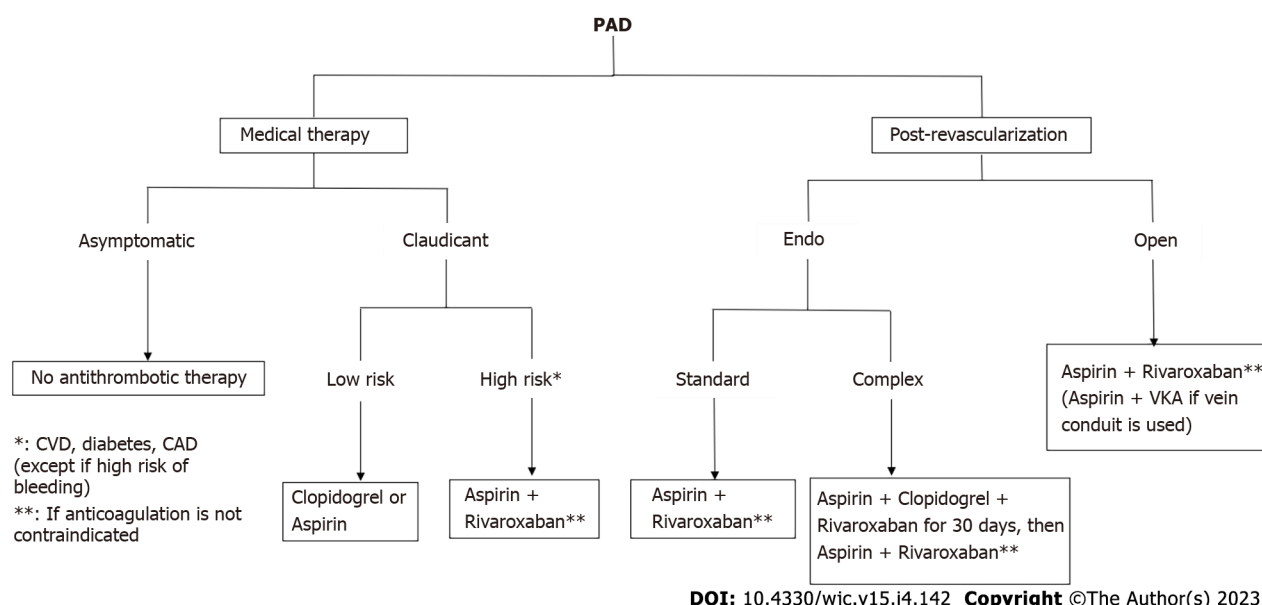


Figure 2 Antithrombotic strategies in patients with peripheral artery disease according to vascular guidelines. PAD: Peripheral artery disease; CVD: Cardiovascular disease; CAD: Coronary artery disease.

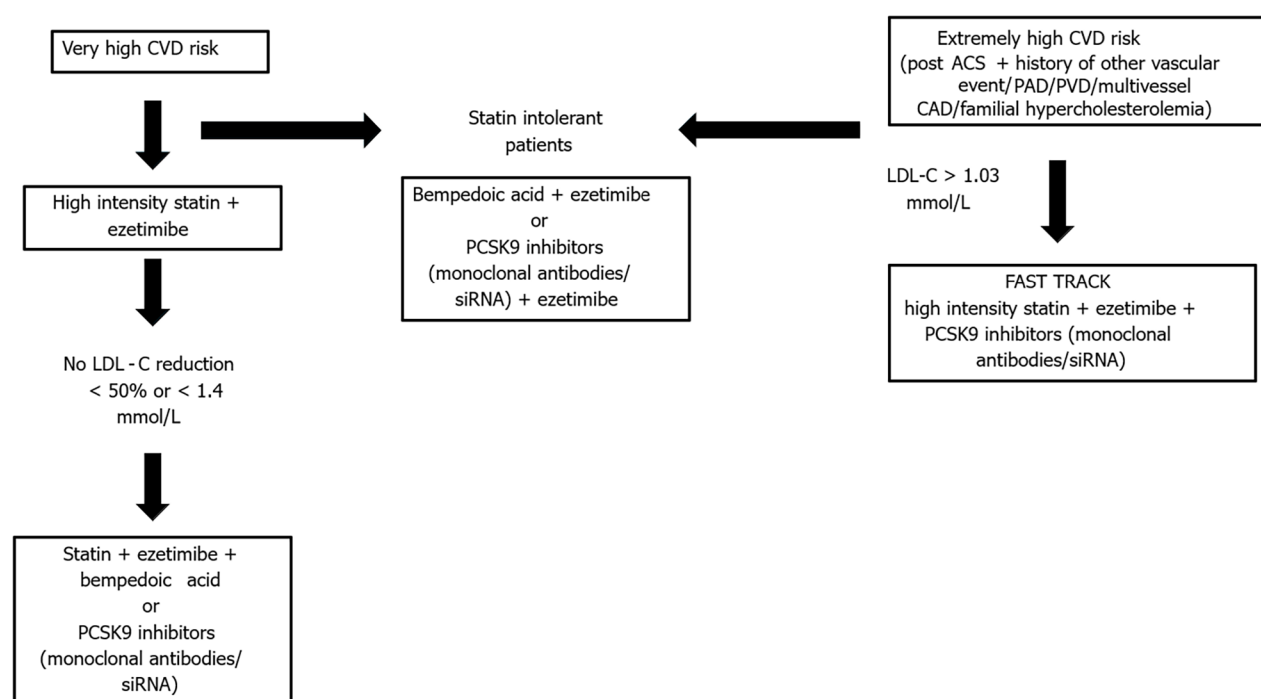
outcomes in terms of MACE and mortality. The issue of under-prescription of statins in PAD patients has also been raised by Parmar[55], in a population of 488 patients who underwent LER. These authors found that statins were the most impactful factor on MACE and MALE after revascularization, even more than all the antithrombotic strategies globally compared. Nevertheless, only 41% of patients in this study were on statin therapy. Furthermore, statins may induce muscle pain, which could affect the adherence to this therapy in PAD patients. In this scenario, the Global guidelines suggest to lower statins to the maximum tolerated dose, adding a non-statin molecule to reduce cholesterol blood levels to the optimum[42].

Recently, PCSK9-i and other new lipid-lowering therapies have been tested in large atherosclerotic populations, with only a small portion of them affected by PAD. The FOURIER trial[47] evaluated evolocumab, a PCSK9-I, in a large cohort of patients, while a PAD subgroup has been subsequently analyzed. The adjunct of evolocumab to statins significantly reduced MACE by 27% and MALE by 37% in this subgroup, regardless of the Rutherford class. On the other hand, the ODYSSEY OUTCOMES trial [50] provided different results with alirocumab. Once again, this was a RCT of patients with acute coronary syndrome (ACS) receiving either the placebo or alirocumab. This drug provided significantly fewer PAD events (*i.e.*: CLI, unplanned amputations, need for limb revascularization) in patients with ACS. Conversely, in a subanalysis of this trial by Jukema[50], patients with concomitant PAD had no benefit in terms of MACE, while the main trial showed positive results in the overall population. This confirms the need for studies specifically designed for PAD patients.

The aforementioned vascular guidelines[8,39-42] give fewer recommendations for lipid-lowering drugs than for antithrombotic therapies in PAD. Both the American and European guidelines generically recommend the use of statins in all PAD patients, with the latter specifying an optimal cut-off of 1.8 mmol/L (*i.e.*: < 70 mg/dL) for LDL-c levels. More specific indications are given by the Global guidelines in patients with CLI[39]. These guidelines suggest the use of moderate or high-intensity statin therapy with rosuvastatin 20-40 mg or atorvastatin 40-80 mg daily, with the same LDL-c target of 1.8 mmol/L. The Canadian guidelines[41] give more detailed indications for aggressive lipid-lowering therapies. All PAD patients should receive the higher tolerated dose of statins; the addition of PCSK9-i or ezetimibe should be considered if the cut-off of 1.8 mmol/L is not reached at the higher dose of statin. Furthermore, triglycerides levels are also mentioned, where the use of icosapent ethyl is suggested when statin therapy alone does not lead to a level of 1.8-5.6 mmol/L. Eventually, while all the previous guidelines give their recommendations for statins to reduce all-cause and CV mortality and morbidity (*i.e.*: Nonfatal MI, nonfatal stroke), these guidelines[41] are the only ones underlying the benefit of a more strict control of lipid levels also on MALES.

Similarly, the recently released 2022 ACC Expert Consensus Decision Pathway[56] on nonstatin therapies firstly integrated the results of the trials with bempedoic acid, alone or in association with ezetimibe, in order to achieve the target of LDL-C in patients with ASCVD or extremely high cholesterol levels.

Therefore, as summarized in Figure 3, LDL-C reduction should be aimed at any vascular patient. However, the achievement of very low levels should be pursued in patients with CAD+PAD, by establishing an aggressive management, with the combination of all the available strategies,



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Figure 3 Current indications to lipid-lowering drugs in patients with coronary and peripheral artery disease. CVD: Cardiovascular disease; LDL-C: Low-density Lipoprotein Cholesterol; PCSK9: Proprotein convertase subtilisin/kexin type 9; siRNA: Small interfering RNA.

immediately after the evidence of the poly-vascular disease, seeking an earlier achievement of the required goal.

CONCLUSION

Patients with concomitant multidistrict artery disease, *i.e.* poly-vascular disease, represent a higher risk subset of patients with worse prognosis. In these patients, the most aggressive tolerated antithrombotic and antilipidemic therapy should be attempted, although accounting for the interindividual differences. Multidisciplinary approach, involving both a cardiologist and vascular surgeon, combining different therapeutic goals and perspectives, could provide additional benefits in the correct tailoring of pharmacological therapy among poly-vascular patients.

FOOTNOTES

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Retrospective Study

Vasospastic angina in women: Clinical backgrounds and prognoses of patients younger than and older than 60 years

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Abstract

BACKGROUND

We frequently encounter cases of women with vasospastic angina (VSA). Additionally, some women with VSA are younger than 60 years old. However, it is unknown whether the characteristics of VSA in women aged < 60 years are different from those in women aged ≥ 60 years.

AIM

To investigate and compare the clinical characteristics and prognosis of VSA in women aged < 60 years from those in women aged ≥ 60 years.

METHODS

We enrolled 94 women with VSA who were diagnosed using the spasm provocation test. According to the age at diagnosis, the patients were divided into two groups: Group Y (age < 60 years, $n = 17$) and Group O (age ≥ 60 years, $n = 77$). Flow-mediated dilation (FMD) and nitroglycerin (NTG)-induced dilation (NID) of the brachial artery were performed and assessed using brachial ultrasonography. Moreover, conventional coronary risk factors, such as atherosclerotic lesions (stenosis > 20%) detected using coronary angiography and focal spasms (coronary spasm within one segment of one coronary artery), and major cardiovascular adverse events (MACE) were assessed in both groups.

RESULTS

Smoking was more prevalent in Group Y than in Group O ($P = 0.04$). FMD was similar in both groups (Group O: $4.3\% \pm 3.2\%$, Group Y: $4.5\% \pm 3.3\%$; $P = 0.75$), whereas NID was higher in Group Y ($20.5\% \pm 8.6\%$) than in Group O ($13.6\% \pm 5.3\%$, $P < 0.01$). Atherosclerosis was not detected in Group Y but was detected in Group O (61%, $P < 0.01$). Focal spasms were less frequent in Group Y (12%) than in Group O (38%, $P = 0.04$). The incidence of major adverse cardiac events did not differ between the two groups ($P = 0.40$).

CONCLUSION

Women aged < 60 years with VSA have less atherosclerotic lesions and focal spasms. These characteristics may be affected by smoking habits and vascular smooth muscle dysfunction.

Key Words: Acetylcholine; Young female; Smoking; Vasospastic angina; Vascular smooth muscle dysfunction

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Core Tip: We investigated whether the clinical background and prognosis of women aged < 60 years with vasospastic angina (VSA) differ from those of women aged ≥ 60 years with VSA. We showed that smoking was more frequent in women aged < 60 years with VSA. We found a significantly greater peripheral vascular response to nitroglycerin in such patients. Coronary angiography revealed fewer atherosclerotic lesions and focal spasms in such patients. Smoking status and vascular dysfunction may have influenced the above clinical characteristics in women aged < 60 years with VSA.

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INTRODUCTION

Vasospastic angina (VSA) is a condition characterized by transient hypercontraction of the epicardial coronary arteries, leading to myocardial ischemia[1,2]. Although the incidence of coronary artery disease is higher in men[3], the incidence of VSA is relatively higher in women[4,5]. Therefore, several reports have investigated gender differences among patients with VSA[5-9], concluding that women have a lower positivity rate than men during the spasm provocation test (SPT)[5-9], and that focal spasms occur more frequently in men than in women[8,10].

Among women with VSA, we have encountered cases of patients younger than 60 years old. In a paper by Kawana *et al*[6] that evaluated the characteristics of women with VSA by age, smoking was more prevalent in younger women with VSA, but the prevalence of hypertension was lower in this population. Additionally, women aged < 50 years with VSA had a worse prognosis. Aside from this study, few reports have examined the characteristics of women with VSA at an early age.

Therefore, in the present study, we retrospectively investigated the differences in clinical characteristics and prognosis between women aged < 60 years and ≥ 60 years with VSA.

MATERIALS AND METHODS

Study patients

This observational retrospective study included female patients with VSA who were diagnosed using SPT at our institution between August 2010 and March 2017 ($n = 107$). The exclusion criteria were as follows: significant coronary stenosis (stenosis > 50%, $n = 3$), or a previous medical history of percutaneous coronary intervention ($n = 3$), heart failure ($n = 4$), and hypertrophic cardiomyopathy ($n = 3$). Ultimately, 94 women VSA were enrolled in the study. The mean and median ages of the patients at diagnosis were 69 ± 10 years and 71 (63, 76) years, respectively; the 25th percentile was 63 years. However, the cut-off age for this study was set at 60 years. Hence, the patients were classified into two groups based on the cut-off age: Group Y (age < 60 years, $n = 17$) and Group O (age ≥ 60 years, $n = 77$, Figure 1). The study protocol was approved by the ethics committee of our institution. Written informed consent was obtained from all participants.

Coronary angiography and SPT

SPT was carried out in accordance with our prior description[4,11,12]. At our institution, SPT of the right coronary artery (RCA) was carried out continuously. Acetylcholine (ACh) dosages of 20 and 50 mg were injected into the RCA following initial coronary angiography (CAG). When coronary spasm was not induced by 50 mg of ACh, ACh was continuously administered until the maximum dose of 80 mg. CAG was then performed after administration of the maximum dose of ACh or induction of coronary spasms, whichever came first. SPT of the left coronary artery (LCA) was carried out without

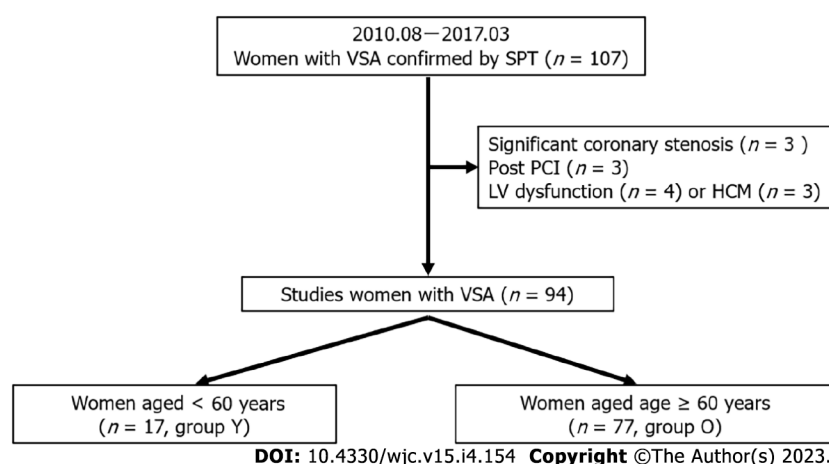


Figure 1 The flowchart of the study. HCM: Hypertrophic cardiomyopathy; PCI: Percutaneous coronary intervention; VSA: Vasospastic angina; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

intracoronary injection of nitroglycerin (NTG) into the RCA if the coronary spasms spontaneously resolved. In such circumstances, NTG injection into the RCA was performed after performing the SPT for the LCA. An intracoronary injection of 0.3 mg NTG was administered to ease spasms if the ACh-induced coronary spasms were severe enough to cause hemodynamic instability; this was referred to as the unavoidable use of NTG[13]. SPT of the LCA was then carried out using 50 and 100 mg of ACh. When coronary spasm was not induced by 100 mg of ACh, ACh was continuously administered until the maximum dose of 200 mg. CAG was then performed after administration of the maximum dose of ACh or the induction of coronary spasms, whichever came first. The final CAG for the LCA was performed after an intracoronary injection of 0.3 mg of NTG.

As previously shown[4], we employed an autoinjector. The coronary artery diameter was measured in accordance with the previous methods[4]. Atherosclerotic lesions were defined as those with a stenosis > 20%. We also explored the likelihood of myocardial bridging (MB), which was defined as systolic reduction > 20% in the coronary artery diameter[14].

Definitions of VSA-related parameters

Angina pectoris was classified into three patterns: resting, exertion, and both resting and exertion. For anginal symptoms, the number of attacks per month, maximum attack duration (minutes), and estimated duration of disease (months) were also calculated. VSA was defined as > 90% narrowing of coronary arteries on angiograms when provoked and accompanied by the presence of usual chest pain and/or the presence of an ST-segment deviation on electrocardiogram (ECG)[15]. Focal spasm was defined as transient vessel narrowing of > 90% within the borders of one isolated coronary segment, as defined by the American Heart Association. Diffuse spasm was defined as 90% diffuse vasoconstriction observed in ≥ 2 adjacent coronary segments of the coronary arteries[10]. Multivessel spasms (MVS) were defined as coronary spasms that occurred in ≥ 2 major coronary arteries. For multivessel spasms, we could not assess when the subsequent SPT was negative after an unavoidable use of NTG[16]. Regarding the presence of coronary spasm per vessel, the frequency of coronary spasms in the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and RCA were reviewed.

Other clinical characteristics measured in the present study

Patients were asked about their smoking status and family history of coronary artery disease. Smoking status was classified as active smokers, former smokers (had stopped smoking for at least 1 mo), or never smokers. In the logistic analysis, smoking was defined as the combined number of active and former smokers. Hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome (MtS), and chronic kidney disease (CKD) were defined based on the standard definitions described in previous papers[4]. Patients or family members were asked about their alcohol consumption, and those who drank at least once a week were defined as having alcohol consumption[17]. Blood chemical parameters, including the estimated glomerular filtration ratio (eGFR, mL/min/1.73 m²) and brain natriuretic peptide level (BNP, pg/mL), were routinely investigated on the same day of CAG. The left ventricular ejection fraction was measured using cardiac ultrasonography. On brachial echosonography, flow-mediated dilation (FMD), as an endothelium-dependent function, and NTG-induced dilation (NID), as an endothelium-independent function, were measured as previously described[18].

All study participants made at least one follow-up visit at our facility, and patients were followed-up as closely as was practical after discharge. The last date of data collection was in October 2022. Information from the medication diaries of patients who had recently made a follow-up visit was

included in the follow-up assessments. We recorded the number of consumed coronary vasodilators monthly and angina events over the past 3 mo. These evaluations were performed on patients who could be assessed at least 6 mo after discharge ($n = 85$). The number of coronary vasodilators used was also evaluated during hospital admission, discharge, and final follow-up. For each patient, cardiac events, including readmission for angina or other cardiovascular conditions, were recorded. Readmission due to cardiovascular conditions or death from cardiac causes were considered as major adverse cardiac events (MACEs).

Statistical analyses

Data are presented as mean $\pm$ standard deviation or median with interquartile ranges for non-normally distributed data and non-continuous variables. Baseline characteristics of the groups were compared using Student's unpaired *t*-tests, Wilcoxon signed-rank tests, or χ^2 analysis, as appropriate. Logistic regression analysis was used to determine the presence of VAS in Group Y. MACEs were analyzed using the Kaplan-Meier survival curve and the logrank test. JMP Ver. 16 (SAS Institute Inc., Cary, NC, United States) was used to perform all statistical analyses. A *P* value < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

There were 17 patients (18%) in Group Y and 77 (82%) in Group O. The patients' characteristics are shown in Table 1. Group Y had a mean age of 54 ± 5 years and Group O had a mean age of 72 ± 7 years; the mean age was significantly lower in Group Y ($P < 0.01$). Although smoking was more prevalent in Group Y ($P < 0.01$), hypertension ($P < 0.01$) and CKD ($P = 0.02$) were less prevalent. A trend toward more frequent alcohol consumption was observed in Group Y ($P = 0.09$).

Regarding the blood chemical parameters, eGFR was higher in Group Y than in Group O ($P = 0.05$), and BNP levels tended to be lower in Group Y ($P = 0.09$, Table 2). Regarding the brachial ultrasonographic parameters (Table 3), the brachial artery diameter at baseline ($P = 0.83$) and FMD ($P = 0.75$) were not different between the two groups, but NID was significantly higher in Group Y ($20.6\% \pm 8.6\%$) than in Group O ($13.6\% \pm 5.3\%$, $P < 0.01$). Brachial ultrasonography was performed after at least 48 h from withdrawal of coronary dilators. The results were similar in patients who had not been taking coronary dilators to rule out the effects of these drugs.

Logistic regression analysis showed that NID [odds ratio (OR): 5.1, $P = 0.02$] and absence of CKD (OR: 7.5, $P < 0.01$) and hypertension (OR: 4.5, $P = 0.03$) were factors responsible for the presence of women aged < 60 years ($R^2 = 0.32$), while smoking tended to be associated with it (OR: 3.7, $P = 0.06$).

VSA-related parameters and the results of CAG-SPT

There were no differences between the two groups on whether angina occurred at rest or with exertion nor in the number of attacks, maximum attack duration, or estimated duration of illness (Table 4). The frequency of coronary dilator intake ($P = 0.02$) and number of coronary dilators taken before admission ($P = 0.01$) were significantly lower in Group Y.

Regarding CAG (Table 5), the prevalence of atherosclerosis was significantly lower in Group Y ($P < 0.01$), but that of MB did not differ between the two groups ($P = 0.94$). Regarding SPT (Table 5), the frequency of focal spasms was significantly lower in Group Y ($P = 0.04$), while the frequency of MVS was not significantly different among those that underwent evaluation ($P = 0.56$). The frequency of coronary spasms in the LAD and RCA was not different between the two groups; however, the frequency of coronary spasms in the LCX was significantly higher in Group Y ($P < 0.01$). The frequency of unavoidable use of NTG was also significantly higher in Group Y ($P = 0.01$). The incidence of ST-segment elevation on ECG during coronary spasms tended to be higher in Group Y ($P = 0.09$).

Prognosis

The number of prescribed coronary dilators at discharge was significantly lower in Group Y ($P = 0.01$). The median follow-up period was 6.4 (3.9, 8.4) years, with no difference between the two groups (Group Y: 4.3 years, Group O: 6.8 years, $P = 0.12$). There was no difference in the number of coronary dilators taken at the time of the last follow-up in patients who had been followed for more than 6 mo ($P = 0.52$), but the number of chest symptoms per month was significantly higher in Group Y ($P < 0.01$). There was no significant difference in the number of MACEs between the two groups (Figure 2, Logrank $P = 0.40$).

DISCUSSION

The present study investigated the clinical characteristics and prognosis of women aged < 60 years with VSA compared to those in women aged ≥ 60 years with VSA. Our results showed that women aged < 60

Table 1 Patients' characteristics

	Group O	Group Y	P value
No. (%)	77 (82)	17 (18)	
Age (yr)	72 ± 7	54 ± 5	< 0.01
Body mass index	23.7 ± 4.5	24.5 ± 5.3	0.50
Coronary risk factors (%)			
Smoking (active/former/never)	3/5/69	3/4/10	< 0.01
Hypertension	58 (75)	7 (41)	< 0.01
Dyslipidemia	55 (77)	10 (59)	0.31
Diabetes mellitus	12 (16)	2 (12)	0.68
Alcohol consumer (%)	10 (13)	5 (29)	0.09
Family history of CAD (%)	18 (23)	5 (29)	0.60
MtS (%)	13 (17)	4 (24)	0.52
CKD (%)	27 (35)	1 (6)	0.02

CAD: Coronary artery disease; CKD: Chronic kidney disease; MtS: Metabolic syndrome; No.: Number; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

Table 2 Blood chemical parameters in the two groups

	Group O	Group Y	P value
Total cholesterol (mg/dL)	202 ± 33	196 ± 37	0.53
Triglyceride (mg/dL)	131 ± 73	119 ± 46	0.54
HDL-cholesterol (mg/dL)	63 ± 17	62 ± 18	0.82
LDL-cholesterol (mg/dL)	113 ± 29	111 ± 32	0.82
Fasting blood sugar (mg/dL)	100 ± 16	101 ± 17	0.93
Hemoglobin A1C (%)	6.0 ± 0.7	5.7 ± 0.6	0.10
C-reactive protein (mg/dL)	0.05 (0.02, 0.13)	0.07 (0.02, 0.15)	0.81
eGFR (mL/min/1.73 m ²)	68.8 ± 16.8	77.5 ± 13.2	0.05
BNP (pg/mL)	22 (14, 54)	15 (10, 29)	0.09

BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration ratio; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

years with VSA were more likely to be smokers and less likely to have hypertension and CKD. Additionally, they had very good peripheral vascular function as indicated by their response to NTG. The results of CAG and SPT showed that there was less atherosclerosis and less focal spasm in women aged < 60 years with VSA. However, the frequency of coronary spasms in the LCX was high, and NTG was unavoidably used in this population. Additionally, the prognosis of women aged < 60 years with VSA was favorable as long as coronary dilators were strictly administered, although their chest symptoms persisted. These clinical characteristics should be considered in the treatment and follow-up of such patients.

Although there have been several reports on the characteristics of women with VSA[5-10], few reports have explored the characteristics of VSA by age[6]. Kawana *et al*[6] classified patients with VSA based on age: Under 50 years, 50–64 years, and over 65 years, and they found that although the prevalence of hypertension and dyslipidemia was lower in younger patients, the prevalence of smoking was higher. In the present study, the prevalence of hypertension and CKD, which was possibly induced by hypertension itself, was also significantly lower in women aged < 60 years, but these findings appear to be age-related and not limited to the presence of VSA or gender[19,20]. Meanwhile, the same was true for the prevalence of smoking in the present study, confirming that smoking is more frequent in younger age groups. Smoking is a risk factor for coronary spasms even in young women[21], and it was

Table 3 Echographic parameters in the two groups

	Group O	Group Y	P value
UCG			
LVEF (%)	68 ± 9	66 ± 6	0.46
Brachial ultrasonography			
All studied patients			
No.	77	17	
Heart rate (/min)	66 ± 10	67 ± 13	0.85
Mean blood pressure	100 ± 14	94 ± 14	0.16
Brachial blood flow			
Baseline (mL/min)	61 ± 44	59 ± 52	0.87
% increase	384 ± 490	327 ± 265	0.59
Brachial artery diameter (mm)			
Baseline	3.5 ± 0.5	3.5 ± 0.5	0.83
Hyperemia	3.7 ± 0.5	3.6 ± 0.5	0.88
After NTG	4.0 ± 0.5	4.2 ± 0.4	0.25
FMD (%)	4.3 ± 3.2	4.5 ± 3.3	0.75
NID (%)	13.6 ± 5.4	20.5 ± 8.6	< 0.01
Patients who did not take any coronary vasodilators			
No.	39	14	
Brachial artery diameter (mm)			
Baseline	3.5 ± 0.5	3.6 ± 0.4	0.68
Hyperemia	3.6 ± 0.6	3.7 ± 0.4	0.60
After NTG	4.0 ± 0.5	4.2 ± 0.4	0.21
FMD (%)	4.1 ± 3.1	4.3 ± 3.5	0.82
NID (%)	14.6 ± 5.7	18.5 ± 6.5	0.04

FMD: Flow-mediated dilation; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; NTG: Nitroglycerin; No.: Number; UCG: Echocardiography; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

reported that smoking causes hypercontraction of vascular smooth muscles through the activation of Rho kinase[22] and/or vascular endothelial dysfunction through increased production of reactive oxygen species[23]. Thus, smoking may be an etiologic factor of VSA in women aged < 60 years.

On the other hand, NID of the brachial artery was higher in women aged < 60 years with VSA and was still a significant and influential factor even when smoking was included in the logistic regression analysis. Meanwhile, FMD did not differ between the two groups. These findings cannot be fully explained but may indicate relative vascular endothelial dysfunction and/or vascular smooth muscle hypercontraction. Smoking may have caused these vascular dysfunctions, but it is also possible that the relative decline in sex hormones during menopause may cause these changes[24]. Furthermore, it is also possible that there is a genetic problem with eNOS that may have caused vascular dysfunction[25], although we have not found significant differences in the family history of CAD between the two groups. Future large studies or registries should carefully evaluate age-specific vascular dysfunction in women with VSA.

Regarding CAD and SPT, women aged < 60 years with VSA had less atherosclerosis, which could be explained by age-related changes regardless of the presence of VSA or gender. Focal spasms were also less frequent in women aged < 60 years, which may also be related to fewer atherosclerotic lesions. Several studies have shown that focal spasm is more likely to occur at sites with atherosclerotic lesions [26,27]. However, the frequency of coronary spasm in the LCX was significantly higher in women aged < 60 years. Sueda *et al*[28] showed that coronary spasms in the LCX was significantly less than those in the RCA or LAD (28%), suggesting that the distribution of muscarinic receptors may differ according to the coronary artery vessel. Furthermore, Sueda *et al*[7] did not report any differences in terms of sex

Table 4 Vasospastic angina-related parameters in the two groups

	Group O	Group Y	P value
Chest symptoms			
Rest/Exercise/Both	60/9/9	14/1/2	0.78
Maximum duration of attack (min)	20 ± 27	16 ± 28	0.10
Diseased duration (M)	5 (1, 48)	12 (3, 42)	0.78
No. of anginal attacks (/M)			
At admission	4 (1, 10)	4 (1, 10)	0.43
At follow-up	0 (0, 1)	2 (0.1, 2.8)	< 0.01
No.	69	16	
Medications			
Taking statins at admission (%)	36 (47)	7 (46)	0.68
Taking antiplatelet drugs at admission (%)	20 (26)	1 (6)	0.07
Taking vasodilators at admission (%)	38 (49)	3 (18)	0.02
No. coronary vasodilators			
At admission	0 (0, 1)	0 (0, 0)	0.01
	0.6 ± 0.7	0.2 ± 0.4	0.01
At discharge	1 (1, 1)	1 (1, 1)	0.01
	1.2 ± 0.5	0.9 ± 0.3	0.02
At follow-up	1 (1, 2)	1.5 (1, 2)	0.52
	1.5 ± 0.9	1.6 ± 0.9	0.53

M: Months; No.: Number; VSA: Vasospastic angina; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

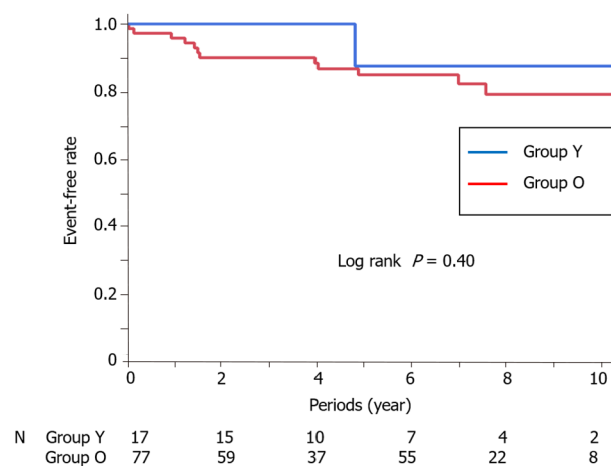


Figure 2 The Kaplan–Meier curve for MACE-free survival during the follow-up period in the two groups. O group: Older than 60 years of age; MACE: Major adverse cardiac events; N: Number; Y group: Younger than 60 years of age.

regarding the frequency of coronary spasms in the LCX. In the present study, SPT was initiated in the RCA and shifted to the LCA; it is possible that the frequency of coronary spasms in the LCX may differ depending on where SPT is initiated. In any case, the fact that coronary spasms in the LCX were more frequent in women aged < 60 years suggests that muscarinic receptor distribution may change with age in women with VSA. The unavoidable use of NTG was reported to be associated with more active coronary spasms[13], which may suggest that women aged < 60 years with VSA have more active coronary spasms.

Table 5 Coronary angiography spasm provocation test parameters in the two groups

	Group O	Group Y	P value
CAG			
Atherosclerotic change (%)	47 (61)	0 (0)	< 0.01
Myocardial bridging (%)	13 (17)	3 (18)	0.94
SPT			
Focal/diffuse/focal and diffuse	16/48/33	0/15/2	0.08
Presence of focal spasm (%)	29 (38)	2 (12)	0.04
Multi-vessels spasm (% , No.)	39 (57, 68)	8 (67, 12)	0.56
Vessels of spasm			
RCA (% , No.)	44 (62, 71)	10 (67, 15)	0.72
LAD (% , No.)	70 (96, 73)	13 (93, 14)	0.62
LCX (% , No.)	5 (7, 72)	5 (38, 13)	< 0.01
An unavoidable use of NTG (%)	14 (18)	8 (47)	0.01
ST deviation during SPT (%)	10 (13)	5 (29)	0.09

CAG: Coronary angiography; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; No.: Number; NTG: Nitroglycerin; RCA: Right coronary artery; SPT: Spasm provocation test; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

Regarding the prognosis, Kawana *et al*[6] reported that women aged < 50 years with VSA had poorer prognoses than those aged ≥ 50 years. In the present study, the prognoses of patients aged < 60 years and ≥ 60 years were similar. This may be due to the small number of cases and the cut-off age of 60 years in this study rather than 50 years. Nevertheless, the fact that focal spasm, a marker of poor prognosis[10,27], was less frequent in patients younger than 60 years and that younger women with VSA have a poorer prognosis[6] and required more coronary dilators may explain the similar prognosis in the two groups. Chest symptoms were significantly more frequent at follow-up in younger patients with VSA, possibly indicating that these patients had more active coronary spasms.

The implications of the present study are as follows: vascular dysfunction is present in relatively young patients with VSA, and since smoking may be a risk factor, it may be important to encourage women to quit smoking immediately. Additionally, because these patients may have more active coronary spasms, it is important to monitor and maintain them with increasing doses of coronary dilators to improve chest symptoms.

This study had several limitations. First, it was a single-center study with a small number of patients, and the distribution of patients was unequal in the studied groups. Thus, the results may not be applicable to all patients experiencing coronary spasms. Furthermore, due to the small number of cases, it was not possible to classify the patients into three groups as in the study of Kawana *et al*[6]. More studies with considerable sample size are needed to support the findings in this study. Second, this study was conducted on women with VSA, and we do not have data from our institution regarding vascular function in men with VSA or in healthy women. Therefore, it is difficult to conclude whether the findings in this study are truly characteristic of women aged < 60 years with VSA. Future large studies and multicenter registries should clarify this issue. Finally, brachial artery echocardiography was performed on the day before SPT and after discontinuation of coronary dilators. We concluded that these findings were true because the results were similar in patients who were not taking coronary dilators. Nevertheless, we cannot rule out the possibility that the results of brachial artery echocardiography may have been influenced by the residual effects of withdrawal of coronary vasodilators.

CONCLUSION

In conclusion, we examined the clinical characteristics and prognosis of women aged < 60 years with VSA and compared them to women aged ≥ 60 years with VSA, revealing that these patients were more likely to be smokers and have vascular dysfunction. The frequency of atherosclerosis and focal spasms was low, but the frequency of coronary spasms in the LCX was high. They were also more likely to unavoidably use NTG, suggesting that they may have more active coronary spasms. Such patients should be carefully monitored by increasing the use of coronary dilators and encouraged to quit smoking, if they smoke. Cardiologists need to be reminded that young women with VSA have high

coronary spasm activity.

ARTICLE HIGHLIGHTS

Research background

We frequently encounter cases of women with vasospastic angina (VSA). Additionally, some women with VSA are younger than 60 years old.

Research motivation

However, it is unknown whether the characteristics of VSA in women aged <60 years are different from those in women aged ≥ 60 years.

Research objectives

The objective of the present study was to investigate and compare the clinical characteristics and prognosis of VSA in women aged < 60 years from those in women aged ≥ 60 years.

Research methods

We enrolled 94 women with VSA who were diagnosed using the spasm provocation test (SPT). According to the age at diagnosis, the patients were divided into two groups: Group Y (age < 60 years, $n = 17$) and Group O (age ≥ 60 years, $n = 77$). Flow-mediated dilation (FMD) and nitroglycerin (NTG)-induced dilation (NID) of the brachial artery were performed and assessed using brachial ultrasonography. Moreover, conventional coronary risk factors, such as atherosclerotic lesions (stenosis > 20%) detected using coronary angiography and focal spasms (coronary spasm within one segment of one coronary artery), and major cardiovascular adverse events (MACE) were assessed in both groups.

Research results

Smoking was more prevalent in Group Y than in Group O ($P = 0.04$). FMD was similar in both groups (Group O: $4.3\% \pm 3.2\%$, Group Y: $4.5\% \pm 3.3\%$; $P = 0.75$), whereas NID was higher in Group Y ($20.5\% \pm 8.6\%$) than in Group O ($13.6\% \pm 5.3\%$, $P < 0.01$). Atherosclerosis was not detected in Group Y but was detected in Group O (61%, $P < 0.01$). Focal spasms were less frequent in Group Y (12%) than in Group O (38%, $P = 0.04$). The incidence of MACEs did not differ between the two groups ($P = 0.40$).

Research conclusions

Women aged < 60 years with VSA have less atherosclerotic lesions and focal spasms. These characteristics may be affected by smoking habits and vascular smooth muscle dysfunction.

Research perspectives

Vascular dysfunction is present in relatively young patients with VSA, and since smoking may be a risk factor, it may be important to encourage women to quit smoking immediately. Additionally, because these patients may have more active coronary spasms, it is important to monitor and maintain them with increasing doses of coronary dilators to improve chest symptoms.

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FOOTNOTES

Author contributions: Oshita C and Uchimura Y contributed to the acquisition of data and Teragawa H contributed to the writing and revision of the manuscript; All the authors approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the JR Hiroshima Hospital Institutional Review Board (Approval No. 2022-38).

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. Furthermore, in the retrospective cohort study, we have shown the information about the present study, on our web site (<http://www.jrhh.sakura.ne.jp/annnai/torikumi.html>), as an opt-out method.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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Observational Study

Right ventricle dysfunction does not predict mortality in patients with SARS-CoV-2-related acute respiratory distress syndrome on extracorporeal membrane oxygenation support

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Abstract

BACKGROUND

The prognostic role of right ventricle dilatation and dysfunction (RVDD) has not been elucidated in patients with coronavirus disease (COVID)-related respiratory failure refractory to standard treatment needing extracorporeal membrane oxygenation (ECMO) support.

AIM

To assess whether pre veno-venous (VV) ECMO RVDD were related to in-intensive care unit (ICU) mortality.

METHODS

We enrolled 61 patients with COVID-related acute respiratory distress syndrome refractory to conventional treatment submitted to VV ECMO and consecutively admitted to our ICU (an ECMO referral center) from 31st March 2020 to 31st August 2021. An echocardiographic exam was performed immediately before VV ECMO implantation.

RESULTS

Males were prevalent (73.8%) and patients with a body mass index > 30 kg/m² were the majority (46/61, 75%). The overall in-ICU mortality rate was 54.1% (33/61). RVDD was detectable in more than half of the population (34/61, 55.7%) and associated with higher simplified organ functional assessment (SOFA) values ($P = 0.029$) and a longer mechanical ventilation duration prior to ECMO support ($P = 0.046$). Renal replacement therapy was more frequently needed in RVDD patients ($P = 0.002$). A higher in-ICU mortality ($P = 0.024$) was observed in RVDD patients. No echo variables were independent predictors of in-ICU death.

CONCLUSION

In patients with COVID-related respiratory failure on ECMO support, RVDD (dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) and by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Key Words: Right ventricle; Echocardiography; Mortality; COVID; Acute respiratory distress syndrome; Right ventricle-pulmonary circulation coupling

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Core Tip: In coronavirus disease-related respiratory failure on extracorporeal membrane oxygenation support right ventricle dilatation and dysfunction (defined as the coexistence of dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher Sequential Organ Failure Assessment values and need of renal replacement therapy) and by a higher in-intensive care unit (ICU) mortality. However, at logistic regression analysis, right ventricle dilatation and dysfunction (even when considered separately) did not result independently associated with in-ICU mortality in these patients.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease can evolve in some cases in severe respiratory failure, refractory to conventional therapies, which requires veno-venous extracorporeal membrane oxygenation (VV ECMO) support, possibly in experienced centers[1-3]. In coronavirus disease (COVID) respiratory disease, right ventricular (RV) dilatation is frequently encountered especially in severe disease[4,5], but, to date, the prognostic role of RV dilatation has not been completely elucidated. In acute respiratory distress syndrome (ARDS) from different etiologies on ECMO support[3] RV dilatation and dysfunction (RVDD) were negatively associated with early outcome, while the prognostic role of RVDD has not been elucidated in patients with COVID-related respiratory failure refractory to standard treatment needing ECMO. We hypothesize that pre ECMO RVDD is related to in-intensive care unit (ICU) mortality, and we tested this hypothesis in 61 consecutive patients with COVID-related ARDS on ECMO support.

MATERIALS AND METHODS

In our prospective observational study, we enrolled 61 patients with COVID-related ARDS refractory to conventional treatment submitted to VV ECMO and consecutively admitted to our ICU (an ECMO referral center) from 31st March 2020 to 31st August 2021. No exclusion criteria. The study protocol was approved by our Ethical Committee ("Comitato Etico Area Vasta Centro" n.17024, approved on March 31st 2020) ("Florence COVID ICU Registry"). The written informed consent for each patient was waived for emerging infectious disease. The need for ECMO support was communicated to the patient's relatives by phone before implantation.

On ICU admission we measured: Troponin (pg/mL), N-terminal-pro brain natriuretic peptide (NT-BNP, pg/mL), C-reactive protein (mg/dL) creatinine (mg/dL), lactate dehydrogenase (UI/L), D-dimer (ng/mL), and interleukin 6 (pg/mL). According to our echocardiography protocol[3,5], an echocardiographic exam was performed immediately before ECMO implantation. Systolic pulmonary artery pressure (sPAP) is obtained using the simplified Bernoulli's equation. RVDD was defined in presence of RVEDA/LVEDA > 0.6 and tricuspid annular plane systolic excursion (TAPSE) < 15 mm (M-mode). Coupling of RV function to the pulmonary circulation was evaluated as the TAPSE to sPAP ratio. Each echo measure is performed three times, and the mean value was recorded[4,6].

All ultrasound cardiac procedures were performed using the necessary protective equipment for professionals. Dedicated machines (Ge HealthCare machine) were used in the COVID ICU and transducers are wrapped in single-use plastic covers. We considered VV ECMO in COVID when respiratory failure persisted despite optimum management including controlled ventilation with tidal volume 6 mL/kg, plateau pressure < 30 cm H₂O, use of neuromuscular blockers, high-positive end-expiratory pressure, and repeated prone positioning sessions[1-3,7,8]. All patients were encouraged to mobilize early[3]. Outcome was death in the ICU.

Statistical analysis

Data have been stored in a dedicated database and analyzed with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL). *P* value less than 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean $\pm$ standard deviation (SD) or median (range), as needed. Comparisons between the groups were performed using Chi square for categorical data, and student's *t* test and Kruskal-Wallis test for continuous data. Logistic regression backwards models have been developed to detect predictor(s) for ICU-death. Variables were selected based on univariate analysis and on clinical criteria. To avoid overfitting, each model included three variables. Receiver operating curve (ROC) was constructed to identify the cut-off for age and duration of pre-ECMO mechanical ventilation in relation to ICU-death.

RESULTS

Our population comprised 61 consecutive patients with COVID-related respiratory failure on ECMO support (Table 1). Patients transferred from peripheral hospitals accounted for the 62% of our population. Males were prevalent (73.8%) and patients with a body mass index > 30 kg/m² were the majority (46/61, 75%). Renal replacement therapy was needed in almost half of the entire population (48%). Renal replacement therapy was started on ICU admission in five patients (17%) and after ECMO start in the remaining 24 patients (83%). The overall in-ICU mortality rate was 54.1% (33/61). At echocardiography left ventricular ejection fraction (LVEF) was normal in all but three patients who had LVEF < 45% because of previously known heart disease.

RVDD vs no RVDD

Table 1 shows the comparison between patients with RVDD and those without. In the entire population, RVDD was detectable in more than half of the population (34/61, 55.7%). In the comparison between the two subgroups, patients with RVDD showed higher values of simplified organ functional assessment (SOFA) (*P* = 0.029) and a longer mechanical ventilation duration prior to ECMO support (*P* = 0.046). Renal replacement therapy was more frequently needed in RVDD patients (*P* = 0.002). A higher in-ICU mortality (*P* = 0.024) was shown in RVDD patients. Higher values of NT-pro BNP were observed in RVDD patients (*P* = 0.014). At echocardiography, RVDD patients exhibited higher values of sPAP (*P* = 0.015), E/e1 (*P* = 0.0003) and lower TAPSE/sPAP (*P* = 0.001). Higher doses of norepinephrine were needed in patients with RVDD (*P* = 0.011) when compared with those without. No differences were detectable in ventilatory parameters between the two subgroups.

Survivors vs no survivors

Table 2 shows the comparison between survivors and no survivors. No survivors were older (*P* = 0.003) and showed a higher SOFA (*P* = 0.010) and a longer mechanical ventilation duration before ECMO implantation (*P* = 0.006). Among biohumoral data, creatinine values were significantly higher in no survivors (*P* = 0.030), with no other significant difference between the two subgroups. Echocardiography, performed before ECMO implantation, did not show any significant difference between survivors and no survivors.

Multivariate logistic regression analysis

Different models were calculated (Table 3). The following parameters resulted independent predictors of in-ICU death: Age, SOFA, time from symptoms' onset, mechanical ventilation preECMO $\geq$ 10 d and creatinine. RV dilatation, RV dysfunction and RVDD (dilatation and dysfunction) were not independently associated with in-ICU mortality. At ROC analysis, the age cut-off was $\geq$ 57 years [area under the curve: 70.5% (95% confidence interval: 57.3- 83.7%), *P* = 0.006, sensitivity 72.7%, specificity 58.0%].

DISCUSSION

The main finding of the present investigation is that, in COVID-related respiratory failure on ECMO support, RVDD (defined as the coexistence of dilatation and dysfunction) is a common finding. The

Table 1 Comparison between patients with right ventricle dilatation and dysfunction and those without, *n* %

Variable	All patients	RVDD (No. 34)	No RVDD (No. 27)	P value
Clinical data				
Age (yr), mean $\pm$ SD	54.3 $\pm$ 10.3	53.8 $\pm$ 9.7	52.9 $\pm$ 11	0.735
Gender, M/F	45/16 (74/26)	28/6 (82/18)	17/10 (63/37)	0.087
BMI (kg/m ²), mean $\pm$ SD	32.9 $\pm$ 5.3	32.4 $\pm$ 5.6	32.7 $\pm$ 4.9	0.836
Charlson index, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.772
Transferred from peripheral hospitals	38 (62)	18 (52)	20 (74)	0.9
Time from symptoms' onset to ICU (d), median (IQR)	13 (10-13)	9 (8-12)	12 (10-14)	0.075
SOFA, median (IQR)	8.0 (7.0-10.0)	10 (8-10)	7 (6-10)	0.029
Mechanical ventilation length to ECMO support (d), median (IQR)	6.0 (8.0-11.0)	8.5 (6-12)	7 (4-10)	0.046
ECMO duration (d), median (IQR)	22 (13-42)	24.5 (9-44)	21 (15-35)	0.765
Renal replacement therapy	29 (48)	22 (65)	7 (26)	0.002
ICU death	33 (54.1)	21 (62)	12 (44)	0.024
Biohumoral data				
Creatinine (mg/dL), median (IQR)	1.00 (0.72-1.86)	0.83 (0.61-1.34)	1.65 (0.78-2.00)	0.025
D-dimer (ng/mL), median (IQR)	3594 (2252-7214)	3748 (1740-12085)	3550 (2368-5007)	0.425
CRP (mg/dL), median (IQR)	142 (88-144)	121 (87-174)	165 (98-212)	0.55
IL-6 (pg/mL), median (IQR)	34 (7.4-70.0)	45 (6.9-105.0)	34 (21-58.0)	0.772
Troponin (pg/mL), median (IQR)	21 (14.0-38.0)	33.0 (14.0-112.0)	21.0 (8.5-48.0)	0.253
NT-pro BNP (pg/mL), median (IQR)	874 (345-1654)	735 (252-1467)	1273 (585-1868)	0.058
LDH IU/L, median (IQR)	465 (375-538)	421 (363-510)	473 (424-542)	0.078
Echocardiographic data				
LVEF (%), mean $\pm$ SD	63.9 $\pm$ 7.6	64.3 $\pm$ 7.9	64.5 $\pm$ 7.5	0.113
RV/LV, mean $\pm$ SD	0.58 $\pm$ 0.17	0.69 $\pm$ 0.08	0.45 $\pm$ 0.14	0.0001
TAPSE (mm), mean $\pm$ SD	18.0 (10.0-21.0)	13.9 (10.0 $\pm$ 14.5)	17.4 (16.0-22.5)	0.015
sPAP (mmHg), mean $\pm$ SD	58.4 $\pm$ 9.4	64 $\pm$ 11	59.1 $\pm$ 7.7	0.015
e/e1	11 $\pm$ 3	12 $\pm$ 3	9 $\pm$ 3	0.0003
TAPSE/sPAP (mm/mmHg), mean $\pm$ SD	0.28 $\pm$ 0.13	0.19 $\pm$ 0.10	0.28 $\pm$ 0.11	0.001
Ventilatory parameters				
PEEP (cm H ₂ O), mean $\pm$ SD	12.2 $\pm$ 2.3	12.4 $\pm$ -2.4	12.1 $\pm$ 2.6	0.64
PO ₂ /FiO ₂ , mean $\pm$ SD	62 (50-88)	66 (54-88)	60 (50-88)	0.442
Norepinephrine, mean $\pm$ SD	0.34 $\pm$ 0.22	0.39 $\pm$ 0.26	0.24 $\pm$ 0.10	0.011

IQR: Interquartile range; RVDD: Right ventricle dilatation and dysfunction; BMI: Body mass index; ICU: Intensive care unit; LOS: Length of stay; CRP: C-reactive protein; IL-6: Interleukin 6, SOFA: Simplified organ functional assessment; ECMO: Extracorporeal membrane oxygenation; NT pro BNP: N terminal pro brain natriuretic peptide; RV: Right ventricle; LV: Left ventricle; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; LDH: Lactate dehydrogenase; LVEF: Left ventricular ejection fraction; PEEP: Positive end-expiratory pressure.

presence of RVDD identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) and by a higher in-ICU mortality. However, at logistic regression analysis, RVDD (even when considered separately) did not result independently associated with in-ICU mortality in these patients.

Growing evidence suggests that, in COVID respiratory failure, varEchoious echocardiographic patterns may be observed across disease severity progression, ranging from isolated systolic pulmonary hypertension to RVDD. Studies are quite often heterogeneous, especially in respect to selected echo parameters and definition of RV dysfunction and dilatation. In a small series of mechanically ventilated

Table 2 Comparison between survivors and no survivors, n %

Variable	All patients	Survivors (No. 28)	No survivors (No. 33)	P value
Clinical data				
Age (yr), mean $\pm$ SD	54.3 $\pm$ 10.3	50.1 $\pm$ 11.6	58.0 $\pm$ 7.3	0.003
Gender, M/F	45/16 (73.8/26.2)	18/10 (40.0/62.5)	6/27 (60.0/37.5)	0.121
BMI (kg/m ²), mean $\pm$ SD	32.9 $\pm$ 5.3	31.8 $\pm$ 4.0	33.8 $\pm$ 6.1	0.138
Charlson index, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.772
Time from symptoms' onset to ICU (d), median (IQR)	13 (10-13)	10 (8-13)	13 (10-15)	0.066
SOFA, median (IQR)	8.0 (7.0-10.0)	7.5 (5.5-9.0)	10.0 (8.0-10.0)	0.01
Mechanical ventilation length to ECMO support (d), median (IQR)	6.0 (8.0-11.0)	6.5 (4.5-9.5)	10.0 (7.0-12.0)	0.006
ECMO duration (d), median (IQR)	22 (13-42)	35 (19-48)	18 (10-30)	0.015
ICU death	33 (54.1)	-	-	-
Biohumoral data				
Creatinine (mg/dL), median (IQR)	1.00 (0.70-1.88)	0.82 (0.60-1.35)	1.60 (0.77-2.00)	0.03
D-dimer (ng/mL), median (IQR)	3694 (2153-7326)	3948 (1740-13095)	3600 (2378-5007)	0.418
CRP (mg/dL), median (IQR)	140 (86-143)	120 (85-172)	164 (97-215)	0.553
IL-6 (pg/mL), median (IQR)	35.5 (7.9-71.0)	46.5 (6.8-107.0)	35.5 (20.5-59.0)	0.851
Troponin (pg/mL), median (IQR)	20.5 (15.0-39.0)	34.0 (15.0-115.0)	22.0 (9.0-50.0)	0.281
NT-pro BNP (pg/mL), median (IQR)	875 (355-1754)	734 (254-1542)	1272 (586-1870)	0.064
LDH IU/L, median (IQR)	466 (378-540)	423 (367-513)	475 (426-543)	0.089
Echocardiographic data				
LVEF (%)	63.9 $\pm$ 7.6	65.6 $\pm$ 8.1	62.5 $\pm$ 6.9	0.113
RV/LV	0.58 $\pm$ 0.17	0.58 $\pm$ 0.19	0.58 $\pm$ 0.16	0.945
TAPSE (mm)	18.0 (10.0-21.0)	19.0 (10.0 $\pm$ 22.5)	18.0 (10.0-21.0)	0.375
RVDD	34 (55.7)	13	21	0.275
sPAP (mmHg)	58.4 $\pm$ 9.4	60.2 $\pm$ 7.6	61.3 $\pm$ 10.7	0.638
E/e1	11 $\pm$ 3	10.7 $\pm$ 2.9	11.6 $\pm$ 3.7	0.34
TAPSE/sPAP (mm/mmHg)	0.28 $\pm$ 0.13	0.29 $\pm$ 0.13	0.27 $\pm$ 0.13	0.692
Ventilatory parameters				
PEEP (cm H ₂ O)	12.2 $\pm$ 2.3	12.3 $\pm$ 2.3	12.2 $\pm$ 2.4	0.91
PO ₂ /FiO ₂	62 (50-88)	66 (54-88)	60 (50-88)	0.442
Norepinephrine (μ g/kg/min), mean $\pm$ SD	0.34 $\pm$ 0.22	0.30 $\pm$ 0.20	0.35 $\pm$ 0.24	0.388

IQR: Interquartile range; RVDD: Right ventricle dilatation and dysfunction; BMI: Body mass index; ICU: Intensive care unit; LOS: Length of stay; CRP: C-reactive protein; IL-6: Interleukin 6; SOFA: Simplified organ functional assessment; ECMO: Extracorporeal membrane oxygenation; NT pro BNP: N terminal pro brain natriuretic peptide; RV: Right ventricle; LV: Left ventricle; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; LDH: Lactate dehydrogenase; LVEF: Left ventricular ejection fraction; PEEP: Positive end-expiratory pressure.

COVID patients, acute pulmonary hypertension (observed in the 39%) was associated with higher 30-d mortality[9]. Likewise, in a retrospective investigation including 214 patients, RV dysfunction, pulmonary hypertension, and moderate to severe tricuspid regurgitation were associated with increased odds for 30-d mortality[10]. In 98 consecutive COVID-related respiratory failure, three different subgroups were identified at serial echocardiograms according to the presence/occurrence and timing of RVDD (defined as the association of RVDD), that is admission RVDD, new onset RVDD, no RV changes. Admission and newly developed RVDD subgroups identified severe COVID respiratory disease which in a high percentage of cases needed ECMO support[11]. In the present investigation, the

Table 3 Multivariate logistic regression analysis (intensive care unit death outcome)

Model	OR	95%CI	P value
Model 1			
Age (yr)	1.09	1.02-1.16	0.015
SOFA	1.26	0.99-1.62	0.062
Admission RV/LV	0.64	0.02-21.42	0.805
Model 2			
SOFA	1.24	0.98-1.56	0.062
RV DYS	0.98	0.31-3.84	0.985
Creatinine (mg/dL)	1.78	0.82-3.11	0.14
Model 3			
Age (yr)	1.1	1.03-1.18	0.005
BMI (kg/m ²)	1.09	0.97-1.22	0.138
TAPSE (mm)	0.97	0.89-1.06	0.544
Model 4			
SOFA	1.29	1.03-1.61	0.026
BMI (kg/m ²)	1.06	0.95-1.19	0.278
TAPSE/SPAP (mm/mmHg)	2.53	0.03-20.92	0.68
Model 5			
BMI (kg/m ²)	1.1	0.98-1.24	0.107
Charlson index	0.59	0.29-1.18	0.133
Time from symptom's onset (d)	1.26	1.02-1.56	0.032
Model 6			
NT pro BNP (pg/mL)	0.99	0.97-1.02	0.517
Mechanical ventilation to ECMO ≥ 10 (d)	4.64	1.42-15.12	0.011
Creatinine (mg/dL)	2.56	1.16-5.67	0.02

BMI: Body mass index; SOFA: Symplified organ functional assessment; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; ECMO: Extracorporeal membrane oxygenation; NT-pro BNP: N terminal pro brain natriuretic peptide; OR: Odd ratio; CI: Confidence index.

study population comprises the most severe state of COVID-related respiratory failure, refractory to standard treatment and requiring ECMO support in whom RVDD (dilatation and dysfunction) is quite common being detectable in more than a half of the entire population. Few data are available on echocardiographic data in patients with COVID-related respiratory failure on ECMO support.

In the series by Bleakley *et al*[11] quite a large proportion of enrolled patients (38/90, 42%) were on ECMO support, but they were not analysed separately. Kopanczyk *et al*[12] performed echocardiography in 11 consecutive patients on ECMO and observed that RV dysfunction (as indicated by abnormal free wall longitudinal strain and fractional area change) was present in the majority (9/11 patients). RV dysfunction was defined as RV dilatation (visual assessment) and abnormal septal motion in the study by Ortiz *et al*[13] who documented that no echo variable was predictor of outcomes (survival to discharge and survival to decannulation) in 64 COVID patients on ECMO (echocardiography performed post cannulation). In a small series of COVID patients on ECMO, we observed, by means of serial echocardiographic exams, that RVDD (defined as the coexistence of dilatation and dysfunction) may be reversible, especially in survivors[13]. We confirm and extend previous findings in a larger series, focusing on the prognostic role (if any) of RVDD for in-ICU death. According to our data, patients with RVDD showed a more severe disease (as indicated by SOFA) and a higher incidence of renal impairment (as inferred by the higher use of renal replacement therapy). Higher values of systolic pulmonary arterial pressure and of NT-pro BNP, observed in RVDD patients, suggest increased RV pressure which might contribute to renal impairment. The lack of differences in creatinine serum values between patients with RVDD and those without can be due to renal replacement therapy itself which does affect creatinine levels. Despite the higher in-ICU mortality observed in patients with RVDD,

RVDD (even when considered separately) are not independent predictor of early death in our population. This might be due to several factors. Firstly, the high incidence of RVDD in these patients, in agreement with previous investigations[3,12,13]. Secondly, at serial echocardiographic assessments, RVDD may be reversible in COVID-related respiratory failure on ECMO support, though a percentage of critically ill COVID patients has been reported to develop RVDD during ICU course[13].

Finally, factors other than RV echo variables can independently predict in-ICU death in COVID-related refractory respiratory failure on ECMO support, such as age and duration of mechanical ventilation. The high frequency of RVDD may be responsible for the lack of association between echocardiographic data and mortality in our patients. Our results are in keeping with those reported by investigations enrolling only critically ill COVID patients who, similarly, were not able to detect a relation between mortality and RV dilatation[13].

In our series, multivariate logistic regression analysis identified the following predictors of in-ICU analysis: Age, severity of disease (as inferred by SOFA and creatinine values) and COVID-disease duration (indicated by time from symptoms' onset) and mechanical ventilation pre-ECMO. A longer time from symptoms' onset to ICU suggests more severe forms of disease, characterized by more pronounced pulmonary derangements, often unresponsive to therapy. Age is a well-known strong predictor in COVID respiratory failure, in line with recent evidence[1] and, though we enrolled patients aged < 65 years according to guidelines, the ROC-determined cut-off was 57 years in our series. Regarding the duration of pre-ECMO mechanical ventilation to date there is no clear indication on the optimal duration of mechanical ventilation before ECMO implantation in COVID disease. Extracorporeal Life Support Organization guidelines report that a period of more than 10 d of mechanical ventilation should be considered a contraindication for ECMO support, while a period of 7 d is reported as a cut-off by other studies[1,2].

Limitations of the study

This is a single centre investigation, including a limited number of patients. On the other hand, ours is a high-volume ECMO centre. Indeed 61 COVID patients on ECMO support were managed at our center in a 15-mo period, treated by the same intensive care team.

CONCLUSION

In patients with COVID-related respiratory failure on ECMO support RVDD (dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

ARTICLE HIGHLIGHTS

Research background

Echocardiography is recognized as a clinical tool in coronavirus disease (COVID)-related respiratory failure needing veno-venous extracorporeal membrane oxygenation (VV ECMO).

Research motivation

The assessment of the prognostic role of right ventricle dilatation and dysfunction (RVDD) in COVID-related respiratory failure refractory to standard treatment requesting ECMO.

Research objectives

In COVID-related respiratory failure on ECMO RVDD is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher sequential organ failure assessment values and need of renal replacement therapy) by a higher in-intensive care unit (ICU) mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Research methods

Observational single center study.

Research results

An echocardiographic examination was performed before ECMO implantation.

Research conclusions

In patients with COVID-related respiratory failure on ECMO support, RVDD is a common finding and identifies a subset of patients characterized by a more severe disease and by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Research perspectives

Risk stratification in COVID-related refractory respiratory failure.

FOOTNOTES

Author contributions: Lazzeri C was the guarantor and designed the study; Batacchi S, Cianchi G, Franci A and Succi F participated in the acquisition, analysis, and interpretation of data; Bonizzoli M, Chiostrì M and Peris A drafted the initial manuscript; and all authors revised the article critically for important intellectual content.

Institutional review board statement: The study protocol was approved by our Ethical Committee ("Comitato Etico Area Vasta Centro" n.17024, approved on March 31th 2020) ("Florence COVID ICU Registry").

Informed consent statement: Patient's consent was waived.

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Observational Study

Perioperative coagulation activation after permanent pacemaker placement

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Abstract

BACKGROUND

Bradyarrhythmias are typically treated with permanent pacemakers (PM). The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequelae. It is still unclear how PM implantation affects the hemostasis system's parameters and how such parameters relate to different consequences after PM placement.

AIM

To assess the blood coagulation factor activity in PM patients throughout the perioperative period.

METHODS

Patients treated in the Department of Surgical Therapy of Cardiac Arrhythmias and Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021 were included in the study. Before surgery, 7 and 30 d after PM placement, peripheral venous blood samples were withdrawn to measure the level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

RESULTS

The study included 146 patients. The activity of factors FV [147.7 (102.1-247.55)% *vs* 103.85 (60-161.6)% *vs* 81.8 (67.15-130.65)%, $P = 0.002$], FVIII [80.4 (60.15-106.25)% *vs* 70.3 (48.5-89.1)% *vs* 63.7 (41.6-88.25)%, $P = 0.039$], FIX [86.2 (70.75-102.95)% *vs* 75.4 (59.2-88.3)% *vs* 73.9 (56.45-93.05)%, $P = 0.014$], FX [188.9 (99.3-308.18)% *vs* 158.9 (83.3-230)% *vs* 127.2 (95.25-209.35)%, $P = 0.022$], FXI [82.6 (63.9-103.6)% *vs* 69.75 (53.8-97.6)% *vs* 67.3 (54.25-98.05)%, $P = 0.002$], FXII [87.6 (67.15-102.3)% *vs* 78.9 (63.4-97.05)% *vs* 81.2 (62.15-97.4)%, $P < 0.001$] decreased at 7 and 30 d after surgery; FII activity [157.9 (109.7-245.25)% *vs* 130 (86.8-192.5)% *vs* 144.8 (103.31-185.6)%, $P = 0.021$] decreased at 7 d and increased at 30 d postoperatively. There were no statistically significant changes in the FVII activity within 30 d after PM placement [182.2 (85.1-344.8)% *vs* 157.2 (99.1-259)% *vs* 108.9 (74.9-219.8)%, $P = 0.128$]. Subgroup analysis revealed similar changes only in patients on anticoagulant therapy. FXII activity decreased in patients on antiplatelet therapy [82 (65.8-101.9)% *vs* 79.9 (63.3-97.1)% *vs* 89.7 (75.7-102.5)%, $P = 0.01$] 7 d after surgery, returning to baseline values at 30 d postoperatively.

CONCLUSION

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement.

Key Words: Hemostasis; Blood coagulation; Cardiac pacemaker; Anticoagulants; Postoperative complications

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Core Tip: Permanent pacemaker placement and anticoagulant therapy are associated with decreased activity of factors V (FV), FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity does not decrease within 30 d after PM placement, which may be suggestive of ongoing endothelial injury.

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INTRODUCTION

Cardiac implantable electronic devices (CIED), which include pacemakers (PM), are widely used to treat patients with arrhythmias and chronic heart failure[1,2]. Bradyarrhythmias are typically treated with permanent PM. The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequelae[1,3,4]. It is still unclear how PM implantation affects the hemostasis system's parameters and how those parameters relate to different problems and other consequences. The aim of our study was to assess the blood coagulation factor activity in PM patients throughout the perioperative period.

MATERIALS AND METHODS

Study population and data collection

The study included patients treated in the Department of Surgical Treatment of Cardiac Arrhythmias and Cardiac Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021. Inclusion criteria for the study were indications for pacemaker implantation and age over 40 years; non-inclusion criteria were presence of a previously implanted pacemaker, contraindications to antithrombotic therapy, pregnancy or breastfeeding, and active cancer or remission for less than 5 years. After the patient consented to participate in the study and signed the informed consent form, the following data were collected: Age, sex, height, weight, underlying disease, comorbidities, history of surgical interventions, the type of antithrombotic therapy used. Peripheral venous blood samples were taken to analyze the activity of the studied blood coagulation factors on the day of surgery.

Operative techniques

PM placement was carried out in accordance with the “European Heart Rhythm Association expert consensus statement and practical guide on optimal implantation technique for conventional PM and implantable cardioverter-defibrillators” [1]. Endocardial leads were implanted *via* cephalic vein; subclavian vein was used as vascular access only when the cephalic vein was not suitable. All patients had the same PM models, single- and dual-chamber, and leads. Atrial leads with active-fixation systems were implanted in the right atrial appendage, whereas all ventricular leads with passive-fixation systems were placed in the right ventricle's apex. The PM was placed either in the pectoralis major muscle or in the subcutaneous tissues above the fascia of the muscle.

Postoperative follow-up period

After the PM placement, the patients were allowed to stay in bed for 12 h. Moreover, an ice load was administered to the surgical site for 2 h in order to prevent PM pocket hematoma. The patients spent an average of 6 d at the hospital. Venous blood sampling was repeated on the 7th and 30th days after PM placement.

Coagulation factors assessment

Venous blood samples were centrifuged; the resulting plasma was used to assess the studied parameters: The level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

Biostatistics

Statistical analysis was performed using IBM SPSS Statistics 26.0 for Windows (SPSS Inc. Chicago, IL, United States). Numbers and percentages were used to express categorical data. The χ^2 test and Fisher exact test were used to analyze categorical data. Shapiro-Wilk test was used to assess normality. Most data were expressed as medians since they were not normally distributed. Wilcoxon test, Mann-Whitney test, Friedman test, Kruskal-Wallis test, and post-hoc tests were used as non-parametric tests for data comparison between two groups. Several cases with normal distribution were analyzed using parametric statistical analysis techniques. *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Patients' characteristics

A total of 213 patients were screened to participate in the study. At the screening stage, 57 (26.7%) patients were withdrawn from the study: 38 (17.8%) refused to participate in the study, 19 (8.9%) had indications for placement of the other types CIED rather than a PM. As a result, 156 patients were included in the study, and 146 patients successfully completed the trial. Among 10 patients who dropped out of the study, 6 died and 4 withdrew their consent (Figure 1).

All patients signed an informed consent. This study was approved by the Local Ethics Committee of the Ryazan State Medical University. The clinical characteristics of the patients are shown in Table 1.

Antithrombotic therapy

All patients in the study received antithrombotic therapy (Table 1). All patients with atrial fibrillation received anticoagulants in accordance with clinical guidelines. Dabigatran etexilate was provided at a dose of 150 (110) mg twice day, apixaban at a dose of 5 (2.5) mg twice daily, and rivaroxaban at a dose of 20 (15) mg once daily. Warfarin was provided once daily; warfarin dosage was adjusted to achieve international normalized ratio of 2 to 3. The rest of the patients received acetylsalicylic acid at a dose of 100 mg once daily due to ischemic heart disease. None of the patients received anticoagulants and antiplatelets simultaneously. Antithrombotic therapy was not canceled or changed during the perioperative period.

Perioperative assessment of coagulation parameters

There was a decrease in the activity of factors FV, FVIII, FIX, FX, FXI, and FXII at 7 and 30 d after the procedure, while the activity of FII decreased after 7 d and increased after 30 d. During the observation period, changes in FI levels and FVII activity were not statistically significant (Table 2).

Subgroup analysis

A subgroup analysis was conducted in order to identify the variables impacting the investigated parameters. The type of antithrombotic medication the patient received had the greatest impact on the variables in this study (Table 3).

Table 1 Baseline characteristics of patients included in the study, *n* (%)

Variable (<i>n</i> = 146)	Data
Age, years	73 (67-81)
Body mass index, kg/m ²	27.5 (25-31)
Gender	
Male	77 (52.7)
Female	69 (47.3)
Pacemaker placement indication	
Atrioventricular block	49 (33.6)
Sick sinus syndrome	47 (32.2)
Atrial fibrillation with impaired atrioventricular conduction	50 (34.2)
Comorbidity	
Ischemic heart disease	146 (100)
Exertional angina	44 (30.1)
Arterial hypertension	143 (97.9)
Atrial fibrillation	96 (65.8)
Congestive heart failure	146 (100)
NYHA Class I	7 (4.8)
NYHA Class II	60 (41.1)
NYHA Class III	79 (54.1)
NYHA Class IV	0 (0)
History of myocardial infarction	28 (19.2)
History of stroke	12 (8.2)
Atherosclerotic peripheral arterial disease	4 (2.7)
Varicose veins	31 (21.2)
History of venous thromboembolism	8 (5.5)
Type 2 diabetes mellitus	39 (21.2)
History of coronavirus disease	4 (2.7)
Antithrombotic therapy	
Antiplatelet therapy (aspirin)	55 (37.7)
Oral anticoagulants	91 (62.3)
Rivaroxaban	57 (39)
Apixaban	20 (13.7)
Dabigatran etexilate	7 (4.8)
Warfarin	7 (4.8)
Surgery features	
Pacemaker	
Single-chamber	50 (34.2)
Dual-chamber	96 (65.8)
Pacemaker placement side	
Left side	142 (97.3)
Right side	4 (2.7)
Vascular access	

Cephalic vein (section)	132 (90.4)
Subclavian vein (puncture)	14 (9.6)
Pacemaker pocket localization	
Above the pectoral fascia	133 (91.1)
Inside the pectoralis major muscle	13 (8.9)
Mean surgery time, min	54 (41-60)

NYHA: New York Heart Association.

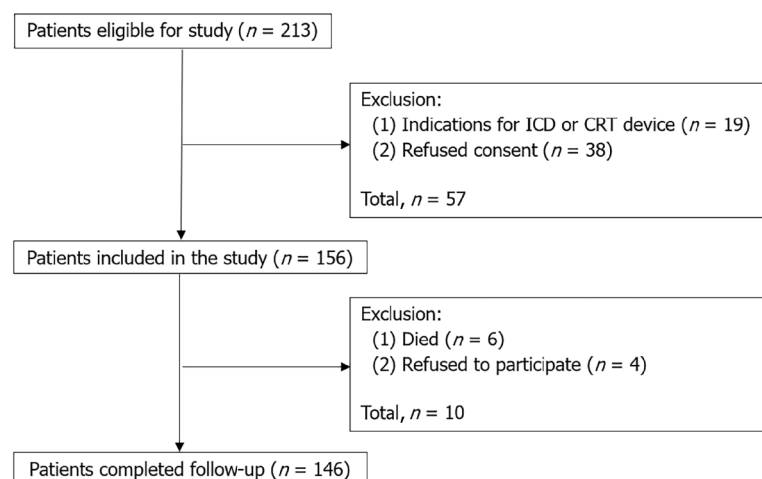
Table 2 Perioperative coagulation parameters (*n* = 146)

Variable	Before implantation	7 d after implantation	30 d after implantation	<i>P</i> value
FI	2.61 (2.05-3.11)	2.76 (2.08-3.42)	2.54 (2.16-2.91)	0.669
FII	157.9 (109.7-245.25) ^a	130 (86.8-192.5)	144.8 (103.31-185.6)	0.021
FV	147.7 (102.1-247.55) ^{a,b}	103.85 (60-161.6)	81.8 (67.15-130.65)	0.002
FVII	182.2 (85.1-344.8)	157.2 (99.1-259)	108.9 (74.9-219.8)	0.128
FVIII	80.4 (60.15-106.25) ^{a,b}	70.3 (48.5-89.1)	63.7 (41.6-88.25)	0.039
FIX	86.2 (70.75-102.95) ^{a,b}	75.4 (59.2-88.3)	73.9 (56.45-93.05)	0.014
FX	188.9 (99.3-308.18) ^{a,b}	158.9 (83.3-230)	127.2 (95.25-209.35)	0.022
FXI	82.6 (63.9-103.6) ^{a,b}	69.75 (53.8-97.6)	67.3 (54.25-98.05)	0.002
FXII	87.6 (67.15-102.3) ^{a,b}	78.9 (63.4-97.05)	81.2 (62.15-97.4)	< 0.001

^a*P* < 0.05 *vs* 7 d after pacemaker implantation.

^b*P* < 0.05 *vs* 30 d after pacemaker implantation.

FI: Factor I; FII: Factor II; FV: Factor V; FVII: Factor VII; FVIII: Factor VIII; FIX: Factor IX; FX: Factor X; FXI: Factor XI; FXII: Factor XII.



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Figure 1 Flowchart diagram providing patients included in the study. ICD: Implanted cardioverter-defibrillator; CRT: Cardiac resynchronization therapy.

Patients with dual-chamber PMs on anticoagulant therapy 7 d after surgery had lower values of FI (*P* = 0.033), and lower activity of FV (*P* = 0.045), FVIII (*P* < 0.001), FIX (*P* < 0.001), FXI (*P* = 0.004); lower activity of FVIII (*P* = 0.049), FIX (*P* < 0.001), FXI (*P* = 0.003) was seen at 30 d after surgery as compared with patients on antiplatelet therapy. There were no differences in the studied parameters between patients receiving anticoagulant therapy with single-chamber and dual-chamber PM as well as different indications for PM placement (*P* > 0.05).

Table 3 Perioperative coagulation parameters in patients on antiplatelet (*n* = 55) and anticoagulant (*n* = 91) therapy

Variable	Antithrombotic therapy	Before implantation	7 d after implantation	30 d after implantation	<i>P</i> value
FI	Antiplatelet	2.66 (2.13-2.99)	2.85 (2.47-3.3)	2.56 (2.19-3.16)	0.513
	Anticoagulant	2.55 (1.9-3.19)	2.58 (1.93-3.44)	2.49 (2.16-2.85)	0.957
	<i>P</i> value	0.675	0.092	0.599	-
FII	Antiplatelet	156.9 (94.5-237.3)	139 (86.8-192.5)	163.5 (112.4-203)	0.289
	Anticoagulant	186.2 (113.8-256.8)	118.5 (86.8-173)	128.4 (99.6-170.5)	0.067
	<i>P</i> value	0.458	0.609	0.263	-
FV	Antiplatelet	164.9 (103.4-267.5)	115.5 (92.8-198.9)	98.6 (82.6-155.3)	0.245
	Anticoagulant	133.3 (96.6-187.9) ^{a,b}	80.1 (45.9-152.8)	73.4 (55.4-84.3)	0.005
	<i>P</i> value	0.196	0.033	0.004	-
FVII	Antiplatelet	203.4 (113-352.1)	200 (116.4-438.3)	223 (107.9-376.6)	0.683
	Anticoagulant	182.1 (87.3-384.6)	122.3 (80.3-209.9)	83.7 (64.6-154.8)	0.153
	<i>P</i> value	0.691	0.024	0.002	-
FVIII	Antiplatelet	82.1 (62.5-114.3)	81.6 (63.8-97.5)	75.5 (59.1-100.5)	0.104
	Anticoagulant	78.5 (58.7-99.7) ^{a,b}	59.6 (41.7-82)	55.1 (40.8-84.4)	0.001
	<i>P</i> value	0.21	0.001	0.033	-
FIX	Antiplatelet	85.4 (74.8-106.9)	84.2 (78-105.8)	96.7 (87.2-104)	0.438
	Anticoagulant	87 (68.4-99.6) ^{a,b}	69.6 (55.6-81.8)	63.2 (45.5-76.8)	0.004
	<i>P</i> value	0.331	<0.001	<0.001	-
FX	Antiplatelet	200 (105.8-308.2)	163.8 (81.7-228.4)	171.6 (120.2-240)	0.708
	Anticoagulant	187.8 (98.6-286.1) ^{a,b}	152.6 (89-248.2)	109.8 (82-163.5)	0.007
	<i>P</i> value	0.837	0.983	0.03	-
FXI	Antiplatelet	87.2 (69.8-100.8)	93.8 (63.1-108.2)	96.7 (84.2-108)	0.957
	Anticoagulant	74.8 (62.5-106.9) ^{a,b}	61 (49.9-82.6)	59.5 (47.5-86.5)	< 0.001
	<i>P</i> value	0.377	0.001	< 0.001	-
FXII	Antiplatelet	82 (65.8-101.9) ^a	79.9 (63.3-97.1)	89.7 (75.7-102.5)	0.01
	Anticoagulant	80.7 (69.4-110.2) ^{a,b}	78.9 (63.4-97)	73.8 (69.8-90.3)	0.001
	<i>P</i> value	0.989	0.629	0.027	-

^a*P* < 0.05 *vs* 7 d after pacemaker implantation.^b*P* < 0.05 *vs* 30 d after pacemaker implantation.

FI: Factor I; FII: Factor II; FV: Factor V; FVII: Factor VII; FVIII: Factor VIII; FIX: Factor IX; FX: Factor X; FXI: Factor XI; FXII: Factor XII.

When evaluating the effect of each individual anticoagulant on the studied parameters, we found that patients who took apixaban had lower FIX (*P* = 0.049) activity at 7 d after surgery, and lower activity of FV (*P* = 0.046), FIX (*P* = 0.015), and FXI (*P* = 0.014) at 30 d after surgery as compared with patients who received acetylsalicylic acid. Patients who took rivaroxaban had lower activity of FIX (*P* = 0.004), FXI (*P* = 0.02) at 7 d after surgery, and lower activity of FIX (*P* = 0.006), FXI (*P* = 0.004) at 30 d after surgery as compared with patients who took acetylsalicylic acid. Patients who took dabigatran etexilate had lower FIX activity at 7 d (*P* = 0.023) and 30 d (*P* = 0.024) after surgery as compared with patients who took acetylsalicylic acid. Patients who took warfarin had lower FIX activity at 7 d (*P* = 0.023) and 30 d (*P* = 0.001) after surgery as compared to patients who received acetylsalicylic acid.

Female patients had higher baseline FVII (*P* = 0.001) and FIX (*P* = 0.003) activity, regardless of antithrombotic therapy type as compared with males.

DISCUSSION

Our aim was to study coagulation in patients with PM in the perioperative period. As a result, we discovered that at 7 and 30 d following surgery, the activity of coagulation factors V, VIII, IX, X, XI, and XII diminished. A more extensive statistical analysis revealed that patients on anticoagulant therapy experienced such changes more frequently. FXII activity in individuals who received acetylsalicylic acid decreased at 7 d after surgery before returning to baseline levels at 30 d after surgery. Patients undergoing antiplatelet and anticoagulant therapy did not show statistically significant changes in FVII activity or FI levels within 30 d of PM implantation.

Coagulation is one of the components of the human hemostasis system. Blood coagulation factors such as transglutaminases, glycoproteins, and serine proteases are part of the coagulation system[5]. The cascade model was once regarded as the primary coagulation model. This paradigm distinguishes between intrinsic and extrinsic coagulation pathways, which include the successive activation of blood coagulation components. Both pathways merge into a common coagulation pathway, which results in the formation of fibrin, which strengthens the thrombus[6,7].

The modern concept of coagulation is a cell-based model that describes the close relationship between the blood coagulation factors, platelets and endothelial cells. The coagulation process is broken down into three parts by the cell model: initiation, amplification, and propagation. When the vascular endothelium is injured during the initiation phase, cells that express tissue factor (such as smooth muscle cells) interact with FVII (initiation phase). This complex triggers the activation of FII, FIX, and FX. In the amplification phase, FII interfaces with the platelet membrane, where FXI, FVIII, and FV activation start. The propagation phase starts when activated FVIII and FIX combine to generate a complex capable of activating a significant amount of FX. Afterwards, FII and FI are activated, much like in the cascade model. Other interactions of blood coagulation factors in the cell-based model of hemostasis are also described, in addition to those described above. Coagulation is controlled by the anticoagulant system of blood. A cell-based model of hemostasis shifts our understanding of the blood clotting process to a different level, not excluding the cascade model[5,6,8].

The majority of PM patients are elderly people who frequently have a variety of comorbidities and illnesses linked to a hypercoagulable state of the hemostasis system. Atrial fibrillation, arterial hypertension, coronary heart disease, chronic heart failure, obesity, and other disorders fall under this category. Prior to PM implantation, bradyarrhythmia significantly influences the development of chronic heart failure and hypercoagulability in such patients[9,10]. Participants in the study who received anticoagulants displayed a decrease in the activity of intrinsic pathway factors such as FV, FVIII, FIX, FX, FXI, or amplification and propagation phases factors (according to the cell-based model). The baseline values of the examined parameters in these patients would likewise be lower than in patients receiving antiplatelet medications, but this was not the case in our study. In this instance, the use of anticoagulants and the elimination of bradyarrhythmia by PM implantation both likely contributed to the decline in the activity of the examined parameters. Elimination of bradyarrhythmia in patients receiving antiplatelets only temporarily reduced FXII activity.

Vascular access to the right ventricle of the heart is necessary for PM implantation operation. The lead is passed through the venous system after the subclavian vein is punctured or the cephalic vein is sectioned during surgery. Conditions are produced at the damaged area to enable the hemostasis system to function. A rise in tissue factor and von Willebrand factor in patients following pacemaker implantation supports this idea[3,9,11]. The second place of activation of the hemostasis system is the area of contact of the lead with endocardium. Gjesdal *et al*[12] showed high platelet activity *in vitro* when stimulated with PM bipolar leads. Palatianos *et al*[13] in an experiment on pigs noted that the largest accumulation of platelets was detected at the distal end of the PM lead. Although it is thought that lead has a low thrombogenicity, blood clots could still form for a variety of reasons, including a disruption of the laminar blood flow through the vein[13,14]. In our work, FVII activity does not decline in patients throughout the course of the 30-d observation period. This might be because tissue factor continues to activate FVII at the locations where the electrode caused endothelium damage. The persistence of FII activity shows that this coagulation route (extrinsic pathway of the cascade model, initiation phase of the cell-based model) is active during the entire observation time.

Our study did not aim to assess each individual anticoagulant medication's effect on the coagulation hemostasis measures. Amplification phase factors FV, FIX, and FXI's activity was shown to be decreased by apixaban and rivaroxaban when compared to acetylsalicylic acid due to FX's inhibition. Patients taking dabigatran etexilate had lower FIX activity because FII was inhibited as compared to patients receiving acetylsalicylic acid[4,5,15].

Many studies on the topic of coagulation in PM patients have been published in the international literature. The majority of these studies focus on how these patients' coagulation patterns relate to deep vein thrombosis (DVT) of the upper extremities and venous thromboembolism in general[3,11,14,16,17]. Zhang *et al*[3] noted an increase in FVIII activity 7 d after surgery. Lelakowski *et al*[11] observed an increase in FVII activity at the same period. The findings of our previous studies have demonstrated the predictive value of D-dimer levels in relation to the occurrence of DVT in the upper extremities following the initial implantation of the PM and the association between a high level of D-dimer and impaired patency of the veins in the upper extremities in patients with already implanted PM[16,18].

One of the limitations of our study was inability to assess the changes of the studied parameters in patients with single-chamber PM who require antiplatelet therapy. Currently, single-chamber PMs in the vast majority of cases are implanted in patients with permanent atrial fibrillation who require anticoagulant therapy. Placement of a single-chamber PM in the atrial position in patients with sick sinus syndrome, who could potentially receive antiplatelet agents and be investigated in this regard, is not common these days[1,19]. The study was also characterized by a limited number of postoperative visits and a certain choice of antiplatelet therapy (acetylsalicylic acid), non-inclusion of certain categories of patients such as younger patients, children, patients with leadless PM, *etc.*

CONCLUSION

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement. We think that further investigation of hemostasis system will contribute to the creation of newer approaches to the detection, prognosis, management, and prevention of numerous hemorrhagic and thromboembolic complications in patients requiring PM implantation.

ARTICLE HIGHLIGHTS

Research background

Bradyarrhythmias are typically treated with permanent pacemakers (PM). The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequelae.

Research motivation

It is still unclear how PM implantation affects the hemostasis system's parameters and how such parameters relate to different complications after PM placement.

Research objectives

To assess the blood coagulation factor activity in PM patients throughout the perioperative period.

Research methods

Patients treated in the Department of Surgical Therapy of Cardiac Arrhythmias and Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021 were included in the study. Before surgery, 7 and 30 d after PM placement, peripheral venous blood samples were withdrawn to measure the level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

Research results

The study included 146 patients. The activity of factors FV [147.7 (102.1-247.55)% *vs* 103.85 (60-161.6)% *vs* 81.8 (67.15-130.65)%, $P = 0.002$], FVIII [80.4 (60.15-106.25)% *vs* 70.3 (48.5-89.1)% *vs* 63.7 (41.6-88.25)%, $P = 0.039$], FIX [86.2 (70.75-102.95)% *vs* 75.4 (59.2-88.3)% *vs* 73.9 (56.45-93.05)%, $P = 0.014$], FX [188.9 (99.3-308.18)% *vs* 158.9 (83.3-230)% *vs* 127.2 (95.25-209.35)%, $P = 0.022$], FXI [82.6 (63.9-103.6)% *vs* 69.75 (53.8-97.6)% *vs* 67.3 (54.25-98.05)%, $P = 0.002$], FXII [87.6 (67.15-102.3)% *vs* 78.9 (63.4-97.05)% *vs* 81.2 (62.15-97.4)%, $P < 0.001$] decreased at 7 and 30 d after surgery; FII activity [157.9 (109.7-245.25)% *vs* 130 (86.8-192.5)% *vs* 144.8 (103.31-185.6)%, $P = 0.021$] decreased at 7 d and increased at 30 d postoperatively. There were no statistically significant changes in the FVII activity within 30 d after PM placement [182.2 (85.1-344.8)% *vs* 157.2 (99.1-259)% *vs* 108.9 (74.9-219.8)%, $P = 0.128$]. Subgroup analysis revealed similar changes only in patients on anticoagulant therapy. FXII activity decreased in patients on antiplatelet therapy [82 (65.8-101.9)% *vs* 79.9 (63.3-97.1)% *vs* 89.7 (75.7-102.5)%, $P = 0.01$] 7 d after surgery, returning to baseline values at 30 d postoperatively.

Research conclusions

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement.

Research perspectives

We think that further investigation of hemostasis system will contribute to the creation of newer approaches to the detection, prognosis, management, and prevention of numerous hemorrhagic and thromboembolic complications in patients requiring PM implantation.

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FOOTNOTES

Author contributions: Kalinin R and Suchkov I were the guarantors and designed the study; Povarov V, Mzhavanadze N and Zhurina O participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript.

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Effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in type 2 diabetes: A systematic review

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Abstract

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD) and cardiorespiratory fitness to a greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

AIM

To evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with T2DM.

METHODS

We performed a search on PubMed, PEDro and CINAHL databases, selecting papers published between December 2012 and December 2022 and identified published randomized controlled trials (RCTs) in the English language that included community or outpatient exercise training programs in patients with T2DM. RCTs were assessed for methodological rigor and risk of bias *via* the Physiotherapy Evidence Database (PEDro). The primary outcome was peak VO₂ and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

RESULTS

Twelve studies were included in our systematic review. The 12 RCTs resulted in 661 participants in total. HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. Peak VO₂ increased in 10 out of 12 studies after HIIT. Ten studies compared HIIT with other exercise regimens (MICT or strength endurance) and 4 of them demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. Moreover, 4 studies explored the effects of HIIT on endothelial function and FMD in T2DM patients. In 2 of them, HIIT further improved endothelial function compared to MICT and/or the control group while in the rest 2 studies no differences between HIIT and MICT were observed.

CONCLUSION

Regular aerobic exercise training has beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Key Words: Type 2 diabetes mellitus; Exercise; High intensity interval training; Cardiorespiratory fitness; Peak VO₂; Endothelial function

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Core Tip: Beneficial effects of high intensity interval training (HIIT) in patients with type 2 diabetes mellitus (T2DM) still remain under investigation and number of studies is limited. We investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in patients with T2DM. We observed that regular aerobic exercise training has beneficial effects on peak VO₂ and flow-mediated dilation in type 2 diabetic patients. Moreover, HIIT may be superior by improving these parameters to a greater extent than moderate-intensity continuous training.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by persistent hyperglycemia due to low production from the pancreas or/and abnormal response of cells to insulin that may lead to disorders of the circulatory, nervous and immune system. T2DM is a usual comorbidity worldwide, corresponding to 462 million people or to 6.28% of the world's population affecting not only the elderly, but also younger adults[1]. Especially in developed countries, prevalence is even higher compared to the global prevalence. Unhealthy lifestyle, junk food consumption, obesity and lack of exercise are major factors, responsible for developing T2DM. In Europe, there are 8529 patients per 100000 cases while in the US the number is 8911 per 100000 cases[1]. Based on mathematical models, scientists predicted the future prevalence of T2DM among youth aged < 20 years in the United States population and the potential trends in incidence. Specifically, number of youths aged < 20 with T2DM will increase from 28000 in 2017 to 48000 in 2060 under the condition that incidence will remain constant

as observed in 2017[2]. Moreover, corresponding relative increases may raise to 673% (95%CI: 362%; 1341%) for T2DM[2].

Endothelium is a significant modulator of the vascular tone and structure, endothelial progenitor cells proliferation and migration, fibrinolysis and coagulation, inflammation, platelet and leukocyte adherence resulting, thus, in vascular homeostasis[3]. T2DM, and specifically insulin resistance and hyperglycemia, may lead to endothelial dysfunction throughout a number of mechanisms, including disturbances of sub cellular signaling pathways common to both insulin action and nitric oxide (NO) production, oxidative stress, endothelin, imbalance of the renin angiotensin system, as well as the secretion of hormones and cytokines by the adipose tissue[4]. Decreased endothelium-dependent vasodilation in diabetic patients is associated with the impaired action of NO secondary to its inactivation resulting from increased oxidative stress[5]. As a result, T2DM patients usually present endothelial dysfunction causing impaired vasodilation, exercise intolerance and significantly reduced aerobic capacity[6-9].

Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases resulting in improvements in body composition, physical capacity, arterial hypertension, insulin resistance, vascular tone, antioxidant status, quality of life, and, most important, endothelial function and exercise tolerance[10-13]. As far as endothelial function is concerned, exercise training has been shown to improve both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with cardiovascular diseases[14]. The improvement of endothelium dysfunction is associated with a significant increase in exercise capacity[14]. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD)[15,16] and cardiorespiratory fitness[17,18] to a greater extent. However, most studies focus on the effectiveness of HIIT in patients with cardiovascular diseases and metabolic syndrome. The beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present the most updated knowledge in literature.

MATERIALS AND METHODS

Search strategy

The search was conducted within 1-month time period, from December 20, 2022 until January 20, 2023 in 3 Large databases; PubMed, PEDro and CINAHL. The aim of the investigators was to identify published studies that included community or outpatient exercise training programs in patients with T2DM. Specific terms were used for the search including ("type 2 diabetes mellitus" OR "diabetes" OR "T2DM" OR "DM") AND ("rehabilitation" OR "exercise" OR "exercise training" OR "aerobic exercise" OR "high intensity interval exercise" OR "HIIT" OR "sprint interval training" OR "high intensity intermittent training"). Studies that occurred from this search were selected according to the PRISMA and the PRISMA checklist. Duplicates were removed from the initial number of studies and the rest were evaluated twice. Firstly, they were screened using only the title and the abstract and then, the full text of the articles was reviewed for eligibility by 2 independent reviewers of different Institutions. Moreover, we performed manual searching of references of all eligible studies, so that to include all potential randomized trials that may not have been identified in the original search. The final evaluation of the process was performed by a university professor.

Study selection criteria

Studies were included in the systematic review only if the necessary eligible criteria were met. Inclusion criteria were: (1) Studies available as full texts in English; (2) published randomized controlled trials (RCTs) in peer-reviewed journals; (3) study groups including patients with diagnosed T2DM under stable medication during the last 3 mo or in the initial stages without medication; (4) aged ≥ 18 years, v. exercise training programs using HIIT with duration of ≥ 2 wk compared to either MICT or controls and; and (5) outcome measures focused on either cardiorespiratory fitness assessed by peak oxygen uptake (peak VO_2) and/or endothelial function through FMD or other indices of microcirculation (leg blood flow during knee-extensions, muscle fractional O_2 extraction through near-infrared spectroscopy, *etc.*). HIIT was defined as exercise sessions performing intervals of exercise at a high intensity (according to the initial VO_2 max or HR max) mixed with brief intervals at a lower intensity or even breaks.

Exclusion criteria were: (1) Non RCTs, reviews, guidelines, commentaries, case reports, editorials or conference abstracts; (2) additional interventions in study groups except for exercise training; (3) studies including patients with other comorbidities except for DM (cardiovascular diseases, obesity, metabolic syndrome); (4) studies including patients with other types of DM such as type 1 DM and prediabetes, v. studies including patients aged < 18 years; (5) exercise training including acute exercise bouts or programs with duration < 2 wk and; and (6) studies including HIIT and other exercise modalities that

were unable to be quantified.

All patients were considered to have controlled type 2 diabetes under medication and normal eating habits that did not cause severe hypoglycemic events.

Quality assessment

All RCTs that were included in the systematic review were assessed for methodological rigor and risk of bias by 2 independent reviewers, using similar methods with a recently published study[19], *via* the Physiotherapy Evidence Database (PEDro). PEDro is an 11-point scale for assessing RCTs for internal validity and control of bias. Maximum score is 10 as the first question does not contribute to total score. A study with a score of 6-10 is considered of excellent quality, a study with 4-5 of fair quality, and a score of 3 or less gives a poor-quality study. If the 2 reviewers did not agree for their quality score, then an independent third reviewer made the final decision.

Outcome measures

The primary outcome measure assessing cardiorespiratory fitness was peak VO_2 index after cardiopulmonary exercise testing. The secondary outcome measure of our systematic review was endothelial function assessed either by FMD or other indices of microcirculation. FMD was calculated as the percent change in diameter following reactive hyperemia compared with the baseline diameters at rest. Both outcomes were evaluated at baseline and post-intervention.

RESULTS

Search results

Search and screening results are demonstrated in the PRISMA flowchart (Figure 1). The initial search strategy identified 5219 articles from PubMed, PEDro and CINAHL databases. The removal of duplicate publications, and title and abstract screening excluded 4966 articles. After a full-text review by the investigators, 241 articles were further excluded. Specifically, 140 articles either did not present HIIT as the main intervention or included acute exercise regimens, 35 articles measured different outcomes than those we defined, 7 articles included patients with other types of DM such as type 1 DM and prediabetes, 12 articles were RCT protocols without results, 39 articles included patients with other comorbidities than T2DM, and 8 articles were not RCTs. After the evaluation, 12 studies were finally included in our systematic review[20-31].

Assessment of the methodological quality of the studies

We assessed methodological quality of the included RCTs using PEDro scale. PEDro scores ranged from 4 to 7. None of the studies scored 3 points or less. Eight out of 12 studies scored 4-5 points, being assessed as fair-quality studies while 4 out of 12 scores 6 points or more being assessed as high-quality studies (Table 1). The weakest field of scoring was blindness of therapists and participants.

Characteristics of participants

The 12 RCTs resulted in 661 participants in total with the majority of them being males (406 *vs* 255 females). HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. The mean age of the participants ranged from 38 to 65 years, while the mean time since the diagnosis of DM ranged from 1.79 to 21.1 years. Mean HbA_{1c} ranged from 6.4 to 7.5% while BMI was from 26.5 to 33.9 kg/m^2 . Studies were mainly conducted in Italy[20], Canada[21], Denmark[22,25,28,29], Thailand[23], Norway[24], the United States[26], the United Kingdom[27], Ireland[30] and China[31]. The main baseline characteristics of patients from the included studies are described in Table 2.

Exercise training protocols

Populations, intervention, comparison, outcomes and study design of the included RCTs are reported in detail in Table 3. Exercise training protocols of the intervention group included HIIT in all studies with small differences in intensity, sets and sessions duration among studies. Eleven out of 12 studies included a second group of T2DM patients with MICT as an exercise regimen[20-26,28-31] while a control group including patients with usual care only was included in 7 studies[22,23,25-27,30,31]. The main HIIT program ranged in duration from 8 wk to 12 mo (12 mo in 1 study, 16 wk in 1 study, 12 wk in 6 studies, 11 wk in 2 studies, 10 wk in 1 study, and 8 wk in 1 study) and sessions were performed from 2 to 5 times weekly. A comprehensive analysis of the characteristics of exercise training programs is demonstrated in Table 3.

Effect of exercise training on cardiorespiratory fitness

The effectiveness of high intensity interval training on cardiorespiratory fitness was assessed by peak VO_2 . Peak VO_2 increased in 10 out of 12 studies[20,22-26,28-31] whereas in 2 studies no difference was observed[21,27]. Moreover, 10 studies[20-26,29-31] compared HIIT with other exercise regimens (MICT

Table 1 Quality assessment of the included studies using the physiotherapy evidence database

	Balducci <i>et al</i> [20], 2012	Terada <i>et al</i> [21], 2013	Karstoft <i>et al</i> [22], 2013	Mitranun <i>et al</i> [23], 2014	Hollekim-Strand <i>et al</i> [24], 2014	Winding <i>et al</i> [25], 2018	Hwang <i>et al</i> [26], 2019	Suryanegara <i>et al</i> [27], 2019	Mortensen <i>et al</i> [28], 2019	Baasch-Skytte <i>et al</i> [29], 2020	Gildea <i>et al</i> [30], 2021	Li <i>et al</i> [31], 2022
Eligibility criteria ^a	√	√	√	√		√	√			√	√	√
Random allocation	√	√	√	√	√	√	√	√	√	√	√	√
Concealed allocation									√		√	
Baseline comparability	√	√	√	√	√	√	√	√	√	√	√	√
Blinded subjects												
Blinded therapists												
Blinded assessors		√	√									√
Adequate follow-up	√	√	√	√			√			√		√
Intention-to-treat analysis		√					√					
Between-group comparisons	√	√	√	√	√	√	√	√	√	√	√	√
Point estimates and variability	√	√	√	√	√	√	√	√	√	√	√	√
Total score	5/10	7/10	6/10	5/10	4/10	4/10	6/10	4/10	5/10	5/10	5/10	6/10

^aEligibility criteria item does not contribute to total score.

and/or strength endurance) while 6 studies compared HIIT with patients of the control group who received usual care[22,23,25,27,30,31]. Four studies[22,23,24,31] demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens, while 6 studies[20,21,25,26,29,30] did not observe statistically significant difference between HIIT and MICT. One single study[27] that compared HIIT to usual care only, failed to show superiority of HIIT in peak VO₂.

Specifically, Balducci *et al*[20] found an increase in peak VO₂ from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg ($P < 0.001$) in the high intensity (HI) group, an increase from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg ($P < 0.001$) in the low intensity (LI) group while no difference was observed between HI and LI groups [mean dif (95%CI): 0.14 (20.65,0.92) $P = 0.866$]. In Karstoft *et al* study[22] patients of the HIIT group increased peak VO₂ from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg ($P < 0.001$), but there was no difference within MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, $P > 0.05$) and CON groups (from 24.8 ± 1.8 to

Table 2 Main baseline characteristics among patients with type 2 diabetes mellitus of each study included in the systematic review

Ref.	Groups	Males/Females (n)	Year after diagnosis	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m ²)	HbA _{1c} (%)
Balducci <i>et al</i> [20], 2012	HI (n = 152); LI (n = 136)	91/61; 83/53	7.8 ± 6.2; 5.9 ± 4.0	59.5 ± 8.3; 58.4 ± 8.9	NA	NA	31.2 ± 4.6; 31.9 ± 4.7	7.24 ± 1.39; 6.99 ± 1.39
Terada <i>et al</i> [21], 2013	HIIT (n = 7); MICT (n = 8)	4/4; 4/3	6 ± 4; 8 ± 4	62 ± 3; 63 ± 5	80.5 ± 9.9; 93.9 ± 18.3	NA	28.4 ± 4.1; 33.1 ± 4.5	6.6 ± 0.6; 6.7 ± 0.6
Karstoft <i>et al</i> [22], 2013	HIIT (n = 12); MICT (n = 12); CON (n = 8)	7/5; 8/4; 5/3	3.5 ± 0.7; 6.2 ± 1.5; 4.5 ± 1.5	57.5 ± 2.4; 60.8 ± 2.2; 57.1 ± 3	84.9 ± 4.9; 88.2 ± 4.7; 88.5 ± 4.7	NA	29.0 ± 1.3; 29.9 ± 1.6; 29.7 ± 1.9	6.9 ± 0.2; 6.6 ± 0.2; 6.4 ± 0.2
Mitranun <i>et al</i> [23], 2014	HIIT (n = 14); MICT (n = 14); CON (n = 15)	5/9; 5/9; 5/10	19.5 ± 0.4; 20.5 ± 0.4; 21.1 ± 0.6	61.2 ± 2.8; 61.7 ± 2.7; 60.9 ± 2.4	66.5 ± 3.7; 65.8 ± 3.1; 67.7 ± 3.2	149 ± 4; 149 ± 5; 152 ± 5	29.6 ± 0.5; 29.4 ± 0.7; 29.7 ± 0.4	60 ± 2 ^a ; 61 ± 2 ^a ; 62 ± 2 ^a
Hollekim-Strand <i>et al</i> [24], 2014	HIIT (n = 20); MICT (n = 17)	12/8; 11/6	4.2 ± 2.3; 3 ± 2.6	58.6 ± 5; 54.7 ± 5.3	NA	NA	30.2 ± 2.8; 29.7 ± 3.7	7.0 ± 1.2; 6.7 ± 0.7
Winding <i>et al</i> [25], 2018	HIIT (n = 13); END (n = 12); CON (n = 7)	7/6; 7/5; 5/2	8 ± 4; 6 ± 4; 7 ± 5	54 ± 6; 58 ± 8; 57 ± 7	84.2 ± 11.1; 82.1 ± 13.7; 87.7 ± 11.3	NA	28.1 ± 3.5; 27.4 ± 3.1; 28.0 ± 3.5	6.8 ± 0.8; 6.9 ± 0.9; 7.0 ± 1.2
Hwang <i>et al</i> [26], 2019	HIIT (n = 23); MICT (n = 19); CON (n = 16)	11/12; 11/8; 8/8	7.8 ± 1.3; 8.3 ± 1.5; 8.2 ± 1.5	65 ± 2; 62 ± 2; 61 ± 2	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	170 ± 3; 170 ± 3; 164 ± 2	31.7 ± 1.3; 31.8 ± 1.4; 33.9 ± 1.4	7.1 ± 0.3; 7.2 ± 0.3; 7.4 ± 0.4
Suryanegara <i>et al</i> [27], 2019	HIIT (n = 13); CON (n = 13)	3/10; 3/10	4.8 ± 1.2; 4.3 ± 1.4	61.1 ± 8.6; 59.8 ± 8.6	90.5 ± 15.0; 91.0 ± 9.8	170.4 ± 7.6; 169.8 ± 8.6	31.3 ± 5.4; 31.9 ± 5.3	53.6 ± 10.5 ^a ; 55.5 ± 6.0 ^a
Mortensen <i>et al</i> [28], 2019	HIIT (n = 11); END (n = 10)	6/5; 7/3	7 ± 4; 5 ± 4	53 ± 7; 57 ± 9	85 ± 12; 86 ± 11	NA	NA	6.8 ± 0.9; 6.9 ± 0.9
Baasch-Skytte <i>et al</i> [29], 2020	10-20-30 (n = 23); MICT (n = 21)	23/0; 21/0	8.0 ± 5.9; 7.0 ± 5.7	61.0 ± 6.2; 61.2 ± 7.1	101.9 ± 22.8; 100.3 ± 13.8	181.5 ± 6.5; 180.4 ± 7.2	30.6 ± 5.4; 30.7 ± 4.4	7.5 ± 1.6; 7.3 ± 1.1
Gildea <i>et al</i> [30], 2021	HIIT (n = 9); MICT (n = 10); CON (n = 9)	6/3; 7/3; 4/5	6.6 ± 3.5; 6.4 ± 3.8; 6.6 ± 3.3	52 ± 10; 53 ± 10; 54 ± 9	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	NA	28.7 ± 3.0; 30.0 ± 5.7; 30.5 ± 3.6	7.3 ± 0.5; 6.9 ± 0.5; 6.8 ± 1.0
Li <i>et al</i> [31], 2022	HIIT (n = 13); MICT (n = 12); CON (n = 12)	13/0; 12/0; 12/0	1.95 ± 0.55; 1.79 ± 0.52; 1.84 ± 0.49	38 ± 6; 39 ± 5; 40 ± 7	75 ± 9.98; 73.1 ± 7.8; 71.76 ± 9.7	166.9 ± 6.25; 165.8 ± 5.56; 166.7 ± 6.86	27.4 ± 5.5; 26.8 ± 4.2; 26.5 ± 5.0	7.2 ± 0.5; 7.02 ± 0.44; 7.06 ± 0.38

^aExpressed in mmol/mol. CON: Control group; NA: Not available; HIIT: High-intensity interval training; HI: Moderate-to-high intensity; MICT: Moderate intensity continuous training; END: Endurance training; LI: Low-to-moderate intensity.

25.2 ± 2.0 mL/min/kg, $P > 0.05$). In addition, increase in peak VO_2 was higher in the HIIT compared to the MICT and the control group ($P < 0.05$). In another study by Mitranun *et al*[23], HIIT group increased peak VO_2 from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg ($P < 0.05$), MICT group from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg ($P < 0.05$) while no difference was observed in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the MICT and the control group ($P < 0.05$). Similar results were demonstrated in 2 other RCTs, the first performed by Hollekim-Strand *et al*[24] in 2014 and the other more recent by Li *et al*[31] in 2022. In the first study[24], HIIT group increased peak VO_2 from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg ($P < 0.001$) and MICT from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg ($P = 0.04$), while HIIT group showed better improvement compared to MICT

Table 3 Population, Intervention, Comparison, Outcomes and Study (PICOS) design of each study included in the systematic review

Ref.	Interventions by group	Frequency	Session duration	Intervention duration	Outcomes	Main results
Balducci <i>et al</i> [20], 2012	Both groups performed mixed aerobic (<i>treadmill, step, elliptical, arm or cycle-ergometer</i>) and resistance exercise [4 resistance exercises, i.e. <i>thrust movement on the transverse plane (chest press or equivalent), traction movement on the frontal plane (lateral pull down or equivalent), squat movement (leg press or equivalent), and trunk flexion for the abdominals, plus three stretching positions</i>]. HI: Aerobic training at 70% of predicted VO ₂ max and resistance training at 60% of predicted 1-RM. LI: Aerobic training at 55% of predicted VO ₂ max and resistance training at 60% of predicted 1-RM	2 times/wk	Varied to obtain the same caloric expenditure per kg body weight in the two groups, independent of intensity	12 mo	Peak VO ₂	↑ peak VO ₂ within HI (from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg, <i>P</i> < 0.001) and LI group (from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg, <i>P</i> < 0.001). No difference in peak VO ₂ between HI and LI groups [mean dif (95%CI): 0.14 (20.65, 0.92) <i>P</i> = 0.866]
Terada <i>et al</i> [21], 2013	HIIT: Treadmill training or cycling intervals 1' (100% VO ₂ max). And 3' (20% VO ₂ max). MICT: continuous treadmill training or cycling (40% VO ₂ max)	5 times/wk	30-60 min	12 wk	Peak VO ₂	No difference in peak VO ₂ within HIIT (from 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, <i>P</i> > 0.05) and MICT (from 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, <i>P</i> > 0.05) groups. No difference in peak VO ₂ between HIIT and MICT groups (<i>P</i> > 0.05)
Karstoft <i>et al</i> [22], 2013	HIIT: Interval walking training with 3-min repetitions at low (< 70% peak energy-expenditure rate) and high (> 70%) intensity. MICT: Continuous - walking training (< 55%). CON: No intervention	5 times/wk	60 min	16 wk	Peak VO ₂	↑ peak VO ₂ in HIIT group (from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg, <i>P</i> < 0.001). No difference in peak VO ₂ in MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, <i>P</i> > 0.05) and CON groups (from 24.8 ± 1.8 to 25.2 ± 2.0 mL/min/kg, <i>P</i> > 0.05). Increase was higher in the HIIT compared to the MICT group (<i>P</i> < 0.05)
Mitranun <i>et al</i> [23], 2014	HIIT: 4-6 intervals (85% VO ₂ max) during 1 min following 4 min of active rest (50% VO ₂ max.). MICT: 50%-65% VO ₂ max. CON: No intervention	3 times/wk	30-40 min	12 wk	Peak VO ₂ , FMD	Peak VO₂: ↑ in HIIT (from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg, <i>P</i> < 0.05) and MICT groups (from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg, <i>P</i> < 0.05), no difference in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, <i>P</i> > 0.05). Increase was greater in the HIIT group compared to the MICT and the control group (<i>P</i> < 0.05). FMD: ↑ in HIIT (from 5.4 ± 1.1 to 7.4 ± 0.9%, <i>P</i> < 0.05) and MICT groups (from 4.8 ± 1.6 to 6.1 ± 1.8%, <i>P</i> < 0.05), no difference in CON group (from 5.1 ± 1.3 to 5.6 ± 1.8%, <i>P</i> > 0.05). Increase was higher in the MICT group compared to the control group (<i>P</i> < 0.05). Increase was higher in the HIIT group compared to the MICT and the control group (<i>P</i> < 0.05)
Hollekim-Strand <i>et al</i> [24], 2014	HIIT: 4 × 4' (90%-95% HR max). MICT: according to guidelines	HIIT: 3 times/wk. MICT: 210 min/wk	HIIT: 40 min. MICT : ≥ 10 min	12 wk	Peak VO ₂ , FMD	Peak VO₂: ↑ in HIIT (from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg, <i>P</i> < 0.001) and MICT groups (from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg, <i>P</i> = 0.04). Increase was greater in the HIIT group compared to the MICT group (difference: 4.1 ± 2.9 vs 1.2 ± 2.2 mL/min/kg, respectively; <i>P</i> = 0.002). FMD: ↑ in HIIT group (from 9.2 ± 9.6 to 18.5 ± 9.6%, <i>P</i> = 0.004), no difference in MICT group (from 13.0 ± 9.8 to 13.0 ± 9.9%, <i>P</i> = 0.99). Increase was higher in the HIIT group compared to the MICT group (difference: 9.2 ± 11.2 vs 0.0 ± 6.2%, respectively; <i>P</i> = 0.03)
Winding <i>et al</i> [25], 2018	HIIT: 10 × 1 min intervals cycling at 95% of peak workload interspersed by 1 min active recovery. END: 40 min cycling at 50% of peak workload. CON: No intervention	3 times/wk	HIIT: 20 min. END: 40 min	11 wk	Peak VO ₂	↑ in HIIT (from 28.4 ± 6.1 to 34.2 ± 6.3 mL/min/kg, <i>P</i> < 0.05) and END groups (from 27.8 ± 5.5 to 30.3 ± 7.5 mL/min/kg, <i>P</i> < 0.05), no difference in CON group (from 27.2 ± 9.1 to 26.3 ± 6.8 mL/min/kg, <i>P</i> > 0.05). Increase was greater in the HIIT group compared to the control group (<i>P</i> < 0.05), but no significant difference between HIIT and END groups (<i>P</i> > 0.05)
Hwang <i>et al</i>	HIIT: 10-min warm-up and a 5-min cooldown at 70% of HR	4 times/wk	HIIT: 40 min. MICT	8 wk	Peak VO ₂	↑ in HIIT group (from 22.3 ± 1.0 to 24.6 ± 1.3 mL/min/kg, <i>P</i> < 0.0001) and

[26], 2019	peak, 4 × 4-min intervals at 90% of HR peak interspersed by 3 × 3-min active recovery at 70% of HR peak. MICT : 10-min warm-up and a 5-min cooldown at 70% of HR peak, 32 min at 70% HR peak. CON : No intervention		: 47 min				MICT group (from 21.6 ± 1.2 to 23.3 ± 1.2 mL/min/kg, $P < 0.005$), no difference in CON group (from 21.4 ± 1.3 to 20.9 ± 1.2 mL/min/kg, $P = 0.4$). No difference between HIIT and MICT groups (increase by 10% in HIIT and 8% in MICT, $P > 0.99$)
Suryanegara <i>et al</i> [27], 2019	HIIT : Cycle ergometry sessions, exercise intensity with scale ranging from 6 to 20 (5 min of warm up of increasing intensity from 9 to 13, then intensity 16-17 with pedal rate > 80 rev/min for five intervals of 2 min for the first week. It inclined 10s for every week until it reached 3 min and 50s of interval after 12 weeks of training. Each interval was followed with 3 min recovery cycle including 90s of passive recovery. CON : No intervention	3 times/wk	40-60 min	12 wk	Peak VO ₂		No difference in peak VO ₂ within HIIT (from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, $P = 0.52$) and within CON group (from 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, $P = 0.37$). No difference in peak VO ₂ between HIIT and the control group ($P = 0.71$)
Mortensen <i>et al</i> [28], 2019	HIIT : 20 min of cycling consisting of 10 times 1 min at 95% Wpeak and 1 min of active recovery 20% Wpeak). END : 40 minutes of cycling at 50% of Wpeak	3 times/wk	HIIT : 20 min. END : 40 min	11 wk	Peak VO ₂ . Leg blood flow		Peak VO₂ : ↑ in HIIT (from 29 ± 6 to 35 ± 7 mL/min/kg, $P < 0.01$) and END groups (from 28 ± 6 to 31 ± 8 mL/min/kg, $P < 0.05$). Leg blood flow : No difference within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, $P > 0.05$) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, $P > 0.01$)
Baasch-Skytte <i>et al</i> [29], 2020	10-20-30 : 10-min low-intensity warmup before completing three 5-min sessions of 10-20-30 training interspersed by 2 min of passive recovery. 5 consecutive 1-min exercise periods divided into 30, 20 and 10 s at low (approximately 30-100 W), moderate (approximately 60-180 W) and maximal (≥ 400 W) intensity. MICT : 50 minutes of moderate-intensity continuous cycling at an intensity of 60%-75% of HR reserve	3 times/wk	10-20-30 : 31 min. MICT : 50 min	10 wk	Peak VO ₂		Peak VO ₂ increased within 10-20-30 and MICT groups after exercise training by 1.8 ± 2.9 and 2.2 ± 3.2 mL/min/kg, respectively ($P < 0.01$). No difference in peak VO ₂ between 10-20-30 and MICT groups ($P = 0.86$)
Gildea <i>et al</i> [30], 2021	5 min warm up and 5 min cool down before and after each session on an aerobic machine (elliptical, treadmill, rowing, or cycle ergometer) in both groups. HIIT : 10 × 60-s bouts of high-intensity cycling interspersed with 60 sec of light cycling at a power output equivalent to 70% of the difference between participant's peak power output (PO peak) and the power output at ventilatory threshold (VT). Target heart rate of 90% HR max. MICT : 50 min of cycling at a power output equivalent to 80%-90% of ventilatory threshold. CON : No intervention	3 times/wk	HIIT : 30 min. MICT : 60 min	12 wk	Peak VO ₂ . Muscle fractional O ₂ extraction [% Δ (HHb+Mb)] versus %PO slope of the first linear segment (slope1)]		Peak VO₂ : ↑ in HIIT (from 26.4 ± 4.0 to 30.0 ± 4.0 mL/min/kg, $P < 0.05$) and MICT groups (from 22.1 ± 4.4 to 27.6 ± 5.1 mL/min/kg, $P < 0.05$). It remained unchanged in the control group (from 21.5 ± 3.6 to 22.0 ± 3.4 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the control group ($P < 0.05$), but no significant difference between HIIT and MICT groups ($P > 0.05$). Muscle fractional O₂ extraction : Improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12, $P < 0.05$) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22, $P < 0.05$). No difference in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25, $P > 0.05$). Improvement was higher in the HIIT and MICT groups compared to the control group ($P < 0.05$), but no significant difference between HIIT and MICT groups ($P > 0.05$)
Li <i>et al</i> [31], 2022	5 min warm-up and 5 min to complete the relaxation and finishing process in both groups. HIIT : 1 min power cycling (80%-95% maximal oxygen uptake (VO ₂ max), 1 min passive or active rest (25%-30% VO ₂ max), and 2 min rounds of eight groups. MICT : Power bike for 30 min of continuous training (50%-70% VO ₂ max). CON : Relevant medicine, exercise, and nutrition knowledge	5 times/wk	HIIT : 25 min. MICT : 40 min	12 wk	Peak VO ₂ (L/min)		HIIT (from 3.4 ± 0.4 to 3.9 ± 0.4 L/min, $P = 0.001$) and MICT groups (from 3.5 ± 0.4 to 3.7 ± 0.5 L/min, $P = 0.001$). It remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, $P > 0.05$). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 <i>vs</i> 0.31 ± 0.13, $P < 0.001$)

CON: Control group; END: Endurance training; HI: Moderate-to-high intensity; HIIT: High-intensity interval training; HR: Heart rate; HHb: Hemoglobin; MICT: Moderate intensity continuous training; Mb: Myoglobin; LI: low-to-moderate intensity; PO: Power output; NA: Not available.

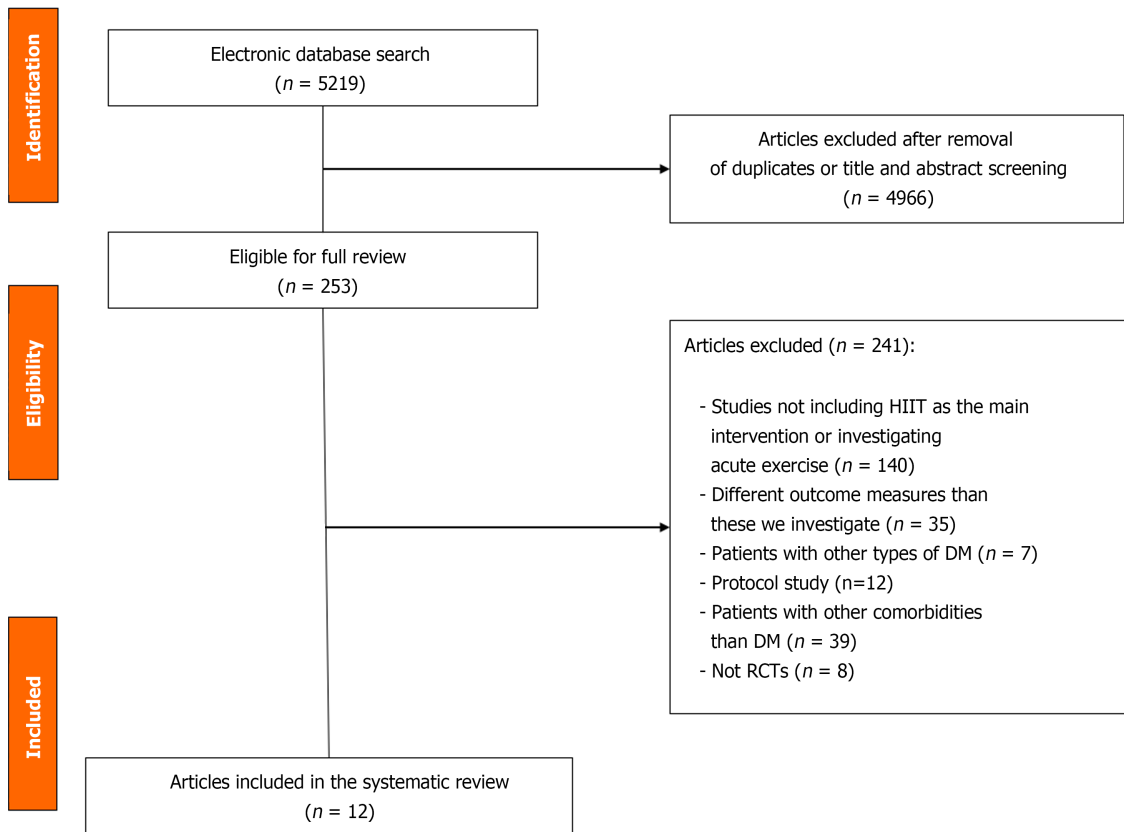


Figure 1 PRISMA flowchart regarding the screening results of the systematic review. DM: Diabetes mellitus; HIIT: High-intensity interval training; RCTs: Randomized controlled trials.

(difference: 4.1 ± 2.9 vs 1.2 ± 2.2 mL/min/kg, respectively; $P = 0.002$). In the second study[31], HIIT group increased peak VO_2 from 3.4 ± 0.4 to 3.9 ± 0.4 L/min ($P = 0.001$) and MICT group from 3.5 ± 0.4 to 3.7 ± 0.5 L/min ($P = 0.001$) while it remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, $P > 0.05$). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 vs 0.31 ± 0.13 , $P < 0.001$).

On the other hand, Terada *et al*[21] did not observe any differences either within (HIIT: From 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, $P > 0.05$; MICT: From 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, $P > 0.05$) or between the 2 groups ($P > 0.05$). More recent studies performed the last 5 years[25,26,29,30], did not manage to show additional benefits of HIIT over MICT, although peak VO_2 improved after exercise training within each group. Finally, a single study[27] which compared HIIT to usual care did not manage to show differences in peak VO_2 within (HIIT: from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, $P = 0.52$; control: From 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, $P = 0.37$) or between the 2 groups ($P = 0.71$).

Effect of exercise training on endothelial function

Four studies[23,24,28,30] explored the effects of HIIT on endothelial function in type 2 diabetes patients. Two of them assessed the influence of HIIT in FMD[23,24], 1 study assessed leg blood flow during knee-extensions[28] and the last one assessed muscle fractional O₂ extraction[30]. In both studies assessing FMD[23,24], FMD further improved in HIIT compared to MICT and/or the control group ($P < 0.05$). In the study of Mitranun *et al*[23], FMD increased from 5.4 ± 1.1 to $7.4 \pm 0.9\%$ ($P < 0.05$) in HIIT and from 4.8 ± 1.6 to $6.1 \pm 1.8\%$ ($P < 0.05$) in MICT group. Control group did not show any difference (from 5.1 ± 1.3 to $5.6 \pm 1.8\%$, $P > 0.05$). Similarly, in the study of Hollekim-Strand *et al*[24] FMD increased from 9.2 ± 9.6 to $18.5 \pm 9.6\%$ ($P = 0.004$) in the HIIT group, but it remained unchanged in the MICT group (from 13.0 ± 9.8 to $13.0 \pm 9.9\%$, $P = 0.99$).

A more recent study by Mortensen *et al*[28] that investigated leg blood flow during knee-extension did not observe any differences within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, $P > 0.05$) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, $P > 0.01$) after exercise training. Finally, Gildea *et al*[30] investigated muscle deoxygenation [deoxygenated hemoglobin and myoglobin, (HHb + Mb)] by near-infrared spectroscopy at the vastus lateralis muscle in adults with T2DM after HIIT, MICT and usual care. They observed that there was improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12 , $P < 0.05$) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22 , $P < 0.05$), but no difference was found in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25 , $P > 0.05$). Beneficial effects of HIIT and MICT were superior compared to usual care ($P < 0.05$), but there was no significant difference between HIIT and MICT

groups ($P > 0.05$).

DISCUSSION

The present systematic review investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in type 2 diabetic patients and compared HIIT with other exercise training regimens including MICT, as well as usual care. Through our systematic review, we demonstrated a significant improvement in peak VO_2 and FMD after HIIT in T2DM. By the findings of the present systematic review we also emerged that HIIT may be superior to MICT in functional capacity indices and endothelial function.

Peak VO_2 is considered the best available index for assessment of exercise capacity[32] and is also a strong predictor of outcomes in many cardiopulmonary diseases[33-35]. Reduced peak VO_2 bears a solid negative prognostic value both in the general population[36] and in high risk patients with cardiovascular diseases[37-39]. Moreover, in T2DM subjects, reduced exercise capacity appears to be a predictor of all-cause mortality[40]. Asymptomatic T2DM patients, with no clinically evident cardiovascular disease or overt diabetic complications, usually present reduced exercise tolerance and reduced maximal aerobic capacity, measured by peak VO_2 , compared to normal subjects as shown through a big number of studies the last years[41-46]. This reduction corresponds to 20%-30% in peak VO_2 in both adults and adolescents[47-49]. Sustained hyperglycemia leading to poor metabolic control and microvascular complications, could clearly indicate a potential pathophysiological mechanism and a relationship between reduced peak VO_2 and diabetes[47,50,51]. Vice versa, low cardiorespiratory fitness seems to be associated with an increased risk for impaired glycemic control[52]. Therefore, improvement on functional capacity may also improve HbA1c in T2DM.

Aerobic exercise intensity seems to be the primary stimulus for improved peak VO_2 in patients with T2DM[53]. In our study, we showed that HIIT is probably superior to other exercise training regimens, and especially MICT, on peak VO_2 and endothelial function in these patients. These findings are in agreement with the findings of previous meta-analyses not only in T2DM, but also in cardiovascular diseases. A recent meta-analysis by Liu *et al*[54] showed that HIIT presents a great improvement in relative peak VO_2 (mean difference: 3.37 mL/kg/min, 95%CI: 1.88 to 4.87, $P < 0.0001$) and absolute peak VO_2 (mean difference: 0.37 L/min, 95%CI: 0.28 to 0.45, $P < 0.00001$) compared to MICT. Another meta-analysis by Xie *et al*[55], included 21 studies involving 736 participants with cardiac diseases and showed that HIIT was associated with greater improvement in peak VO_2 (mean difference 1.76 mL/kg/min, 95%CI: 1.06 to 2.46 mL/kg/min, $P < 0.001$) and VO_2 at anaerobic threshold (mean difference 0.90 mL/kg/min, 95%CI: 0.0 to 1.72 mL/kg/min, $P = 0.03$). Finally, another recent meta-analysis by Gomes-Neto *et al*[56] investigated the effects of HIIT *vs* MICT in coronary artery disease patients. Authors included 12 studies with 609 patients and showed that HIIT resulted in improvement in peak VO_2 weighted mean difference (1.3 mL/kg/min, 95%CI: 0.6-1.9, $n = 594$) compared with MICT.

As far as endothelial function is concerned, our study showed that HIIT results in greater improvement in FMD and other indices of microcirculation compared to MICT and usual care in T2DM. A recent meta-analyses by Qiu *et al*[57] investigated different types of exercise on endothelial function in T2DM. Authors included 16 datasets and, although they found that exercise training resulted in an overall improvement in FMD by 1.77% (95%CI: 0.94%-2.59%), however, HIIT did not significantly improve FMD over MICT. The relationship between FMD and endothelial function is quite significant, as it has been shown that every 1% increase in FMD is correlated with an estimated 13% risk reduction of cardiovascular events[58]. Moreover, this increase in FMD from a non-pharmacological therapy is even larger than those from pharmacological interventions like statins[59] or phosphodiesterase inhibitors[60], which result in an improvement in FMD by 0.94% (95%CI: 0.38%-1.5%) and 2.19% (95%CI: 0.48%-3.90%), respectively.

Potential pathophysiological mechanisms regarding the beneficial effects of exercise training on endothelial function have been proposed over the years. Three of them seem to be the most prevailing. The first one supports that the increase in blood flow caused by exercise training augments shear stresses on the endothelium, leading to increased nitric oxide synthesis and bioavailability[61]. The second one describes reduction in oxidative stress and the expression of pro-inflammatory molecules after exercise training, which are considered as initiating factors for endothelial dysfunction[62]. Finally, the last one suggests the promotion of endothelial repair and the facilitation of vascular angiogenesis, as a result of the restoration of the function of endothelial progenitor cells after exercise training[63,64].

Arterial stiffness in another characteristic dysfunction in T2DM patients, being recognized as an important predictor for hypertension. Pulse wave velocity (PWV) and augmentation index (Aix) are both criteria for clinical assessment of arterial stiffness[65]. Previous studies have shown that aerobic exercise significantly reduces both PWV[66,67] and Aix[66], increases systemic arterial compliance and, indeed, there is an inverse relationship between exercise intensity and reductions in arterial stiffness, which may suggest that HIIT could be a more effective modality than MICT[66,67]. HIIT is thought to induce a greater amount of shear stress on arterial/vascular walls, particularly in exercising muscles, through utilizing small periods of higher intensity activity, which may explain the larger benefits seen

in vascular function outcomes[68,69]. The well-established beneficial effects of HIIT on endothelial indices in T2DM patients result in improvement in arterial stiffness, as arterial stiffness is mainly influenced by vascular endothelial function[70]. HIIT has been reported to increase endothelial eNOS protein content and NO availability and cause significant improvements in brachial artery endothelial-dependent dilatation and aortic stiffness in patients with elevated CVD risk[15]. Finally, arterial stiffness-associated indices such as arterial velocity pulse index and arterial pressure volume index seem to significantly improve after HIIT, lowering close to the normal ranges[71].

Clinical perspectives

Patients with T2DM may present endothelial dysfunction, impaired functional capacity, exercise intolerance and poor prognosis after a few years since the diagnosis due to complications. The present systematic review aims to evaluate the additional beneficial effects of HIIT programs on prognostic cardiorespiratory fitness indices such as peak VO_2 , as well as endothelial function in type 2 diabetic patients in comparison to other aerobic exercise regimens. Moreover, it tries to present all the potential pathophysiological mechanisms of diabetes on endothelial dysfunction and, thus, exercise intolerance. Exercise has been proven to be safe and efficient. Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs. The importance of HIIT does not limit only to cardiorespiratory or endothelial indices, but there are also practical benefits in T2DM patients' performance by improving their duration and strength in daily activities and reducing their fatigue and dyspnea, indicating thus, improvement in their quality of life. Other additional benefits of aerobic exercise are better glycemic control, improvement in arterial stiffness, as well as improvement in their lipidemic and inflammatory profile.

Limitations

Randomized controlled studies regarding the effectiveness of HIIT in patients with T2DM are limited in literature and, therefore, this field still remains under investigation. A potential limitation of the systematic review is that the included studies may present heterogeneity of the study samples, due to different mean age, different duration since diagnosis, and different functional capacity at baseline. As a result, the effects of HIIT on cardiorespiratory fitness indices in patients of different age (for instance between 18y and 70y) may be different due to different arterial stiffness levels.

Our hypothesis of heterogeneity is based on observed differences among means of age, duration since diagnosis, *etc.* among samples of the included RCTs and cannot be confirmed by statistical methods. The reason that we did not perform a meta-analysis was that we did not have access to data of all the included RCTs. Another limitation is that there were studies without adjustment for multiple comparisons and potential confounders in their results. However, the results were consistent and clear in all studies supporting final conclusions. Finally, patients who undertook an exercise intervention may have been more motivated with better functional status than those who did not participate in training programs and, thus, we could not exclude a potential inclusion bias.

CONCLUSION

Regular aerobic exercise training has been shown to have beneficial effects on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes mellitus. HIIT seems to be superior by improving these parameters to a greater extent than MICT. This type of exercise training regimen should be established as significant part of the non-pharmacological therapeutic strategy of this metabolic syndrome. Larger multicenter RCTs are required in order to better understand the potential mechanisms of exercise in T2DM and its therapeutic targets, and define its main characteristics including type, duration, frequency and intensity.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. The improvement of endothelial dysfunction is associated with a significant increase in exercise capacity.

Research motivation

High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving endothelial indices and cardiorespiratory fitness to a

greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

Research objectives

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present updated knowledge in literature.

Research methods

A search on three large databases was performed, selecting randomized controlled trials (RCTs) published between 2012 and 2022 regarding exercise training programs in patients with T2DM. The primary outcome was peak VO₂ and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

Research results

Twelve RCTs resulted in 661 participants in total. Peak VO₂ increased in 10 out of 12 studies after HIIT. Four out of 10 studies demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. In 2 out of 4 studies, HIIT further improved endothelial function compared to MICT and/or the control group.

Research conclusions

Regular aerobic exercise has been proven to be safe and efficient and presents beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Research perspectives

Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs.

FOOTNOTES

Author contributions: Dimopoulos S designed the research; Kourek C performed the research; Kourek C, and Dimopoulos S analysed the data; Kourek C wrote the paper; All authors revised the paper.

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New scoring system for acute chest pain risk stratification: Is it worth SVEAT-ing it?

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Abstract

The emergency room is a very potent environment in the hospital. With the growing demands of the population, improved accessibility to health resources, and the onslaught of the triple pandemic, it is extremely crucial to triage patients at presentation. In the spectrum of complaints, chest pain is the commonest. Despite it being a daily ailment, chest pain brings concern to every physician at first. Chest pain could span from acute coronary syndrome, pulmonary embolism, and aortic dissection (all potentially fatal) to reflux, zoster, or musculoskeletal causes that do not need rapid interventions. We often employ scoring systems such as GRACE/PURSUIT/TIMI to assist in clinical decision-making. Over the years, the HEART score became a popular and effective tool for predicting the risk of 30-d major adverse cardiovascular events. Recently, a new scoring system called SVEAT was developed and compared to the HEART score. We have attempted to summarize how these scoring systems differ and their generalizability. With an increasing number of scoring systems being introduced, one must also prevent anchorage bias; *i.e.*, tools such as these are only diagnosis-specific and not organ-specific, and other emergent differential diagnoses must also be kept in mind before discharging the patient home without additional workup.

Key Words: Chest pain; Acute coronary syndrome; SVEAT score; HEART score; TIMI score; Risk stratification scores

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Core Tip: Despite several studies, scoring systems, and artificial intelligence -guided tools available to triage symptoms of chest pain, physicians are often struck with the dilemma before discharging patients from the endoplasmic reticulum. The reason is that chest pain etiologies such as acute coronary syndromes (ACS) can present atypically and, when misdiagnosed, can lead to catastrophic consequences. Tools such as the HEART score and recently published SVEAT score are robustly validated methods of triaging this conundrum. However, while we delineate how they differ, one must be mindful that most patients with ACS could present with chest pain, but not every chest pain is due to ACS.

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TO THE EDITOR

We read with great interest the retrospective cohort study by Antwi-Amoabeng *et al*[1] entitled “SVEAT score outperforms HEART score in patients admitted to a chest pain observation unit.” It is a well-written study that validated that the performance of the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score is superior as compared to History, Electrocardiography, Age, Risk factors, and Troponin (HEART) score in stratifying acute chest pain in low to intermediate risk patients for 30-d major adverse cardiovascular events (MACE). The study assessed the potential usefulness of the SVEAT score developed by Roongsritong *et al*[2] in a prospective observational study by comparing it with HEART and TIMI (Thrombolysis In Myocardial Infarction) risk scores.

Acute chest pain is the second most common reason for adults presenting to the emergency department after trauma, of which only 5.1% of cases are caused by acute coronary syndrome (ACS)[3, 4]. Patients with ACS symptoms with less than a 1% probability of 30-d MACE or death are classified as low-risk chest pain[5]. High-sensitivity troponins are used to diagnose myocardial infarction and detect myocardial injury[6].

Before 2008, widely used risk scores for ACS like GRACE, PURSUIT, and TIMI mainly focused on high-risk patients[7-10]. In 2008, Six *et al*[11] developed the HEART score in a single-centric study to better guide ER physicians to triage acute chest pain in low-risk patients aiding in safe early discharge, which was further validated by Backus *et al*[12] in a multicentric study stating that low HEART scores had a low likelihood of an ACS and high HEART score predicted higher MACE in 6 wk. Of the currently available risk stratification scores commonly used, the HEART score clinical decision pathway is the most widely employed[13]. Head-to-head comparison studies between GRACE, TIMI, and HEART scores showed that HEART scores had better predictability of MACE in low-risk patients[14]. It is also proven to reduce objective cardiac testing in 30 d, reduce the length of hospital stay and increase early discharges compared to usual care as per ACC/AHA[15].

However, the HEART score includes traditional cardiac risks factors, such as hypertension, diabetes, smoking, and obesity, which have limited value in diagnosing ACS, especially in patients older than 40 [16]; hence, these have been eliminated from the SVEAT score. Instead, the history of vascular events was included in the SVEAT score, as shown in Table 1[2]. Using more objective data in the SVEAT score reduces uncertainty and inter-rater variability inherent to other scores caused by arbitrary, subjective criteria. In addition, as stated by the authors, the SVEAT score incorporates more points for factors with higher risk association and negative points for factors with a lower risk associated with acute coronary events, ranging from +5 to -2. This, in turn, provides a broader range of cumulative scores, helping achieve superior stratifications between subgroups.

The HEART score has a threshold of 3 for stratifying as low risk, while the SVEAT score of 4 was chosen as a cut-off for low risk to achieve a 30-d MACE of 0.8%, calculated retrospectively in the index article. The HEART score identified less than 60% of the low-risk patients, whereas an additional 28% of low-risk patients were identified using the SVEAT score as compared to the HEART score[2,11,12]. Moreover, the HEART score allocates the highest score of ‘2’ for troponins, while the cut-off for low-risk stratification is 3. Hence, with the HEART score, there is a disclaimer that if there is positive high sensitivity troponin despite the score being less than or equal to 3, *i.e.*, low-risk score, experts recommend further workup and admission[13]. However, a score of ‘5’ with the SVEAT score system is allocated if the troponin level is over 0.7 ng/mL. This, by default, ensures that the patient is not in the low-risk group if troponin is significantly elevated. Also, vascular disease has one of the most quantifiable associations with cardiac mortality, which was given a higher individual score in the SVEAT score system[17].

Table 1 Summarizing differences between the HEART and SVEAT scores

Scoring variables	HEART score	SVEAT score
Symptom-Chest pain	Stratifies symptoms subjectively, <i>i.e.</i> , based on level suspicion. (This is open to bias based on the provider)	Stratifies symptoms more objectively by using well-defined terminologies for chest pain, hence being less open to bias
Risk factor	Includes hyperlipidemia, hypertension, diabetes mellitus, smoking, and a family history of obesity, and scoring is based on their frequency. Does not take recent coronary disease into account	Includes recent myocardial infarction, PCI/CABG, or any prior vascular event
EKG	Positively scores any EKG changes. If none are present, score 0. No negative scores	Gives a score of 3 for dynamic ST or T wave changes, higher than HEART (2). It also assigns a negative score when there are no EKG changes in the presence of ongoing chest pain
Age	Assigns a score of 2 for all patients over 65 yr	Assigns a score of 2 for all patients over 75 yr. It also assigns a negative score when the patient is < 30 yr
Troponin	Is applicable for both Troponin I and T assays. No negative scores for a normal Troponin	Validated for the 4 th generation ultra-sensitive Troponin I assay only. Assigns negative scores for normal Troponin levels after > 4 h of chest pain

CABG: Coronary artery bypass grafting; EKG: Electrocardiographic; PCI: Percutaneous interventions; ST: Subthemes; SVEAT: Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin.

Both scores examine the risk stratifying of patients presenting with chest pain due to coronary artery disease. They do not consider other life-threatening illnesses in patients with chest pain, such as aortic dissection, pulmonary embolism, or esophageal rupture. This is important to note since chest pain can cause anchorage bias, and a low score can create a false sense of security, leading to premature discharge. While promising, the SVEAT score has several limitations, as mentioned by the authors, including the need for further validation in multicentric studies with diverse populations. Additionally, we need comprehensive follow-up data regarding prognostication for a longer duration. As the authors state, the individual scores are assigned rather arbitrarily than using a more formally weighted logistic regression model. Further studies could also be performed to validate if a combination of scores can increase reliability and precision in identifying low-risk patients with acute chest pain.

Acute chest pain etiology also differs in a gender-specific manner, with conditions such as coronary artery spasm, subacute coronary artery dissection, and takotsubo being significantly more prevalent in women, unlike obstructive CAD, which is more prevalent in men[18-21]. However, given the absence of conventional risk factors and ECG changes in the conditions mentioned above, screening and specific stratification remain challenging with any available scoring system, including the SVEAT system.

In conclusion, we would like to reiterate that using a well-validated scoring system is crucial to educate patients about chest pain, its implications, and key management measures. Before discharging someone with a low HEART or SVEAT score, patients must be asked if they live alone, have access to phones, are ambulatory, and how far they are from a tertiary medical facility. If these resources are unavailable, the patient should be considered a non-low risk and admitted to the hospital for further workup.

FOOTNOTES

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Extracorporeal veno-venous ultrafiltration in congestive heart failure: What's the state of the art? A mini-review

Andrea Urbani, Filippo Pensotti, Andrea Provera, Andrea Galassi, Marco Guazzi, Diego Castini

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Abstract

Hospitalizations for heart failure exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. Rates of rehospitalizations or emergency department visit at 60 days are remarkable regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion. Ultrafiltration (UF) has been considered a promising alternative to stepped diuretic therapy and it consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump. Fluid removal with ultrafiltration presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation. However, the conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood. The best way to assess fluid status and therefore establish the fluid removal target is also still a matter of debate. Herein, we provide an up-to-date systematic review about the role of ultrafiltration among patients with fluid overload and its gaps in daily practice.

Key Words: Fluid overload; Ultrafiltration; Diuretics; Heart failure

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Core Tip: This mini review aimed to evaluate the role of ultrafiltration in congestive heart failure and to compare this approach to standard therapy essentially based on diuretics. Evidences are still controversial and matter of debate, however it is clear that the use of ultrafiltration has beneficial effects on outcomes such as rehospitalization for heart failure and symptoms attenuation. This review of the literature also highlighted the pivotal role of a non-invasive multiparametric assessment of fluid overload to guide physicians through tailoring patient's decongestion.

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INTRODUCTION

Hospitalizations for heart failure (HF) exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. In addition, up to 1 in 4 patients (24%) is readmitted within 30 d and 50% of patients are readmitted within 6 mo[1,2]. Recurrent fluid overload in HF has uniformly been associated with worse outcomes independently of age and renal function[3]. Data from the Diuretic Optimization Strategies Evaluation trial show that 42% of patients with acutely decompensated HF reached the composite end point of death, rehospitalizations or emergency department visit at 60 d regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion[4]. Therefore, the need for adjunctive treatment strategies to standard stepped diuretic therapy in patients presenting with fluid overload in the context of decompensated HF is critical. One promising therapy is extracorporeal veno-venous ultrafiltration (UF). Ultrafiltration consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump [5].

The fluid removed from the intravascular compartment is constantly replaced by fluid from the third space configurating the so called "intra-vascular refill" phenomenon, thus allowing gradual and controlled fluid overload resolution[6]. Despite fluid removal with UF presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation, results from clinical studies regarding efficacy and safety have been variable.

Herein, we provide an up-to-date systematic review about the role of UF among patients with fluid overload and its gaps in daily practice.

PATHOPHYSIOLOGY AND CONSEQUENCES OF FLUID OVERLOAD

The initial trigger of fluid overload is a reduced cardiac output that results from failing myocardium. This process causes an arterial hypovolemia which triggers a cascade of events designed to increase intra-arterial blood volume. The main mechanism involved is a neurohumoral activation of the renin-angiotensin-aldosterone (RAAS) axis that increases renal and sodium avidity, thereby resulting in an increase of effective blood volume. In a setting of HF, proximal sodium and water retention are so elevated that distal nephron chronically undergoes low sodium delivery, maintaining persistent RAAS activation[7]. Also, increased sympathetic tone leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume. This expands the effective circulating volume by redistribution in a setting where volume expansion is already ongoing[8]. At the beginning, these changes occur as compensatory mechanisms to maintain effective circulating blood volume, over time they become harmful with the development of pathological inappropriate blood volume and interstitial fluid expansion contributing to fluid overload and organ congestion. An excessive effective circulating blood volume leads to hemodynamic congestion with increased central filling pressures[9]. Deranged hemodynamics and neurohormonal activation leading to excessive tubular reabsorption produce long-standing venous congestion. Elevation of central venous pressure is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure that decrease net glomerular filtration[10]. Hence, in this context, venous congestion of the kidneys rather than arterial underfilling is associated with decreased renal blood flow and an increase in creatinine[6,11]. Moreover, congestion within peripheral vascular tissues can produce endothelial activation followed by up-regulation of inflammatory cytokines, which promotes additional fluid retention[12,13]. Therefore, reducing congestion should be the foremost goal in patients with HF and fluid congestion[6].

DETECTING FLUID OVERLOAD IN HF

Historically, the gold standard to evaluate fluid overload has been pulmonary artery catheterization (PAC) that allows a direct measurement of right atrial pressure and pulmonary capillary wedge pressure (PCWP)[14]. For several years it has been widely used but then, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial showed that the use of PAC to guide diuretic therapy in comparison with serial clinical assessment did not improve mortality[15]. Currently, due to its invasive nature and the lack of evidence, the use of Swan Ganz catheterization is restricted to a selected group of critically ill patients in tertiary hospitals with high level of user competence.

For what concern the non-invasive assessments of congestion, a multiparametric point of care ultrasound (POCUS) can play a key role. In the [Figure 1](#), we make a comprehensive list of all the most used POCUS parameters.

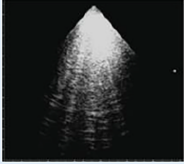
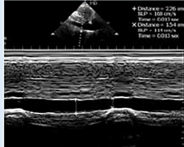
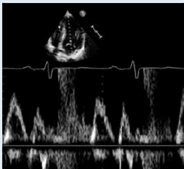
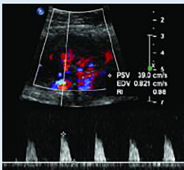
Lung ultrasound (LUS) can be used to assess interstitial oedema and pleural effusion in patients with known or suspected HF and detects the so-called B-lines that originates from the extravascular fluid[16, 17]. B-lines are hyperechoic artefacts which appear as vertical lines originating from the pleural surface [18]. More than three B-lines in more than two intercostal spaces bilaterally are considered diagnostic of interstitial and alveolar oedema in acute HF[8,19]. In comparison to chest X-ray, lung ultrasound is more accurate for the diagnosis of interstitial oedema and HF, although B-lines can occur in other condition such as interstitial lung disease and non-cardiogenic pulmonary oedema[16,20,21]. Echocardiography can, also, be used to non-invasively and quickly estimate right and left-sided filling pressure. An appraisal of the right atrial pressure can be performed by evaluating the collapsibility and width of the inferior vena cava (IVC)[22]. Any variation in right atrial pressure is transferred backward, and modifies IVC size, in fact a significant increase in right atrial pressure, as seen in HF, would eventually result in IVC distention. Pulsed doppler and tissue Doppler are useful tools in estimating left-sided filling pressure. The E/e' ratio > 14 has high specificity for increased filling pressures, especially if E-wave deceleration time is short and A-wave velocities are low[23,24]. Furthermore, congestion and high central venous pressure lead to increased renal interstitial pressures that affects primarily renal venous flow which can be evaluated with Doppler ultrasound. Specifically, the presence of an intermittent renal venous flow rather than continuous as in healthy subjects has been strongly related with an increased central venous pressure measured invasively and has been associated with a worse prognosis in both acutely decompensated HF and among stable patients with chronic HF[25,26]. Despite diagnosis of congestion is currently made with the combination of signs and symptoms, a suggestive X-ray and the measurement of elevated natriuretic peptides (NPs), these additional non-invasive POCUS-guided approach can increase the accuracy of the diagnosis and, more importantly, can be helpful in tailoring patient's decongestion during the hospitalization ([Table 1](#)).

USE OF DIURETICS IN ACUTE HF AND DIURETIC RESISTANCE

Diuretic agents, especially loop diuretics, have been for decades the backbone of the therapy for fluid overload[30,31]. Guidelines recommend the use of intravenous loop diuretic rather than oral as first line therapy and an early as possible administration because of its association with reduced in-hospital mortality[32]. The initial diuretic regimen depends on whether the patient is diuretic naïve or not. In fact, diuretic naïve patients should receive an initial dose of at least 20-40 mg of intravenous furosemide, whereas patients already on an ambulatory diuretic regimen should receive 1-2 times the 24-h home dose intravenously. A spot urine sodium content of > 50-70 mEq/L and an hourly urine output of > 100-150 mL during the first 6 h usually identifies patients with an initial acceptable diuretic response[33,34]. If these targets are not reached, a prompt doubling of loop diuretic dose is usually required and should be repeated until maximal dose of loop diuretics is administered; as maximal dose of loop diuretic is given, an addition of another diuretic agent should be considered as increasing the loop diuretic dose does not improve natriuresis any further. Despite diuretics are highly effective in the early stages of acute HF, in a significant subset of patients loop diuretics become increasingly ineffective with disease progression due to the onset of diuretic resistance[35]. A recent definition of diuretic resistance has been proposed which implies a failure to increase fluid and sodium (Na⁺) output sufficiently to relieve volume overload, edema, or congestion, despite escalating doses of a loop diuretic to a ceiling level (80 mg of furosemide once or twice daily or greater in those with reduced glomerular filtration rate or HF) [36]. Diuretic resistance is the result of several factors such as impaired absorption, decreased renal blood flow, hypoalbuminemia and proteinuria, all leading to a reduced levels of active diuretics in the tubular lumen[35,37]. Unfortunately, clinical signs and symptoms are often unreliable to detect diuretic resistance. A poor diuretic response predicts mortality rate after discharge, subsequent rehospitalization, or renal complications from congestive HF[36]. Therefore, finding more effective treatments for fluid removal is an unmet need.

Table 1 Differences between ultrafiltration and diuretics

Loop diuretics	Isolated ultrafiltration
Hypotonic urine	Isotonic plasma water
Direct neurohormonal activation	No direct neurohormonal activation
Unpredictable elimination of sodium and water	Precise control of rate and amount of fluid removal
Diuretic resistance	Restoration of diuretic responsiveness
Hypokalemia and hypomagnesemia	No effect on plasma concentration of potassium and magnesium
No need for anticoagulation	Need for anticoagulation
No extracorporeal circuit	Need for extracorporeal circuit

Parameters assessed by POCUS indicative of fluid overload	Echographic windows and transducer positions	Pathological reference values	Clinical and prognostic significance	Ref.
B-Lines 	8 chest zones measured with phased-array or curvilinear transducer placed in the intercostal spaces	A cut off-value of ≥ 3 B-lines in at least two intercostal spaces per hemithorax	Indicates interstitial oedema and identifies acute HF in patients with dyspnea with high sensitivity (94%-97%) and specificity (96%-97%)	[27]
IVC size 	Subcostal view with curvilinear or phased-array transducer at 1.0 to 2.0 cm from the junction with the right atrium	An IVC smaller than 21 mm that collapses more than 50% is considered normal	It might detect increasing intravascular volume even prior to any change in symptoms or body weight	[28]
Doppler left sided filling pressure (E/e' ratio) 	Apical 4-chamber view with Doppler imaging and tissue doppler	E/e' ratio > 14	It indicates rising filling pressure especially if E deceleration time is short and A-wave velocities are low	[23]
Doppler Intermittent renal venous flow 	Left lateral decubitus position using a convex or sector transducer aligned with the lowest intercostal space offering a longitudinal view of the right kidney	When central venous pressure increases, renal venous flow becomes firstly pulsatile and then biphasic	It is an earlier marker of development of congestion and suggests a poor prognosis	[29]

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Figure 1 Direct and indirect non-invasive estimation of fluid overload with point of care ultrasound. IVC: Inferior vena cava; POCUS: Point-of-care ultrasound; HF: Heart failure.

HOW DOES VENO-VENOUS UF WORK?

As briefly described in the introduction, the mechanism of action of UF is based on the use of a transmembrane pressure gradient generated by a pump, which through a semi-permeable membrane causes the removal of plasma water from whole blood. The net effect at the end of the process is the achievement of an isotonic concentration between the ultrafiltrate and the plasma water removed from the circulation[10].

UF requires a venous access to fulfill the filtration process through the hemofilter and the subsequent reintroduction of the ultrafiltered plasma into the systemic circulation[38].

Optimal anticoagulant therapy by continuous infusion of heparin is also required to preserve the function of the filter during the whole process.

The **Figure 2** schematically shows the UF process; the blood, after being extracted from the patient by venous access, is transferred to the extracorporeal circuit of the UF and then reintroduced into the bloodstream.

Newer devices allow, *via* a double-lumen venous catheter placed in the jugular or basilic vein, a blood draw with minimal recirculation.

There are various methods by which the UF process can be achieved: isolated UF, hemofiltration and UF in combination with dialysis.

Isolated UF is only a method of fluid control, whereas all the others can simultaneously achieve a certain degree of blood purification with different mechanisms. For example hemodialysis accomplishes blood purification with solutes moving from high concentration to low concentration along the electrochemical gradient whereas UF, as stated above, the substances travel due to a pressure gradient.

According to a duration-based classification, UF techniques can be classified as acute or isolated, intermittent or continuous (< 24 h) and slow continuous (> 24 h)[39].

With pure UF, an extracorporeal blood pump, either by suction applied to the ultrafiltrate compartment (negative pressure) or by resistance induced in the venous line (positive pressure) transfers the blood through the filter where the UF process is achieved.

Advantages of pure UF include the avoidance of arterial puncture, short exposure to systemic anticoagulation and, furthermore, it does not require specialized dialysis personnel[40].

Using an appropriate UF rate allows the extracellular fluid to gradually fill the removed intravascular space, thus keeping the volume constant; this effect differs UF from diuretics which remove intravascular volume without causing adequate filling from the extravascular space, the main site of congestion in patients with HF.

On the other hand, if the UF rate is too high, the rate by which the intravascular volume is removed exceeds the reabsorption of fluid from the interstitium into the vascular space, thus losing the real benefit of using UF.

Therefore, to obtain a real benefit from UF, the challenge is to find the correct rate of decongestion while maintaining an adequate circulating blood volume[41].

PROS AND CONS OF DIURETIC THERAPY VS UF

With the usage of loop diuretics, the reduction of net body water is achieved through the removal of hypotonic urine whereas UF determines the production of an iso osmotic and isonatremic diuresis. Thus, for any amount of fluid withdrawn, the net quantity of sodium removed is greater with UF than with diuretic agents.

The use of loop diuretics, moreover, causes also an inhibition of sodium chloride uptake in the macula densa thus enhancing the RAAS system activation.

On the other hand, UF through iso-osmotic and isonatremic diuresis maintains the same uptake of sodium chloride from the macula densa, avoiding RAAS system activation.

Thereby, the prolonged use of loop diuretics increases water and sodium retention in the proximal tubule with subsequent reduction of net sodium delivering in the loop of Henle decreasing the efficacy of loop diuretics to relieve the congestion.

The final goal of the ultrafiltrative process determines an euvoletic state which is obtained by withdrawing intravascular volume which is equal in size to that reabsorbed from the extracellular space [41].

Compared with standard intravenous diuretic therapy UF, by reduction of neurohormonal pathways, also improve functional capacity in patients with HF.

As explained in the study of Agostoni *et al*[42], UF unequivocally improved the functional performance of patients with HF. Cardiopulmonary exercise test obtained after 4 d shows higher values of peak VO₂ and better VD/VT ratio in UF patients compared with standard diuretic therapy. The authors suggest that favorable influences of UF on the functional capacity are related to the protective role of vasopressin and atrial peptides during and after UF that allows a more "physiological" fluid metabolism and lung decongestion in patient with HF. The study also demonstrated that UF was a more powerful stimulus than loop diuretics on the release of norepinephrine, with much less effect on the RAAS system[42]. In **Table 1** we highlighted main differences of using UF or diuretics.

EVIDENCES ABOUT THE USE OF UF IN HF FROM RCTS

The first two randomized clinical trial (RCT) in which an UF-based decongestion was compared to a diuretic-based approach have been the Relief for Acutely Fluid-Overloaded Patients With

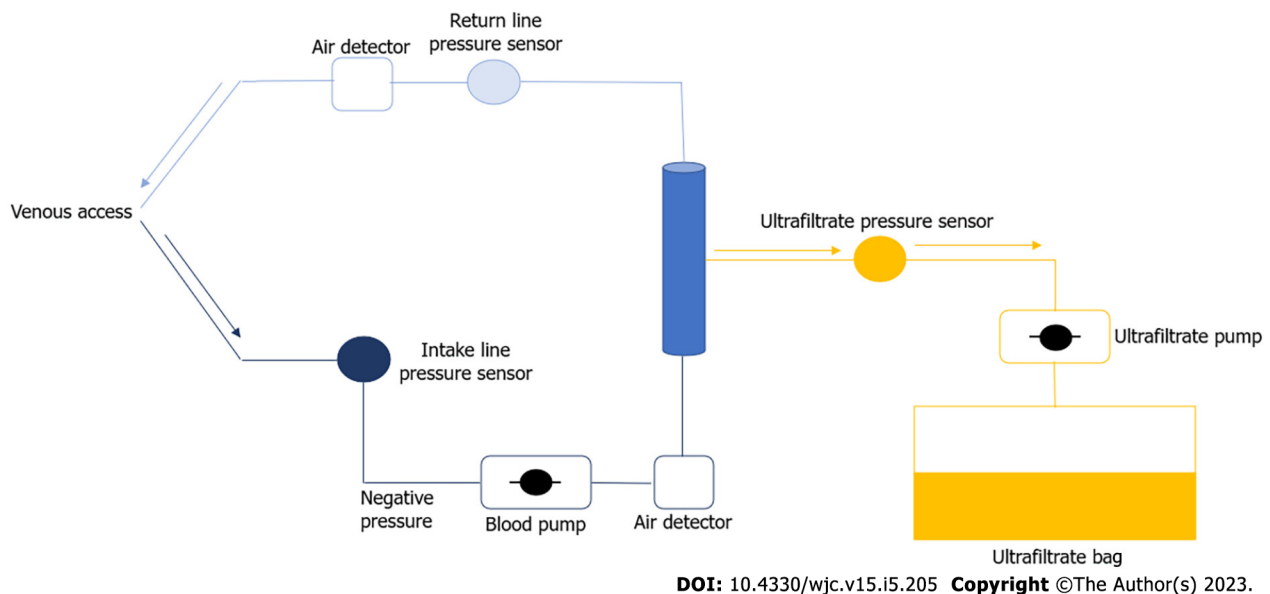


Figure 2 A schematic representation of the ultrafiltrative process.

Decompensated Congestive Heart Failure (RAPID-CHF) and the Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease (UNLOAD) trial[43,44].

In the RAPID-CHF, authors demonstrated the feasibility and the potential beneficial effects of UF (with Aquadex system) *vs* usual care among patients admitted to the hospital for an acute decompensation of congestive HF (20 UF, 20 usual care). These patients received a single, 8-h course of UF with fluid removal rates determined by the attending physician (to a maximum of 500 cc/h), whereas usual care patients were treated with diuretics according to the guidelines. Weight loss after 24 h from enrollment, used as primary end-point, was greater in the UF group although did not reach a statistical significance. This trial also highlighted that at 1-d and 30-d follow-up patients had a sustained and more significant symptoms relief (dyspnea) compared to the usual care. Furthermore, there were no differences between groups in terms of hemodynamic parameters (*e.g.*, blood pressure, heart rate) and adverse events.

However, the authors concluded that the small sample size ($n = 40$) reduced the significance of this study and did not allow to draw definitive conclusions about the potential beneficial role of UF in this subset of patients.

The investigators of the UNLOAD trial compared early UF strategy (at 24 h from hospitalization) *vs* diuretics in a population of 100 patients admitted with acutely decompensated HF in a prospective, randomized, multicenter trial. In the UF group, fluid was removed at an average fixed rate of 241 mL/h for 12 h. In the standard-care group, average daily diuretic dose of intravenous furosemide or equivalent was 181 mg during the 48 h after randomization. The study demonstrated a clear trend of each outcome in favor of UF; weight loss (primary endpoint), dyspnea improvement and net fluid loss assessed at 48 h from enrollment resulted statistically significant ($P = 0.001$) in the UF arm of the study as compared to diuretics arm. Furthermore, the UF group had fewer patients re-hospitalized for HF at 90 d [16 of 89 (18%) *vs* 28 of 87 (32%), $P = 0.037$].

One of the main limits of both the RAPID-CHF and UNLOAD trial was to not include a comprehensive assessment of hemodynamic parameters during the study.

Giglioli *et al*[45], in their ULTRADISCO trial performed a standardized evaluation of hemodynamic status obtained using Pressure Recording Analytical Method monitoring system by radial artery cannulation. Stroke volume indexed, cardiac index, cardiac power output, systemic vascular resistance was measured during hospitalization, at discharge, and at 1 and 3-mo follow-up among patients with acute decompensated HF (ADHF) treated with UF (using PRISMA system) *vs* conventional diuretics strategy. As a result, authors demonstrated that UF benefits can go beyond the net fluid loss and clinical improvement by significantly ameliorating hemodynamic status[45].

A different kind of population was target of the CARRESS-HF trial. In this study Bart *et al*[46] compared UF with a diuretic-based stepped pharmacologic therapy in patients hospitalized with ADHF with signs of congestion and worsening renal function (defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter between 12 wk before and 10 d after the index admission for HF.) Ultrafiltration was performed at a fixed fluid-removal rate of 200 mL per hour. Both the primary endpoints (weight loss and serum creatinine variation) and secondary endpoints (clinical and laboratoristic) resulted statistically not significant. This trial also showed more adverse events in the UF arm such as bleeding, catheter thrombosis and advanced kidney failure. The reasons of these results remain

still unclear although it is possible that the patients involved are not the subpopulation in which UF achieve its potential beneficial effect[46].

In the CUORE trial, investigators randomized highly selected patients with severe systolic congestive HF to UF (using Dedyca system) or standard therapy. Those patients randomized to UF had a significantly lower frequency of rehospitalization for congestive HF than control subjects and this result was maintained for up to 1 year. Furthermore, the overall reduction in rehospitalizations was linked to more significant maintenance of a body weight, renal function and lower diuretic dose in the first 6 mo after discharge[47].

The AVOID-HF trial, in contrast with the CARRESS-HF trial, remains faithful to the findings of other studies mentioned above in which UF is beneficial when applied early during the episode of HF decompensation. The AVOID-HF has the largest sample size with a total of 224 patients randomized to UF arm (using Aquadex system) or standard diuretic therapy and has a predefined decongestion dose adjustment protocol. The trial was interrupted prematurely for slow enrollment rate. Despite only one third of the sample size was achieved from the investigators, this trial showed a trend toward reduction in rehospitalization for HF in the first 90-d of discharge[48].

Lastly, Hu *et al*[49], in their single center experience trial has demonstrated that early UF effectively and safely reduces volume overload in patients with ADHF. Patient were enrolled in the first 24 h of admission randomly assigned into early UF ($n = 40$) or torsemide plus tolvaptan ($n = 60$) groups. Criteria of inclusion were acutely decompensated HF patients of age more than 18 years old and who had 1 or more sign of congestion (lung rales on auscultation, chest X ray documenting pulmonary congestion, congestive hepatomegaly and/or ascites, jugular venous pulse > 10 cm; lower limb edema, B-type NP > 400 pg/mL). Primary and secondary efficacy endpoint were increase in urine output, weight loss, reduction of dyspnea and brain natriuretic peptide; each endpoint reached statistical significance[49].

In conclusion, Table 2 summarize the different RCTs designs and outcomes.

PATIENT SELECTION CRITERIA ACCORDING TO THE LITERATURE

Given current data, it has not been yet clearly defined which subpopulation of patients suffering from acute HF refractory to diuretic therapy can benefit from UF. The conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood.

Heterogeneity of HF patients (*e.g.*, baseline clinical characteristics, hemodynamic profile, severity of renal functional impairment), the timing and the UF protocols used in the trials contributed to these inconsistent results.

As mentioned, guidelines recommend this therapeutic option in patients with a lack of hemodynamic and laboratory response despite maximal diuretic therapy[30,31]. Unfortunately, data regarding which patients may benefit the most from this strategy are scarce.

However, despite the conflicting results of the RCTs, we can still assume some broad indications from them. According to CARRESS-HF, UF may not be useful among patients with ADHF and worsening renal function[46]. Furthermore, in contrast with all other trials, the median time from the index hospital admission (the admission qualifying the patient for enrollment in the study) to randomization was 34 h. This data reinforce the belief that a more effective UF process could be related to an earlier beginning of treatment.

From some of the trials that demonstrated an effectiveness of UF, we can suggest how continuous, or at least frequent, assessment of hemodynamic stability and fluid overload are essential prerogatives before and during the treatment[45,48].

Baseline clinical characteristics of the patient and protocol used in these trials suggest in which clinical setting UF may be used.

KNOWLEDGE GAPS, FUTURE DIRECTIONS AND ONGOING CLINICAL RESEARCH

Ultrafiltration has been principally used in decompensated HF patients as an escalation after diuretic failure or in the presence of cardiorenal syndrome. Earlier utilization of UF can expedite and maintain the compensation of acute HF by simultaneously reducing volume overload without causing intravascular volume depletion and re-establishing acid base and electrolyte balance. Despite the crucial need of alternatives to diuretics-based decongestive strategy there are still several gaps of knowledge about the correct use of UF. What clearly emerges from the literature is the lack of strong evidences able to support the routine use of UF as first and early step of treatment whereas the overall potential and beneficial effect remains clear.

To draw definitive conclusions, we need more data coming from new RCTs. At the moment, REVERSE-HF, a multicenter randomized controlled trial, is ongoing across the United States.

Table 2 Overview of most relevant randomized controlled trials on ultrafiltration-based decongestive therapy

RCTs	Target population	UF device	Primary and secondary endpoint	Results
RAPID-CHF (2005)	ADHF, <i>n</i> = 40	Aqualex system, 8-h course	Weight loss at 24 h of treatment (Primary endpoint); Volume removal after 24 h	Weight reduction resulted not statistically significant (<i>P</i> = 0.24); Volume removal was significantly more in UF arm (<i>P</i> < 0.001)
UNLOAD (2007)	ADHF, <i>n</i> = 200	Aqualex System, Mean fluid removal rate 241 mL/h	Weight loss at 48 h; Dyspnea score at 48 h	Weight loss resulted significantly increased in UF arm (<i>P</i> < 0.001), whereas there were no differences between groups in Dyspnea score (<i>P</i> = 0.588)
ULTRADISCO (2011)	ADHF, <i>n</i> = 30	PRISMA, treatment duration 46 h	Changes in hemodynamics assessed using PRAM: SVi, CI, CPO, SVR were measured during hospitalization, at discharge, and at 1 and 3-mo follow-up	UF arm as compare to standard care had a significant improvement of global hemodynamic status
CARRESS-HF (2012)	ADHF, <i>n</i> = 188; Recent increase in serum creatinine ≥ 0.3 mg/dL	Aqualex System at a fixed rate of 200 mL/h	Bivariate changes in sCr and change in weight 96 h after randomization	
CUORE (2014)	ADHF, LVEF $\leq 40\%$, <i>n</i> = 56	Dedyc system	HF rehospitalization at 1 yr	UF arm has a significant lower endpoint incidence (<i>P</i> = 0.002)
AVOID-HF (2016)	ADHF, <i>n</i> = 224	Aqualex system at an adjusted rate on a per protocol established basis	Time to first HF event (HF rehospitalization or unscheduled outpatient or emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge	30-d HF rehospitalizations: 11 of 2876 (UF arm) vs 24 of 2882 (diuretics arm), <i>P</i> = 0.06
Hu <i>et al</i> [49], 2021	ADHF, <i>n</i> = 100	FQ-16 type HF ultrafiltration dehydration device (Beijing Hartcare Medical Technology Co., Ltd)	Weight loss and an increase in urine output on days 4 and 8 of treatment; Secondary outcome evaluated: BNP, NYHA class, IVC collapse index, JVP	Early ultrafiltration group had a significantly greater weight loss (<i>P</i> < 0.001) than the torsemide + tolvaptan group and urine increase (<i>P</i> < 0.001); Secondary outcomes that were followed up demonstrated a clear trend towards benefits of UF as compared to diuretics arm

ADHF: Acutely decompensated heart failure; BNP: Brain natriuretic peptide; CI: Cardiac index; CPO: Cardiac power output; IVC: Inferior vena cava; JVP: Jugular venous pressure; HF: Heart failure; NYHA: New York Heart association; PRAM: Pressure Recording Analytical Method; sCr: Serum creatinine; SVi: Stroke volume indexed; SVR: Systemic vascular resistance; UF: Ultrafiltration; RCT: Randomized clinical trial.

An important target of decongestive therapies to achieve is the so-called dry weight; however, the best way to assess fluid status and dry weight is still a matter of debate.

POCUS can, potentially, be a helpful tool for a quick and objective fluid status assessment. There are several echographic markers of the high pressures associated with congestive process, as described above, which have been proposed[50].

However, there is still a paucity of combined POCUS scoring systems able to predict adverse outcomes of patients with clinical and laboratoristic signs of congestion. One of the proposed scoring systems is Venous Excess Ultrasound grading system of the severity of venous congestion[51].

Bioelectrical impedance (BIA) is, also, an attractive non-invasive method for assessing the total body water. Measurements of bioimpedance vector require 2 pairs of electrodes to be placed on the wrist and ankles. This method, potentially, could help the physician to guide the reduction of patient's fluid overload as showed in some trials[52].

Several authors have investigated if an objective tool such as BIA is better than clinical findings for guiding UF in hemodialysis patients. As a result of several RCTs, BIA-based interventions in hemodialysis patients for correction of overhydration have little to no effect on all-cause mortality, whereas BIA improved systolic blood pressure control. These results should be interpreted with caution as the size and power of the studies are low. Further studies, larger or with a longer follow-up period, should be performed to better describe the effect of BIA-based strategies on survival[53].

In a study by Hanna *et al*[54], they proposed that a protocol driven-UF with invasive PCWP as hemodynamic parameter can guide the physician for a safe and effective interruption of ultrafiltrative system, reaching the goal of sustained value ≤ 18 mmHg for more than 4 h.

The use of biomarkers able to show acute kidney injury can help physician to assess fluid status and guide decongestion. At the state of art, serum creatinine is the sole biomarker used in daily practice to guide fluid removal. However, serum creatinine can be elevated also in the context of volume depletion without acute tubular damage. Conversely, this parameter can be normal in documented tubular injury due to the delayed achievement of detectable changes of this analyte. It is therefore evident that we need to uncover new useful biomarkers able to be more specific for kidney damage. Neutrophil gelatinase-associated lipocalin (NGAL) attracts as a newly more specific biomarker of acute kidney

injury; NGAL is not elevated in case of volume depletion as serum creatinine. In vitro studies found other genes expressed only after brief dose of ischemia as kidney injury molecule-1, tissue inhibitor of metalloproteinase-1, and clusterin, although none of these genes were expressed after volume depletion, despite the rise in serum creatinine in both models[55].

CONCLUSION

In conclusion, ultrafiltration represents an attractive alternative to pharmacologic therapy. More long-term data about safety, incidence of rehospitalization for HF and cost-effectiveness are crucial to definitely allocate this treatment also as a main option. Furthermore, we need more comprehensive and non-invasive tools to guide physicians in the fluid status management of congested patients.

FOOTNOTES

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Acute heart failure as an adverse event of tumor necrosis factor inhibitor therapy in inflammatory bowel disease: A review of the literature

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Abstract

Tumor necrosis factor inhibitors (anti-TNFs) are widely used therapies for the treatment of inflammatory bowel diseases (IBD); however, their administration is not risk-free. Heart failure (HF), although rare, is a potential adverse event related to administration of these medications. However, the exact mechanism of development of HF remains obscure. TNF α is found in both healthy and damaged hearts. Its effects are concentration- and receptor-dependent, promoting either cardio-protection or cardiomyocyte apoptosis. Experimental rat models with TNF α receptor knockout showed increased survival rates, less reactive oxygen species formation, and improved diastolic left ventricle pressure. However, clinical trials employing anti-TNF therapy to treat HF had disappointing results, suggesting abolishment of the cardioprotective properties of TNF α , making cardiomyocytes susceptible to apoptosis and oxidation. Thus, patients with IBD who have risk factors should be screened for HF before initiating anti-TNF therapy. This review aims to discuss adverse events associated with the administration of anti-TNF therapy, with a focus on HF, and propose some approaches to avoid cardiac adverse events in patients with IBD.

Key Words: Tumor necrosis factor inhibitors; Inflammatory bowel disease; Heart failure; Adverse event; TNF α receptor

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Core Tip: Tumor necrosis factor inhibitors (anti-TNFs) are widely used for the treatment of inflammatory bowel diseases (IBD). However, heart failure, although rare, is an adverse event associated with the use of anti-TNFs in these patients. This review discusses the adverse events, especially heart failure, associated with the administration of anti-TNF therapy. We believe that our study makes a significant contribution to the literature because it discusses the current understanding in the field and proposes approaches to avoid the occurrence of adverse events due to anti-TNFs in patients with IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), presents with chronic and progressive intestinal inflammation with periods of remission and activity, affecting mainly young people, with a peak of incidence between the third and fourth decades of life[1]. The etiopathology of IBD is poorly established, but it is believed to be related to an inappropriate inflammatory response to gut microbes in predisposed individuals[2]. There is still no curative therapy for IBD. Thus, treatment aims to alleviate symptoms, restore quality of life, and delay the progression and development of complications[3]. The choice of therapy depends on the location, activity, and severity of the disease, along with previous response to therapy and presence of complications. Evaluation of individual patient characteristics and the cost/benefit ratio of medications are also considered[4]. The therapeutic arsenal currently includes aminosalicylates (mesalazine and sulfasalazine); local and systemic corticosteroids (budesonide, prednisone, methylprednisolone, and hydrocortisone); immunosuppressants (azathioprine and 6-mercaptopurine); JAK inhibitors (tofacitinib); and biological therapies such as tumor necrosis factor inhibitors (anti-TNFs; infliximab, adalimumab, certolizumab pegol, and golimumab), anti-integrin antibody (vedolizumab), and anti-IL-12/23 antibody (ustekinumab)[4]. As anti-TNFs are widely used therapies, their adverse effects should be recognized in a timely manner to avoid patient morbidity and mortality. They are administered for the induction and maintenance of therapy in patients who fail to respond to conventional therapy. Infliximab, adalimumab, and certolizumab pegol are approved for use in CD. and infliximab, adalimumab, and golimumab, in UC[4]. Contraindications to their use include active infection, demyelinating disease, cancer, and heart failure (HF) [absolute in the New York Heart Association (NYHA) functional classification III–IV][5]. This review aims to discuss adverse events due to the use of anti-TNF therapy, with a focus on HF. Additionally, we performed a literature review on cases of HF secondary to the use of anti-TNFs in patients with IBD.

ADVERSE EVENTS WITH USE OF ANTI-TNF THERAPY

Infliximab is a human–mouse chimeric monoclonal antibody administered intravenously. Adalimumab and golimumab are fully humanized monoclonal antibodies that are injected subcutaneously. Certolizumab pegol is a conjugated Fab antibody fragment administered subcutaneously. In CD, anti-TNFs (infliximab, adalimumab, and certolizumab pegol) are indicated for inducing remission in moderate-to-severe disease with inadequate response or intolerance to conventional therapy (steroids and/or thiopurines). They are effective in patients who are biological therapy-naïve and biological therapy-refractory. Patients who achieved remission with anti-TNF agents need to continue the maintenance treatment. The effects of suspending anti-TNF therapy after long-term remission are not established; therefore, the decision must be individualized. In cases of complex perianal fistulas, the use of infliximab or adalimumab is recommended for induction and maintenance[4]. In UC, anti-TNFs are recommended in cases of moderate-to-severe active colitis, along with adalimumab, golimumab, or infliximab for inducing remission[6]. These drugs are recommended as maintenance therapy with or without thiopurines in patients who attained remission. In severe acute colitis refractory to intravenous steroids, infliximab may be a therapeutic rescue therapy[6,7]. Hypersensitivity reactions are among the most common adverse events with administration of anti-TNFs; they are either acute (during or within 24 h of the infusion) or delayed (24 h to 14 d after the infusion)[8]. The acute reactions are rapid in approximately 2% of the reactions, but < 1% lead to a severe reaction[9]. The presence of antibodies against infliximab increases the risk of infusion reactions[10], and case studies suggest that hypersensitivity to adalimumab is also due to the presence of anti-drug antibodies[11].

Neutropenia, thrombocytopenia, and anemia are also observed. Neutropenia may occur due to a blockade of TNF α (regulates proinflammatory factors involved in the differentiation and maturation of hematopoietic progenitor cells) that may mediate marrow failure due to inhibition of stem cell differentiation[12,13]. Isolated thrombocytopenia after administration of anti-TNF therapy has been reported by Salar *et al*[14] in 2007 and Casanova *et al*[15] in 2012, respectively; however, the cause/effect mechanism remains unclear. It may be related to autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes, or an idiosyncratic reaction. Anemia related to the use of anti-TNF remains debatable. Some studies have reported aplastic anemia due to administration of infliximab in rheumatoid arthritis[16] and infliximab-induced autoimmune hemolytic anemia[17].

Further, dermatological manifestations, such as eczema, psoriasis, infections, acne, dermatitis, and other erythema, are also reported. Psoriasis is a common adverse effect of anti-TNF therapy, occurring in approximately 1.5%–5% of the patients, mostly women, within an average of 2–6 mo after starting the therapy[18,19]. Autoimmune disorders, such as lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optic neuritis, inflammatory eye disease, central nervous system demyelination, and peripheral neuropathies, are also reported[20]. Demyelination may occur, but it is unclear whether there is a causal relationship[21]. As anti-TNFs are immunosuppressive agents, they can increase the risk of infections of bacterial, viral, or fungal origin. Uncommon infections, such as listeriosis, have also been linked to the administration of anti-TNF therapy, with a higher risk in the first year of therapy[22,23]. Anti-TNFs can reactivate latent tuberculosis in immunocompromised individuals, emphasizing the importance of screening with clinical history, chest X-rays, and tuberculin tests before initiation of the therapy[24,25]. A high risk of infection with varicella zoster virus is observed in patients with IBD, and those receiving anti-TNF have a high risk of herpes zoster[26]. However, screening for a herpes virus infection is not required before the initiation of therapy[25]. Hepatitis B virus reactivation can also occur during anti-TNF therapy or after its withdrawal[27]. In the case of hepatitis C, biological agents do not present with a contraindication during concomitant infection and have a good safety profile; however, they are contraindicated in acute infections[28]. In patients with human immunodeficiency virus (HIV) infection, the risk/benefit of administering anti-TNFs should be weighed due to the increased risk of opportunistic infections[29]. Screening for hepatitis B and C viruses and HIV with serological tests is also recommended[25]. The possibility of cytomegalovirus infection recurrence by reactivation of latent infection is low after the use of biological therapy in most cases[8]. Screening before therapy is not required[25]. Fungal infections related to anti-TNF use are also reported, particularly in those with risk factors, such as opioid use, leukopenia, advanced age, and more severe disease[30]. The blocking of TNF α possibly alters the cytotoxic immune response to fungal infections[31]. Warris *et al*[32] reported a case of pulmonary aspergillosis in a patient with CD receiving infliximab. Histoplasmosis was also reported in a case series by Lee *et al*[33] after infliximab infusions in immunocompromised patients.

Malignancies (mainly non-melanoma skin cancer, melanoma, and lymphomas) are reported in patients with IBD due to chronic intestinal inflammation and the carcinogenic effects of immunosuppressive drugs[8,34,35]. TNF can trigger apoptosis by activating caspases, and its inhibition can lead to growth and/or metastases and tumor recurrence[36]. However, whether the use of anti-TNF monotherapy increases the overall risk of cancer in patients with IBD remains unclear[37]. Studies conducted by Biancone *et al*[38,39], Caspersen *et al*[40], and Fidler *et al*[41] failed to observe an increased risk of lymphoma, leukemia, or other hematologic malignancies with the use of anti-TNF monotherapy. Cardiovascular effects have also been reported, including HF, as discussed below.

HEART FAILURE

HF is a clinical syndrome secondary to the inability of the heart to pump sufficient blood to supply peripheral metabolic demands or to do so under increased filling pressures. Acute HF (AHF) has been increasingly described as a condition with unique pathophysiology, distinct from that of chronic heart failure, and is among the most common causes of hospitalization in the elderly[42]. The patients can be categorized into new-onset (*de novo*) HF and worsening chronic HF. The latter accounts for the greater number of hospitalizations. Patients with *de novo* HF may have no prior risk factors, such as in myocarditis, but more commonly have preexisting conditions that favor the development of HF, or present with structural heart diseases without overt symptoms. Those with chronic HF may have precipitating factors for decompensation, including infections, poor adherence to treatment, and medications for other comorbidities[42,43]. Data on pathophysiology of AHF suggests that, apart from the architectural changes in the left ventricle due to increasing filling pressure and activation of the renin-angiotensin-aldosterone system, the inflammatory activation plays a pathogenic role in the progression of HF due to association with increasing stiffness of the vessels that leads to HF decompensation[42–48]. Several conditions may be classified as risk factors for HF, including ischemic heart disease, hypertension, hyperlipidemia, diabetes, smoking, hypertensive heart disease, valvular heart disease, Chagas disease, congenital heart disease, and deposit diseases[49].

HF is diagnosed after thorough anamnesis, investigation of personal risk factors, family history, and current symptoms, such as dyspnea, edema of the lower extremities, orthopnea, paroxysmal night dyspnea, and palpitations[42]. The general clinical examination may indicate an increase in the respiratory rate and a decrease in oxygenation levels, edema, cachexia, and signs of poor perfusion, such as altered mental status. A detailed examination may indicate an increased jugular pulse, reflecting the increased left ventricle filling pressure, auscultation of the S3 and S4, along with mitral regurgitation murmur due to dilation of the left ventricle. The signs of pulmonary congestion include crackling sound on inspiration and dullness of the lung bases on percussion due to pleural effusion. The abdominal examination may show hepatomegaly due to an increase in central venous pressure, along with ascites due to right HF[50-52]. Patients should also be assessed using complementary tests, including renal function, levels of N-terminal-pro hormone B-type natriuretic peptide (NT-pro BNP), and electrolytes. The imaging examinations include electrocardiogram, chest radiography, and echocardiogram[53-56]. The treatment for AHF depends on whether the patient presents with congestion, low output, or both. Four hemodynamical profiles have been postulated for better organization of the medications employed in the early management of AHF, as demonstrated below and summarized in Figure 1[57,58].

It is also important to assess patient's prognosis on admission to determine the requirement of advanced HF therapy, such as implantable cardiac devices or heart transplant[59]. Patients are considered to have worst prognosis if they are aged > 65 years; have a history of multiple hospitalizations; fail to adhere to treatment; present with functional classification NYHA III or IV; and have cachexia, syncope, sleep apnea, type II diabetes, or depression. Other factors include having had a reversed cardiac arrest; having pulmonary disease or cognitive dysfunction; having poor perfusion, congestion, tachycardia, persistent hypotension or low tolerance to exercise; having altered electrolyte levels, such as sodium < 130; having elevated BNP, troponin, or cytokines; having hemoglobin < 11 g/dL, creatine > 2.75 mg/dL, or urea 92 mg/dL; and showing atrial fibrillation in electrocardiogram, complete left bundle block, alternating T wave, long QT, low heart rate variability, progressive left ventricle dilatation, ejection fraction < 30%, right ventricle dysfunction, mitral or tricuspid regurgitation, restrictive pattern or decreased cardiac output, increase in pulmonary pressures, and peripheral vascular resistance[59].

HEART FAILURE AS AN ADVERSE EVENT OF ANTI-TNF USE

TNF α is found in both healthy and damaged hearts. Thus, it is challenging to understand its mechanisms of action. It binds to two different receptors: TNF α receptor-1 (TNFR1) and -2 (TNFR2) that are generally expressed on the heart cells[60,61]. In HF, TNF α induces β -adrenergic receptor uncoupling, increases oxidation and formation of nitric oxide, increases levels of inflammatory cytokines, and downregulates levels of contractile proteins, thus contributing to myocardial dysfunction. Long-term TNF α signaling leads to alterations in the heart geometry due to hypertrophy, apoptosis, and fibrosis[62]. The role of TNF α in HF pathophysiology is complex. Its effects are concentration-dependent and function *via* two different pathways: Survivor activating factor enhancement (SAFE) pathway functioning under low TNF α concentrations, and death-promoting pathway functioning in high TNF α concentrations. The SAFE pathway involves stimulation of other cytokines, such as cardiotrophin-1, that act on glycoprotein 130 receptor, leading to eccentric hypertrophy due to sarcomere organization in series. This pathway is observed in athletes with left ventricle hypertrophy[63-65]. In addition to the concentration of TNF α , its repercussion on the cardiac muscle depends on the receptor that it binds to as binding to TNFR1 may be cardio-damaging and binding to TNFR2 may be cardioprotective[60,66,67]. The mechanisms of HF caused by the use of anti-TNF are summarized in Figure 2.

Studies with animal models have suggested that TNFR1 Levels are upregulated after myocardial infarction without change in TNFR2 Levels. Other studies showed an absence of cardio-protection in acute ischemic models of TNFR1- and TNFR2-knockout rats, suggesting the involvement of both the receptors for maintaining a healthy heart[68,69]. In another knockout model study, Hamid *et al*[70] explored the left ventricle remodeling after myocardial infarction; the study indicated that TNFR1 knockout improved the left ventricle ejection fraction, reduced left ventricle dilatation through cardiomyocyte hypertrophy and apoptosis, and also decreased fibrosis and inflammation. In contrast, knockout of TNFR2 reversed the effects, suggesting a strong protective role of TNFR2. However, knockout of both the receptors increased survival rates, reduced reactive oxygen species formation, and improved diastolic left ventricle pressure; thus, this indicated the ambivalence of role of TNFRs on the heart health[68-70]. Further, Cacciapaglia *et al*[5] developed an *in vitro* model for TNF α preconditioning, exposing the cardiac cells to a lower dose of TNF α . The results suggested that the cells developed more resistance to subsequent TNF α toxic dose exposure and conferred more protection against oxidation and apoptosis.

From animal models to human randomized control trials, the concept of cardiac detrimental effects of TNFRs inspired the studies ATTACH, RECOVER, and RENAISSANCE (the last two are combined as RENEWAL) that were designed to understand the effects of infliximab and etanercept on HF with optimized clinical treatment. The ATTACH study failed to observe improvement and, surprisingly,

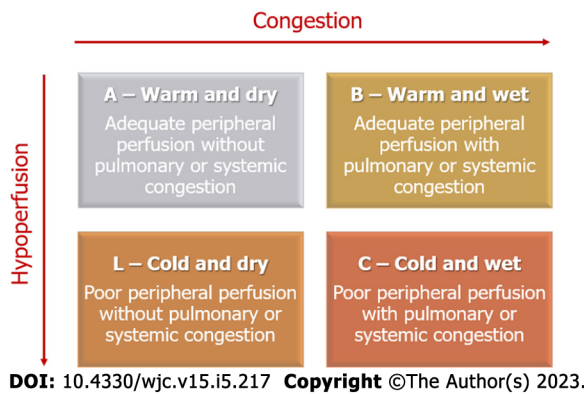


Figure 1 Clinical profiles of acute heart failure. Patients with acute heart failure present differently at admission depending on the degree of congestion and hypoperfusion of the tissues. Such profile differentiation provides guided treatment with better outcomes.

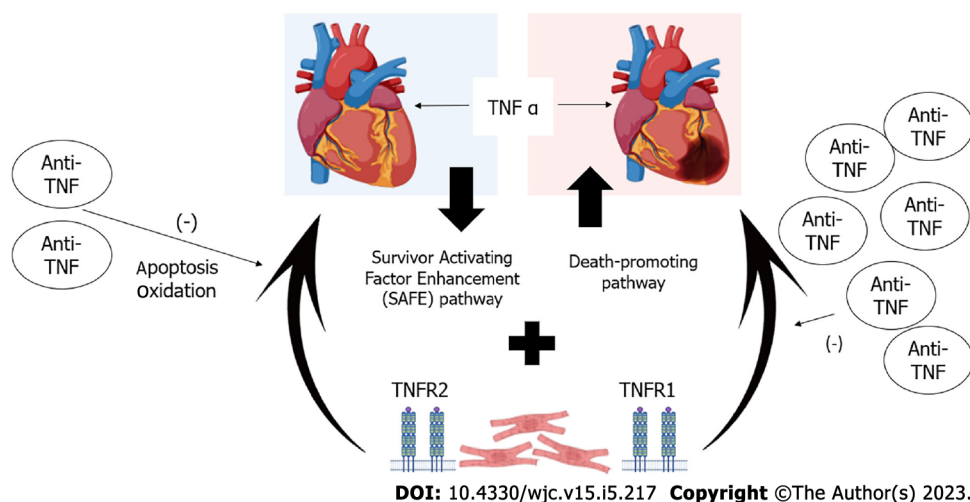


Figure 2 Mechanisms of heart failure caused by the use of anti-tumor necrosis factor agents. Tumor necrosis factor (TNF)- α is found in both healthy and damaged hearts and its effects are concentration dependent via two pathways: The survivor activating factor enhancement pathway working at low concentrations and the death-promoting pathway working at high concentrations. In addition to the concentration, its repercussion in the muscle depends on the receptor to which TNF- α (TNFR1) and -2 (TNFR2) binds, with the latter being cardioprotective. Thus, it is suggested that the development/worsening of heart failure in patients using anti-TNF is due to a suppression of the cardioprotective concentration of TNF α , making cardiomyocytes susceptible to apoptosis and oxidation or also to selective cytotoxicity.

indicated worsening of HF after therapy discontinuation. The RENAISSANCE study also showed an increased hazard ratio for the worsening of HF in the treatment group than that in the control group [71]. The disappointing clinical results, along with evidence from experimental models, suggest that the current rationale for the worsening of HF while administering anti-TNF α is that the dose employed in the randomized controlled trials abolishes the cardioprotective concentration of TNF α , therefore making the cardiomyocytes susceptible to apoptosis and oxidation[5]. A consensus is lacking on whether TNF α functions as a parallel phenomenon to, and not the cause for, HF, along with a possible selective cytotoxicity of anti-TNF α on cardiomyocytes in HF[62]. A study by Chung *et al*[72] evaluated the safety of infliximab in patients ($n = 150$) with moderate-to-severe HF (NYHA III or IV). The patients randomly received placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg at 0, 2 and 6 wk and were followed for 28 wk. There was no improvement in the clinical status of patients who received infliximab at 14 wk, and after 28 wk, there were more hospitalizations in the infliximab 10 mg/kg group ($n = 20$) due to worsening of the HF condition, along with adverse clinical events persisting for up to 5 mo after discontinuation of therapy. Abedin *et al*[73] reported a case of acute coronary syndrome after infliximab infusion in a patient without previous heart disease. The patient was a 49-year-old Hispanic woman with rheumatoid arthritis and previously well-controlled hypertension. She presented to the emergency department 10 min after the start of infliximab infusion (20 mg had been infused). The patient had no other risk factors and no family history of coronary artery disease.

Kwon *et al*[74] followed patients with rheumatoid arthritis, psoriatic arthritis, and CD who were treated with an anti-TNF agent (etanercept or infliximab). A total of 47 patients developed HF; of these, 81% had no previous symptoms and 19% had worsening of preexisting symptoms. Among those who

developed HF, 50% had no risk factors. The median interval between the first infusion of anti-TNF and diagnosis of HF was 3.5 mo (24 h to 24 mo). Keating *et al*[75] reported a case of anti-TNF-induced AHF. The 32-year-old patient had hypothyroidism and a bicuspid aortic valve and presented with Turner syndrome and CD. Biological therapy with adalimumab was initiated due to no response to budesonide. Examination indicated a transthoracic echocardiogram with normal ejection classification (> 55%). Eighteen weeks after administering adalimumab, the patient was admitted to the emergency department with edema and dyspnea. Further, we reported a case of AHF 6 mo after administering infliximab in a 50-year-old woman with CD and diabetes and a previous history of arterial hypertension. The patient presented with cardiac symptoms after optimization of the infliximab dose (10 mg/kg)[76]. The standard treatment is administered after diagnosis of HF due to anti-TNF α therapy. The current guidelines show evidence of the best prognosis for therapy for HF with low ejection fraction, while specific treatment for preserved ejection HF is unavailable. Treatment for low ejection fraction HF includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitor, beta-blockers, aldosterone inhibitor, and, more recently, sodium-glucose cotransporter-2 inhibitors. Symptomatic medication includes diuretics, vasodilators, and digoxin. AHF may require intravenous administration of inotropes and vasopressors[77]. Studies have suggested that the use of anti-TNFs should be discontinued, and a new class of medication should be selected for treatment of the primary disease; these studies also highlighted a lack of specific guidelines for the management of cardiovascular disease in patients with IBD[8,78,79]. Some therapeutic options for the treatment of IBD in case of adverse reactions to anti-TNFs include Janus kinase (JAK) inhibitors (tofacitinib), anti-IL-12/23 antibody (ustekinumab), and anti-integrin antibody (vedolizumab).

Tofacitinib can be used in patients with moderate-to-severe UC who are intolerant or refractory to treatment with anti-TNFs. Despite its ease of rapid onset of action, oral administration, and low immunogenicity, it is also having risks such as venous thromboembolism and hyperlipidemia[80]. However, long-term data on adverse cardiovascular events with tofacitinib are lacking in patients with IBD, and it remains unclear whether the risk of venous thromboembolism is disease- or drug-related[79]. Ustekinumab, a monoclonal antibody, is an option in patients with CD and with moderate-to-severe UC intolerant or refractory to anti-TNFs. In IBD, the relationship of cardiovascular events in these patients is unclear[81,82]. Vedolizumab, a humanized monoclonal antibody, is also an option in patients with CD and with moderate-to-severe UC refractory or intolerant to anti-TNFs, with better outcomes in patients not treated with anti-TNFs[83,84]. Randomized and observational studies have not reported an increase in cardiovascular events in patients with IBD[85-88]; however, an increase in cerebrovascular events, such as stroke and cerebral hemorrhage, is reported[79]. The selection of the most appropriate medication in this scenario is challenging. The clinicians should carefully analyze the different medication classes available, with their safety and efficacy profiles, to define a personalized treatment strategy for each patient, considering risk factors inherent to the patient and the proposed medication, while aiming for the best outcome.

CONCLUSION

The recommendations for HF screening prior to IBD treatment with anti-TNF α drugs are lacking. Some guidelines suggest screening, while others only mention avoidance of biological drugs when a patient presents with class III/IV HF. The European Crohn's and Colitis Organization (ECCO) reports that patients with IBD have a modest increase in the risk of ischemic heart disease, especially in women; however, they have not mentioned requirement of screening tests for cardiovascular diseases before administration of biological therapy[1,4,7,89,90]. The guidelines of the American College of Gastroenterology and the Brazilian Consensus on Inflammatory Bowel Diseases have also not provided recommendations for screening these patients[6,91,92]. The guidelines of the British Society of Gastroenterology recommend that the use of anti-TNFs be contraindicated in cases of congestive HF and that screening be performed before starting treatment; however, they have no suggestions on the best strategies for screening[93]. Considering the indication of anti-TNF α drugs for other immune mediated diseases, although with a very low certainty, guidelines on rheumatoid arthritis recommend the following strategies: Inclusion of a non-TNF inhibitor in place of a TNF inhibitor for patients with NYHA class III or IV HF and also switching to a non-TNF inhibitor instead of a TNF inhibitor for patients who develop HF[94]. The stratification of patients with HF should not be challenging as a simple clinical examination is sufficient to identify patients with NYHA classes III and IV disease. However, issues arise when the patients present with severe HF and are oligosymptomatic, especially if they are not accustomed to exerting themselves on a regular basis. As patients may develop HF after pregnancy, viral infections, or alcohol abuse, yet not present with any symptoms consistent with NYHA III or IV, this makes them susceptible to underdiagnosis. Taken together, in the absence of evidence supporting heart disease screening prior to initiating anti-TNF α drugs, and considering the current availability of a low-cost, radiation-free test that can easily assess the patient's heart function, such as echocardiogram, we recommend that an initial cardiac evaluation be a part of the patients' routine care. We suggest increasing employment of an echocardiogram for diagnosing HF prior to initiating

treatment. This strategy may prevent the incidence of adverse events in patients receiving this treatment. We hope that this review highlights this topic and would encourage future studies to clarify the benefits of using HF screening tools in patients with IBD prior to the use of anti-TNF medications to control inflammatory processes and restore quality of life, without causing further damage to the patients. It is reinforced that anti-TNF therapy has changed the course of treatment for IBD and other immune-mediated diseases in recent decades, altering its progressive and disabling course. Due to the more frequent use of these therapies, concerns about safety arise, and this article reinforces the importance of studying the subject in greater depth, including investigating the role of cardiac receptors and their relationship with the appearance of adverse events in these patients. Another point worth mentioning is the need for new algorithms and protocols, especially for populations at risk, in order to avoid the unwanted effects of the prescribed therapy.

FOOTNOTES

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Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship

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Abstract

The incidence of both atrial fibrillation (AF) and coronary artery disease (CAD) increases with advancing age. They share common risk factors and very often coexist. Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. In this review, we delineated this complex relationship, identified a common theme between the two, and discussed how the knowledge of this relationship translates into a positive and meaningful impact in patient management. Recent research indicates a high prevalence of CAD among AF patients undergoing coronary angiography. Further, the incidence of AF is much higher in those suffering from CAD compared to age-matched adults without CAD underlying this reciprocal relationship. CAD adversely affects AF by promoting progression *via* re-entry and increasing excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF in turn accelerates atherosclerosis *via* endothelial dysfunctional and inflammation and together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout cardiovascular system. In a nutshell, the two form a vicious cycle wherein one disease promotes the other. Most AF recommendations focuses on rate/rhythm control and prevention of thromboembolism. Very few studies have discussed the importance of unmasking coexistent CAD and how the treatment of underlying ischemia will impact the burden of AF in these patients. Inflammation and endothelial dysfunction remain central to both disease processes and form a handsome therapeutic target in the management of the two diseases. The

relationship between AF and CAD is complex and much more than mere coincidence. The two diseases share common risk factor and pathophysiology. Hence, it is impractical to treat them in isolation. Accordingly, we share the implications of managing underlying ischemia and inflammation to positively impact and improve quality of life among AF patients.

Key Words: Atrial fibrillation; Coronary artery disease; Antithrombotic therapy; Ischemia; Early rhythm control; Endothelial dysfunction

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Core Tip: Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. In this review, we delineated this complex relationship, identified a common theme between the two, and discussed how the knowledge of this relationship translates into a positive and meaningful impact on patient management.

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INTRODUCTION

Cardiovascular diseases including coronary artery disease (CAD) and atrial fibrillation (AF) along with other cardiovascular diseases remain the leading cause of morbidity and mortality worldwide[1]. The prevalence of both CAD and AF increases with advancing age and they often coexist[2-5]. However, this relationship is not a mere coincidence and recent evidence points to the intricate relationship between the two. Dedicated studies have demonstrated a high prevalence of CAD among nonvalvular AF patients, with majority of AF (> 50%) patients having underlying CAD as identified by invasive or computed tomography coronary angiography[5-7]. This is significantly higher than the prevalence of CAD in the general population, which is estimated to be about 12%-14%. Furthermore, there is abundant evidence that AF is an independent risk factor for CAD and incident acute coronary syndromes[4,8,9]. The interrelationship of the two is further highlighted by the fact that the people with coexistent AF and CAD have a more severe CAD and higher SYNTAX scores compared to those without AF[8,10]. Also, the morbidity and mortality is significantly higher when CAD is associated with paroxysmal or persistent AF with increased odds for developing heart failure, ventricular arrhythmias, and major adverse cardio-cerebro vascular events (MACCEs)[4,8-10]. However, despite the obvious association, this relationship is also influenced by a number of confounding risk factors such as diabetes, hypertension, age, and obesity which are common to both CAD and AF. Hence, this leads to confusion in establishing causality and reverse causality solely based on the results from registries and observational studies.

A recent mendelian randomization study by Yan *et al*[4] shed important light on this relationship and concluded beyond doubt that CAD is an independent risk factor for AF after removing all bias. Furthermore, they made an argument that treatment and prevention of AF is crucial to prevent MACCE among CAD patients[4]. Hence, the two might be more closely related than thought, and logically the therapeutic strategies are expected to be similar as well.

PATHOPHYSIOLOGICAL BASIS OF THE RELATIONSHIP

The basic pathology in CAD is the formation and progression of atherosclerotic plaques in coronary arteries leading to narrowing and resultant myocardial ischemia. Indeed, this process is identical in other vascular beds involved by atherosclerotic process and manifests as variable clinical presentation depending on the vasculature involved. In the heart, the same can manifest as acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) depending upon the progression and stability of the atherosclerotic plaques. The major pathophysiological pathways involved in initiation and progression of AF include re-entry and focal ectopic activity. The re-entry is in turn promoted by the short refractoriness, slowed conduction, and atrial remodeling as a result of atrial dilatation. The enhanced automaticity of the atrial tissue stems from the enhanced early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs)[9,11].

Common risk factors

The two diseases share identical risk factors, which trigger varied pathophysiological responses culminating in either or both of the two diseases. Diabetes mellitus (DM), hypertension, advancing age, dyslipidemia, obesity, smoking, and decreased physical activity are the major risk factors for CAD as per abundant evidence in the scientific literature. Indeed, these very same risk factors remain the most commonly implicated factors responsible for the initiation and progression of AF[8,9,11,12]. The interplay of the various risk factors and their role in the pathogenesis of AF and CAD have been demonstrated in [Figure 1](#).

DM particularly in the setting of poorly controlled blood sugars is a major risk factor for initiation of AF. Research has shown a consistent positive correlation between increasing hemoglobin A1C and AF burden. The most popular hypothesis for this association is the structural alteration and fibrosis in atrial myocardium as a result of inflammation, endothelial dysfunction, formation of reactive oxygen intermediates, and deposition of advanced glycation end products[13,14]. All of these to a large extent result in microvascular dysfunction and atrial tissue hypoxemia. Prolonged action potential duration secondary to ischemia pave the way for EADs and DADs. Often there is coexistent autonomic neuropathy and dysfunction in DM, which together with altered calcium (Ca^{2+}) and I_{na} homeostasis contributes to the progression of AF[15].

Hypertension remains the most common risk factor for both AF and CAD. It increases the risk of development of AF by more than 30% for any given age[16]. Left ventricular hypertrophy and subsequent diastolic dysfunction in longstanding hypertension contributes to atrial dilatation and dysfunction. Furthermore, alterations in the renin angiotensin aldosterone system along with the increased expression of pro-inflammatory cytokines induce atrial fibrosis[17,18]. The net result of these pathogenic mechanisms is the development of focal aberrant ectopic firing due to altered Ca^{2+} homeostasis and the development of re-entry circuits along clinical or subclinical fibrosis in atrial myocardium[19].

Obesity is often associated with other cardiovascular comorbidities, which contribute to enhanced overall MACCE risk. In addition, many advocate that obesity is an inflammatory disease process characterized by increased expression of various pro-inflammatory cytokines and resultant endothelial dysfunction. This often correlates with increased left atrial volume and fibrosis, which have a pathogenic role in the development of AF[20]. According to certain estimates, the risk of AF increases in a linear fashion with increasing body mass index (BMI) and roughly a 1 kg/m² increase in BMI confers a 4% increased risk of developing AF[9,21].

Positive feedback cycle

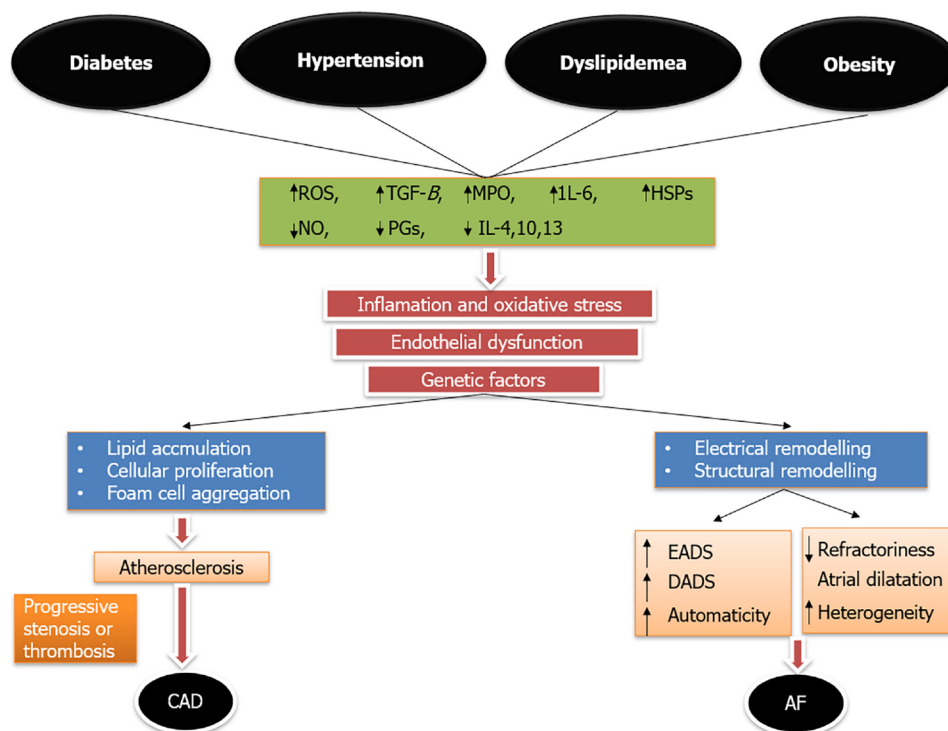
Besides sharing common risk factors, CAD and AF by themselves have a direct relationship with each other. A positive feedback mechanism between the two, culminates in a vicious cycle resulting in increased the burden of the two diseases. CAD comprising both macrovascular and microvascular disease leads to ischemia of the atrial tissue which precedes local inflammation and culminates in fibrosis and prolonged conduction times, all of which trigger the three principle mechanisms involved in the pathogenesis of AF which are focal ectopy, re-entry and neural alteration. In addition, there is heterogeneity in the electrical conduction, altered Ca^{2+} and sodium currents, and autonomic system dysregulation, all of which promote the progression and persistence of AF[4,8,9,11,12,22,23] ([Figure 2](#)).

On the other end, AF by itself can induce the two key pathogenic mechanisms involved in CAD, namely endothelial dysfunction and inflammation. Decreased release of nitric oxide coupled with increased expression of von Willebrand factor is the key pathogenic process in endothelial dysfunction [9,11,17]. AF also triggers systemic and myocardial inflammation by virtue of enhancing expression of protease-activated receptors and inflammatory cytokines, which not only initiate atherosclerotic process but also contribute to plaque instability and resultant ACS. Besides this, the beat-beat variability resulting in inefficient contractility and reduced cardiac output also contribute to reduced coronary blood flow and resultant ischemia independent of atherosclerotic CAD. Coagulation system activation coupled with enhanced platelet activity due to increased expression of p-selectin and cluster of differentiation 63 (CD63) on endothelial cells leads to micro and macro thrombi, which not only increases the risk of cerebrovascular accident but also ACS[24-26] ([Figure 3](#)).

The two more often than not coexist and together they confer worse outcomes than when the two occur in isolation. When AF complicates pre-existing CCS or ACS, it leads on to higher MACCE events including stroke, heart failure, and cardiogenic shock and also doubles overall cardiovascular mortality [8,9,11,27]. Further, it complicates clinical decision making and predisposes an individual to not only increased thrombotic events but also to major bleeding events secondary to aggressive antithrombotic therapy, which is often indicated. As a result, there is a need for a comprehensive assessment and management of the two diseases in conjunction and not as separate disease entities. The two diseases more often than not are linked in their etiopathogenesis and warrant kindred treatment to break the links which propagate the two diseases.

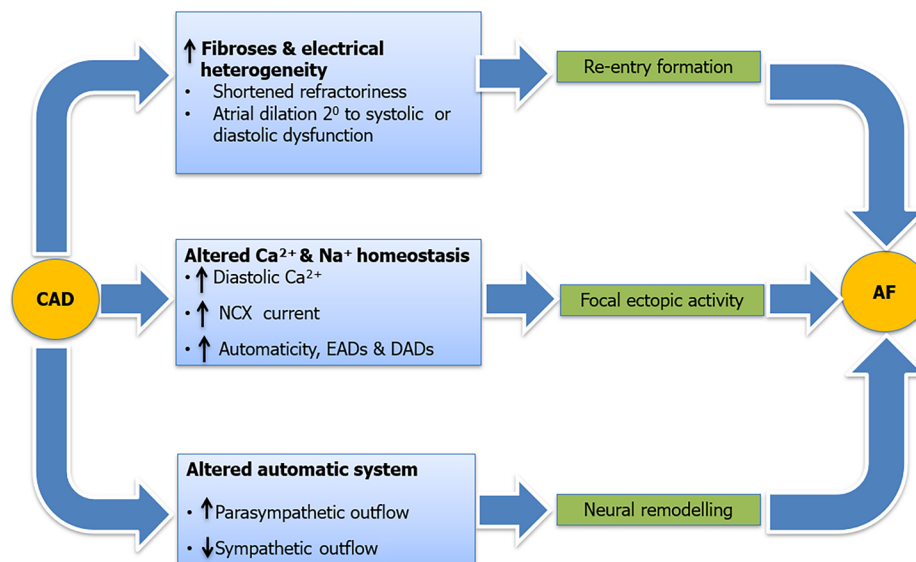
Differences in pathogenesis of AF in CAD patients compared to those without CAD

The vast majority of patients suffering from AF (> 85%) have underlying CAD or cardiovascular risk



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Figure 1 Interplay of various common risk factors in the pathogenesis of coronary artery disease and atrial fibrillation. Variable genetic expression manifests as varied clinical phenotype in the form of either or both atrial fibrillation and coronary artery disease in an individual. AF: Atrial fibrillation; CAD: Coronary artery disease; EAD: Early after depolarization; DAD: Delayed after depolarization; HSPs: Heat shock proteins; IL: Interleukin; MPO: Myeloperoxidase; NO: Nitric oxide; PGs: Prostaglandins; ROS: Reactive oxygen species; TGF- β : Transforming growth factor beta.



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Figure 2 Pathogenic mechanism that predisposes an individual suffering from coronary artery disease to develop atrial fibrillation. AF: Atrial fibrillation; CAD: Coronary artery disease; NCX: Na⁺/Ca²⁺ exchanger; EAD: Early after depolarization; DAD: Delayed after depolarization.

factors including hypertension, diabetes, obesity, and dyslipidemia. In less than 15% of all AF patients, none of these risk factors are present[28,29]. Most of them are relatively younger and commonly labeled as lone AF. Familial AF also contributes to a fraction of lone AF patients with well-defined chromosomal abnormalities most notably 10q22-q24[9,29]. The basic difference in the pathophysiology of AF in individuals having underlying cardiovascular risk factors and CAD predominantly is that they have structural alterations in the atrial tissue, which predispose them to develop electrical remodeling or directly lead to re-entry and ectopy culminating in AF. On the other hand, AF occurring in younger individuals without any risk factors is often attributable to the electrical remodeling as a result of

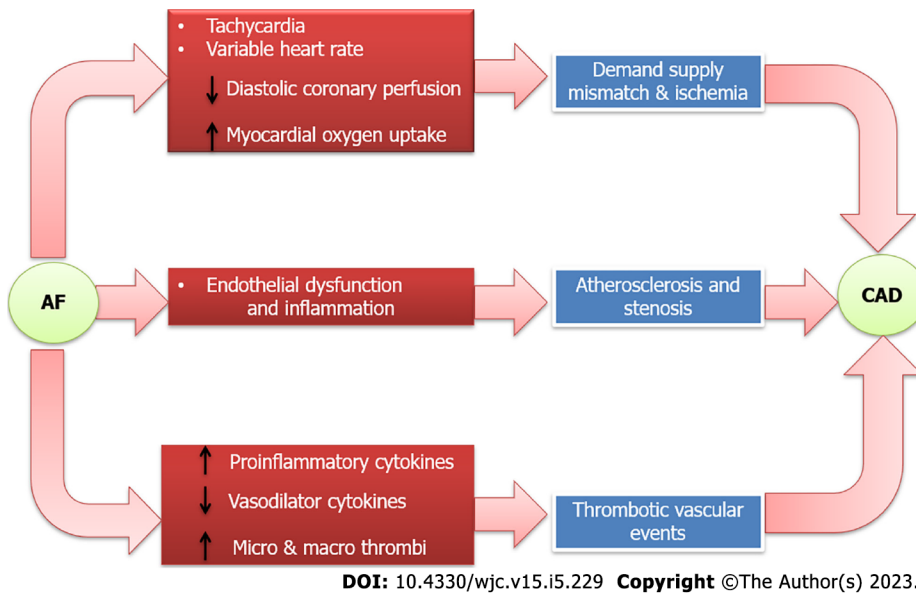


Figure 3 Pathogenic mechanisms that predispose an individual suffering from atrial fibrillation to develop coronary artery disease. AF: Atrial fibrillation; CAD: Coronary artery disease; NCX: $\text{Na}^+/\text{Ca}^{2+}$ exchanger.

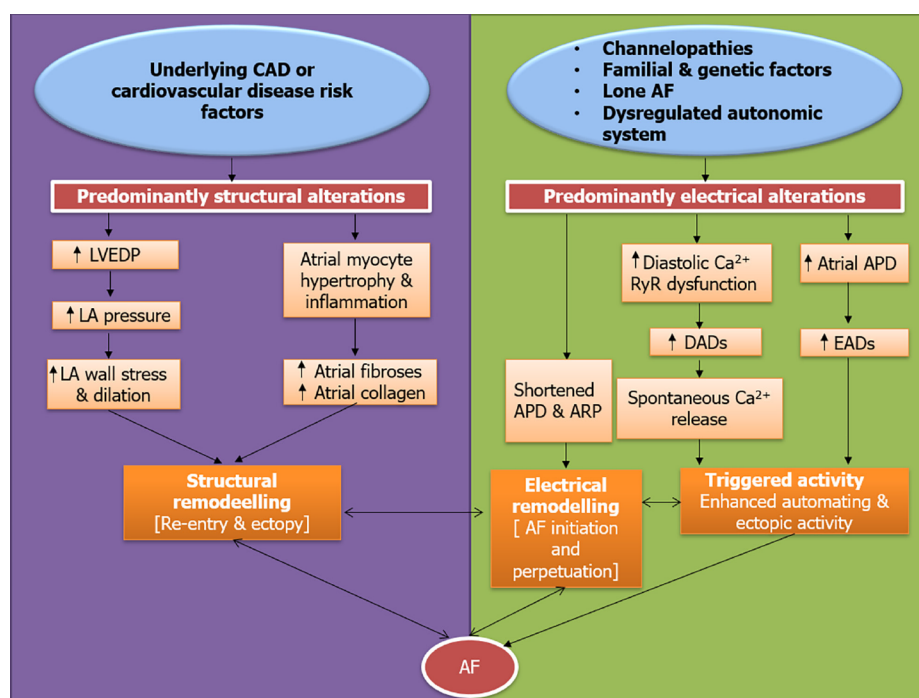
abnormal Ca^{2+} homeostasis, dysregulated ryanodine receptors, altered action potential durations, and reduced atrial refractory period. All of these culminate in changes in ion channel function, enhanced automaticity and atrial ectopy, which is a precursor to AF[28-30]. Whatever may be the initial insult, the pathways soon converge and either of the structural or the electrical remodeling ultimately aggravates the other resulting in a vicious cycle of AF initiation and progression (Figure 4). Another important difference is in the clinical presentation and outcomes. Patients with underlying cardiovascular risk factors and CAD have less symptoms related to AF, but rather commonly present with complications related to AF including heart failure or stroke. By contrast, the risk of thromboembolism is relatively lesser in the lone AF/familial AF patients, who very often present to outpatient clinics with symptoms related to AF such as recurrent palpitations or dyspnea[28,30]. Given the aggressive disease course with accelerated atherosclerosis and thromboembolism in those with underlying cardiovascular risk factors, there is a need for the aggressive control of risk factors and institution of effective antithrombotic therapies to prevent complications.

IMPLICATION ON $\text{CHA}_2\text{DS}_2\text{VASc}$ SCORE AND STROKE RISK

A consistent pool of evidence points towards the increased burden of AF in those having coexistent CAD compared to those without CAD[8,11,27]. Furthermore, this increased duration and burden of AF translates into increased MACCE events in patients with coexistent CAD compared to those without CAD. Therefore, it makes sense that people with AF and coexistent CAD need better risk factor modification, pharmacological therapy for CAD, and more aggressive antithrombotic therapy to prevent adverse outcomes[6,31].

Among the components of the $\text{CHA}_2\text{DS}_2\text{VASc}$ score, the symbol 'V' stands for vascular disease. The widely accepted determinants of this vascular disease as per the guidelines are prior myocardial infarction, peripheral artery disease, or the presence of an aortic plaque. Most of the current guidelines and online medical calculators thus do not account for CAD as a determinant of 'V' while calculating the $\text{CHA}_2\text{DS}_2\text{VASc}$ score[32,33]. Therefore, this gives an impression that underlying CAD status (excluding past myocardial infarction) has no bearing on stroke risk as determined by the $\text{CHA}_2\text{DS}_2\text{VASc}$ score.

However, in a recent, large, prospective study by Steensig *et al*[6], underlying CAD not only was very frequent among AF patients, but more importantly CAD was strongly associated with elevated thromboembolic risk beyond the usual components of the $\text{CHA}_2\text{DS}_2\text{VASc}$ score[6]. Hence, the study made a strong case for inclusion of significant angiographically proven CAD in the 'V' component of the $\text{CHA}_2\text{DS}_2\text{VASc}$ score to more comprehensively account for the thromboembolic risk in a given individual with AF. Indeed, this made a turning point in the approach to managing AF patients and the same was reflected in the European Society of Cardiology 2020 AF guidelines. For the first time, angiographically proven CAD was included as a determinant of in the 'V' in the $\text{CHA}_2\text{DS}_2\text{VASc}$ score [34]. Since then, the inclusion of significant CAD has gained acceptance among practicing cardiologists as evidenced by a recent survey by the European Heart Rhythm Association, wherein 79% of the



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Figure 4 Key differences in the pathogenesis of atrial fibrillation in patients with underlying coronary artery disease or risk factors compared to those without underlying cardiovascular risk factors. AF: Atrial fibrillation; APD: Action potential duration; ARP: Absolute refractory period; CAD: Coronary artery disease; DAD: Delayed after depolarization; EAD: Early after depolarization; LA: Left atrium; LVEDP: Left ventricular end-diastolic pressure; RyR: Ryanodine receptor.

respondents were aware of the inclusion of significant CAD and employed the same in their practice [35].

A recent study by Shi *et al* [36] shed new insights into the stroke risk in AF patients. They concluded that among AF patients with coexistent CAD, the stroke risk was not dependent on AF but on the atherosclerotic risk factors and the presence of CAD. They made a strong case for aggressive risk factor modification in particularly underlying CAD for stroke reduction in AF patients [36].

CLINICAL IMPACT OF UNDERLYING CAD ON AF

Recent evidence supports the close association of AF and CAD. Not only does underlying CAD increase the odds of developing AF but it also has significant therapeutic and clinical implications. Consistent literature points towards increased MACCE in AF patients, who have underlying CAD compared to those without underlying CAD. Furthermore, complexity in administering appropriate antithrombotic regimen is a challenge and it predisposes an individual to increased minor and major bleeding events. Hence, given the significant therapeutic and prognostic implications of CAD on AF, a more holistic and balanced approach is needed while managing the two diseases, as it is impractical to treat either one in isolation. Table 1 highlights the prominent studies over the last three decades, which have analyzed the clinical impact of underlying CAD in AF patients [6,36-44]. Consistently, underlying CAD in AF patients has been shown to correlate positively with worse overall outcomes.

“COMBINED APPROACH” TO REDUCING THE BURDEN OF THE TWO DISEASES

A recent article by Fanaroff *et al* [27] and the accompanying editorial nicely summarize the impact of coexistent AF and CAD on various clinical endpoints [27,45]. The main theme of the paper was the heightened thrombogenicity when the two occur together and authors concluded that the downstream risk of recurrent ACS and percutaneous coronary intervention (PCI) was extremely high in these group of patients compared to when they occurred in isolation. While they focused on only one and a very important aspect of this relationship, others have gone beyond the antithrombotic therapy. Another very relevant aspect is the enhanced atherogenicity throughout the systemic vasculature, which has been well documented in literature and elaborated upon in this review. The coexistence of the two sets in motion a vicious cycle that culminates in accelerated atherosclerosis and its various clinical manifest-

Table 1 Prominent studies over the last three decades highlighting the clinical impact of underlying coronary artery disease in patients suffering from atrial fibrillation

Ref.	Year	Type of study	Number of patients	Principal findings and comment
Petersen <i>et al</i> [37]	1990	Double blind RCT	516	Active angina was the only independent predictor of stroke on multivariate analysis [OR of 3.3 (95%CI: 1.3-8.9, $P = 0.02$)]
Ezekowitz <i>et al</i> [38]	1995	RCT	516	Active angina was an independent predictor of silent brain infarctions (15% <i>vs</i> 5% in those without angina; $P = 0.02$)
Van Walraven <i>et al</i> [39]	2003	Metanalysis of 6 RCTs	2501	Observed rate of stroke or TIAs was 3-fold higher in group with history of angina (5.6 <i>vs</i> 1.4 events/100 patient years; $P = 0.002$)
Goto <i>et al</i> [40]	2008	Observational cohort study	63589	MACCE events were consistently higher at 12 mo in AF patients with concomitant CAD compared to those without CAD (19.70 <i>vs</i> 14.52; $P < 0.05$)
Olesen <i>et al</i> [41]	2012	Registry based cohort study	87202	Stroke risk significantly higher in AF patients who had underlying CAD or past history of MI [HR of 1.14 (1.03-1.27)]
Rasmussen <i>et al</i> [42]	2011	Observational cohort study	3315	Risk of stroke or death significantly higher among those with underlying CAD [HR of 1.99 (1.46-2.72)]
Anandasundaram <i>et al</i> [43]	2013	Systematic review of 19 observational studies	6465	Atherosclerotic vascular disease was a significant independent predictor of stroke, thromboembolism and mortality in AF patients ($P < 0.05$)
Steensig <i>et al</i> [44]	2018	Prospective cohort study	12690	CAD was independently associated with increased risk of ischemic stroke in AF patients. Concomitant CAD increased stroke risk by 29% compared to AF patients without CAD [crude IRR of 1.62; (1.41-1.87)]
Steensig <i>et al</i> [6]	2018	Observational cohort study	96430	CAD was an independent predictor of composite endpoints [adjusted IRR, 1.25; (1.06-1.47)] over and above the usual components of vascular disease in CHA ₂ DS ₂ VASC score
Shi <i>et al</i> [36]	2021	Observational cohort study	2335	Risk of stroke was more dependent on underlying atherosclerotic risk factors than AF per say ($P < 0.001$)

AF: Atrial fibrillation; CAD: Coronary artery disease; CI: Confidence interval; HR: Hazard ratio; IRR: Incidence rate ratio; MACCE: Major adverse cardio-cerebro vascular event; MI: Myocardial infarction; OR: Odds ratio; RCT: Randomized control trial; TIA: Transient ischemic attack.

ations[9,28,30]. Besides the increased thrombogenicity and atherogenicity conferred as a result of the coexistence of the two diseases, there is a direct relationship of one with the other disease. Such that, one disease can directly lead to the other and vice versa (Figures 2 and 3). Hence, targeting and breaking the common links between the two makes sense and should be considered in any individual suffering from either of the two diseases (Figure 5).

THERAPEUTIC STRATEGIES FOR DISRUPTING THE VICIOUS CYCLE

Similar to all cardiovascular diseases, the prevention starts with risk factor control and modification right at the primary care level. Controlling the most commonly implicated risk factors including physical activity, obesity, dietary modifications with reduced intake of sweetened foods and salt, smoking cessation, blood pressure control, and management of dyslipidemia and blood sugars when altered leads to a reduction of both CAD and AF[9,11]. The optimal control of these risk factors markedly reduces ones odds of developing CAD and AF by inhibiting common initiating pathways and weakening the links between them two (Figure 5).

When one of the two diseases is diagnosed in a given individual, every attempt should be made to unmask the other disease as very often the two are associated. Coexistent CAD has been reported in more than half of AF patients in various studies[5-7,46]. Thus, diagnosing the concomitant CAD by invasive or noninvasive seems logical. This translates into optimal management of not only the masked CAD and in reducing the burden of AF but also predicts an individual's thromboembolic risk and guides optimal antithrombotic regimen[6,27]. Similarly, in those with CAD and other risk factors, the occurrence of MACCE events including stroke and heart failure should be followed by active surveillance for paroxysmal or persistent AF by appropriate rhythm monitoring tools. Unmasking paroxysmal AF guides institution of oral anticoagulants which leads to significant reduction of not only thromboembolic risk but also myocardial infarction among CAD patients.

Besides primary prevention, in those with established CAD and/or AF, the key to improve outcomes is simultaneous and optimal control of both the disease. Accordingly, given the intricate relationship between the two, it is impractical to treat the two in isolation. Most therapies that reduce the burden of either of these diseases, invariably also modifies and reduces the burden of the other disease. For

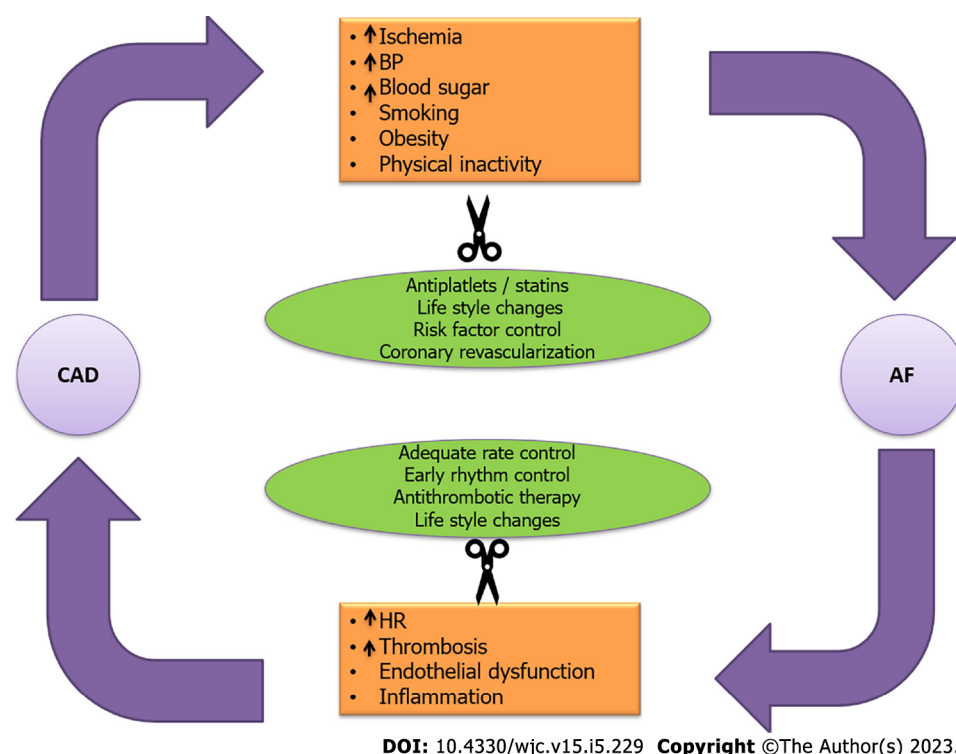


Figure 5 Vicious cycle between coronary artery disease and atrial fibrillation that culminates in a positive feedback as a result of the connections as highlighted in the orange boxes. Strategies to break this cycle are also depicted in the green ovals. AF: Atrial fibrillation; BP: Blood pressure; CAD: Coronary artery disease; HR: Heart rate.

example, statins that are used in CAD, have been shown to reduce the incidence and burden of AF[47]. Also, therapies aimed at reducing the burden of CAD including PCI or bypass graft surgery, have shown to significantly reduce the burden of concomitant AF and improve morbidity and mortality. Likewise, therapies such as rate control in AF patients using beta blockers or calcium channel blockers also significantly reduce coronary ischemia and myocardial oxygen uptake[48].

SPECIFIC THERAPIES

Antithrombotic agents

Antithrombotic agents encompass both antiplatelet and oral anticoagulants. Both CAD and AF are characterized by heightened thrombogenicity in the blood and resultant ischemic events. This is logarithmical increase in this thrombogenicity when the two coexist. To further complicate clinical decision making, there is an increased risk of bleeding as well attributable to these antithrombotic drugs. Balancing ischemic and bleeding risk in a given patient remains the top priority and necessitates adherence to clinical practicing guidelines.

The choice of antithrombotic agents in coexistent CAD and AF depends upon the clinical status of the underlying CAD. In patients suffering from CCS and AF, the consensus is towards the use of oral anticoagulants alone, preferably using the newer oral anticoagulants (NOACs). Recent research has shown that NOACs alone fair comparably to the combination of NOACs and aspirin but with the advantage of significantly lower risk of bleeding.

The decision making in AF patients with ACS and those undergoing PCI and stenting is however complex. In patients with ACS the recommendations are combining a P2Y₁₂ antiplatelet agent with an oral anticoagulant (preferably NOAC over vitamin K analogues) for at least 6-12 mo after ACS and then continuing only oral anticoagulant beyond 1 year. In those undergoing PCI, the guidelines recommend triple antithrombotic therapy including aspirin, P2Y₁₂ agent and a NOAC for the 1st month following PCI, followed by dual therapy with a P2Y₁₂ agent and NOAC for 6-12 mo and continuing only a NOAC in most patients beyond the 1st year. However, despite the evidence and clear guidelines only a minority of AF and CAD patients receive optimal antithrombotic therapy largely attributable to the gaps in knowledge, fear of bleeding or physician preference rendering these patients at high risk of recurrent ischemic events[27,49,50].

Statins

Statins have emerged as one of the most important and first-line therapy for prevention and treatment of CAD. Besides its lipid-lowering effects, it has pleiotropic effects on the form of reduction in inflammation in the atherosclerotic plaques and improving plaque stability. Recent studies have shown that the early initiation of statin therapy in ACS patients help in reducing the incidence of atrial and ventricular arrhythmias[47,51]. These beneficial actions are in part attributable to the improved autonomic control and improved myocardial stability. A large recent meta-analysis has shown that prior statin use markedly reduced the incidence of new-onset AF after admission for ACS[47]. Hence, early statin use and adequate lipid control are essential for reducing AF burden among CAD patients.

Rate controlling and antianginal agents

Tachycardia in AF predisposes patients with underlying CAD to recurrent myocardial ischemia due to increased myocardial oxygen consumption and reduced diastolic coronary perfusion at higher heart rates. This not only translates into worse symptoms but roughly doubles the risk of ACS in this population. Hence, rate control is the initial and most crucial step in managing people with both CAD and AF. Beta blockers and nondihydropyridine calcium channel blockers are the preferred agents in this regard and the resting target heart rate is less than 110/min[9,48]. Ivabradine is ineffective in controlling heart rates in AF patients and on the contrary may even aggravate AF as was seen in the SIGNIFY trial and a recent meta-analysis[52,53]. Hence, it should be avoided in AF. Digoxin, although an effective drug in controlling the heart rates in AF patients especially those with left ventricular dysfunction, is best avoided in patients with CAD for the fear of predisposition to arrhythmias and worsening myocardial ischemia due to increased myocardial oxygen consumption[48].

Among the choice of antianginal agents in patients symptomatic despite adequate rate control, ranolazine is preferred among the second-line drugs, as it prevents the automaticity in atrial tissue by suppressing diastolic depolarization and atrial tissue excitability in addition to suppressing the early and delayed after depolarizations. All of this results in the increased initiation and progression of AF. Moreover ranolazine use is tied to better rhythm control in AF patients in a recent meta-analysis[54,55]. Trimetazidine is a second-line antianginal used especially in those with underlying left ventricular dysfunction. It largely has a neutral effect on underlying AF and can be used as an add-on therapy in those with ischemic cardiomyopathy and AF. Limited data have suggested that favorable effects on P-wave duration and dispersion may help reduce the incidence of AF in these subgroup of patients[56]. The use of nitrate and nicorandil in AF should be avoided as these have been tied with increased incidence and aggravation of underlying AF in CAD patients[48].

Early rhythm control strategy

Early rhythm control strategy preferably with catheter ablation has been increasingly realized as an effective means of reducing the overall MACCE events in patients suffering from AF[57-59]. The benefit is most in those with high comorbidly burden and in those with a recent diagnosis of AF. There has been a clear trend in the superiority of rhythm control compared to rate control in recent years largely attributable to the incremental benefit of early rhythm over rate control alone in terms of improved overall symptoms and quality of life scores and reduced heart failure hospitalizations, stroke, dementia, and overall cardiovascular death[57,58]. This has reflected in increasing recommendations for catheter ablations in multiple subsets of patients including those with underlying CAD. Since AF is common in patients with underlying CAD and high comorbidity burden, all attempts should be made to diagnose it early and accordingly if symptoms are not controlled despite initial medical therapy and rate control, catheter ablation should be considered.

Targeting endothelial dysfunction

Robust evidence points towards the central role of endothelial dysfunction in CAD initiation and progression. Further, endothelial dysfunction now is increasingly realized as an important mediator in AF pathogenesis as well[60]. Often it coexists with other cardiovascular comorbidity such as diabetes, hypertension, dyslipidemia, and obesity. Decreased expression of nitric oxide, inflammation, increased oxidative stress, increased apoptosis, and vascular remodeling all contribute to endothelial dysfunction at the cellular level. Endothelial dysfunction as diagnosed by flow-mediated vasodilation often correlates with increased systemic vascular complications and poor outcomes[61]. Endothelial dysfunction is a dynamic thing and is reversible to large extent with appropriate intervention. At present, the only therapy to improve endothelial dysfunction includes aggressive risk factor modification including smoking cessation, appropriate blood pressure and blood glucose control, weight reduction, and exercise. Pharmacological therapies including antithrombotic therapies and statins also have shown incremental benefit in addition to lifestyle intervention. Other pharmacological agents including calcium channel blockers, angiotensin inhibitors, antioxidant agents, betablockers, phosphodiesterase inhibitors, nicorandil, ivabradine, and L-arginine have also shown some benefit in small studies but it is yet early stages to comment on the role of these agents in improving endothelial dysfunction in clinical practice[9,60,61].

Table 2 Impact of various antidiabetic agents on the burden of atrial fibrillation and coronary artery disease and their surrogate endpoints

Antidiabetic drug class	Impact on AF burden/ surrogate end points	Impact on CAD burden/ surrogate end points
Insulin[71]	Increased (↑)	Neutral or increased (-/↑)
Metformin[72]	Reduced (↓)	Reduced (↓)
Sulfonylureas[71]	Neutral (-/↑)	Increased (↑↑)
Thiazolidinediones[73]	Reduced or neutral (-/↓)	Increased (↑↑)
DPP-4 inhibitors[74]	Reduced (-/↓)	Reduced (↓)
GLP-1 receptor agonists[75]	Neutral or slightly increased (-/↑)	Reduced (↓↓)
SGLT-2 inhibitors[76]	Reduced (↓↓)	Reduced (↓↓↓)

AF: Atrial fibrillation; CAD: Coronary artery disease; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide 1; SGLT-2: Sodium-glucose cotransporter-2.

Therapies targeting inflammation

Inflammation is implicated in pathogenesis of both CAD and AF. The testimony of the same lies in the fact that many antiinflammatory drugs have shown incremental benefit in reducing the incidence and burden of either of the two diseases. While evidence is more robust for its positive impact in CAD, data are emerging on its role in AF patients[62,63]. Two large randomized studies have already shown the positive impact of colchicine and canakinumab in reducing MACCE events in CAD patients attributable to decreased inflammation[64,65]. On the other hand emerging evidence shows that therapies targeting inflammation indeed prevent the occurrence or decrease the recurrences of AF in CAD patient. Recent studies have shown that colchicine or corticosteroids administration after catheter ablation can help reduce recurrence of AF[63].

Effect of diabetes and antidiabetic drugs on AF and CAD

Diabetes remains one of the largest independent risk factors for development of atherosclerosis. Approximately one-third of all patients suffering from diabetes have concomitant CAD, which remains the leading cause of morbidity and mortality in the diabetic population[66]. Recent evidence points to the excess prevalence of AF in diabetic population, independent of other cardiovascular risk factors[67, 68]. Furthermore, patients with concomitant AF and diabetes have worse clinical outcomes including excess stroke, dementia, and heart failure compared to AF in the absence of diabetes[67,69]. Diabetes confers enhanced systemic vascular atherogenicity and thrombogenicity, which in part is driven by endothelial dysfunction and inflammation, a pathogenic process very similar to both AF and CAD. The major contributors to this pathogenesis include the direct glucose and free fatty acid toxicity at the cellular levels, which results in excess of reactive oxygen species, advanced glycation end-products, upregulation of the polyol, hexosamine, and protein kinase C pathways. This results in dysregulated cellular metabolism and mitochondrial function, which are essential for normal endothelial function and its antiinflammatory and antithrombotic properties[67,68]. As such, this relationship is very relevant while managing patients with AF and/or CAD. Naturally, there is a desire to use antidiabetic drugs, which help improve the burden of these diseases. Table 2 illustrates the prominent effects of various classes of antidiabetic drugs on AF and CAD. Expectedly, the antidiabetic drugs, which improve the clinical endpoints of either CAD or AF, are expected to confer a beneficial effect on the other disease as well. Overall, antidiabetic drugs that have consistently shown incremental benefit in reducing burden of either AF and CAD include sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and metformin. Accordingly, we believe that these agents should preferentially be used during institution of antidiabetic therapy in these patients ahead of agents, which have neutral or harmful effects on either of the two diseases (sulfonylureas, thiazolidinediones)[68,70].

CONCLUSION

The relationship between AF and CAD is complex and the two are intricately related at the pathophysiological level. The two diseases share common risk factors and pathogenesis and often culminate in a vicious cycle. Hence, it is impractical to treat them in isolation. The worsening of one is invariably accompanied by accelerated progression of the other disease as well. Accordingly, we share the implications of this relationship in diagnoses and management of the two diseases. In this review, we discuss the key strategies to break the cycle and highlight the recent, evidence-based therapeutic

options to break the common links between the two and reduce morbidity and mortality.

FOOTNOTES

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Current knowledge and contemporary management of non-A non-B aortic dissections

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Abstract

Non-A non-B aortic dissection (AAD) is an infrequently documented condition, comprising of only a small proportion of all AADs. The unique anatomy of the aortic arch and the failure of the existing classifications to adequately define individuals with non-A non-B AAD, have led to an ongoing controversy around the topic. It seems that the clinical progression of acute non-A non-B AAD diverges from the typical type A and B dissections, frequently leading to serious complications and thus mandating early intervention. Currently, the available treatment methods in the surgical armamentarium are conventional open, endovascular techniques and combined hybrid methods. The optimum approach is tailored in every individual case and may be determined by the dissection's location, extent, the aortic diameter, the associated complications and the patient's status. The management of non-A non-B dissections still remains challenging and a unanimous consensus defining the gold standard treatment has yet to be reached. In an attempt to provide further insight into this perplexing entity, we performed a minireview of the literature, aiming to elucidate the epidemiology, clinical course and the optimal treatment modality.

Key Words: Aortic dissection; Aortic disease; Aortic surgery; Thoracic aorta disease; Aortic arch dissection

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Core Tip: The available treatment options in the surgical armamentarium are conventional open surgery with standard aortic arch replacement or frozen elephant trunk (FET), interventional therapies such as the thoracic endovascular aortic repair (TEVAR) and hybrid techniques combining TEVAR with debranching of the supra-aortic vessels. In the case of a favorable arch anatomy, TEVAR is the preferable treatment option. Alternatively, when the entry tear is located in the proximal segment of the aortic arch, a hybrid arch repair, aortic arch replacement or even FET should be given thorough consideration.

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INTRODUCTION

As part of the cluster of the clinical entities related to acute aortic syndromes[1], acute aortic dissection (AAD) is a challenging and life-threatening cardiovascular emergency[2], with approximately 6 new cases per 100000 population per annum[3]. In an AAD, an intimal tear compromises the medial layer's structural integrity, separating the aortic wall layers. Subsequently, a "new" false lumen is formed, allowing blood to enter the tunica media[3]. If not addressed, it has a significant propensity for developing into a fatal disorder due to rupture, myocardial infarction, cardiac tamponade, aortic valve insufficiency[4], or even end-organ malperfusion[5]. Since the second half of the previous century, the Stanford and DeBakey classifications are the primary systems, which have consistently determined the patients' management. However, by default, they both fail to distinguish and address dissections confined or involving the aortic arch[5]. von Segesser *et al*[6] were the first to introduce the term "non-A non-B" when referring to intima tears sparing the ascending aorta.

Non-A non-B AAD can be defined as an entry intimal tear, located beyond the left subclavian artery (LSA), with the dissection extending retrogradely into the aortic arch (descending entry type), or as an entry tear located between the innominate and the LSA (arch entry type), with or without distal extension of the dissection[7]. It seems that there is scarcity of data regarding their natural history, clinical course and management[8]. Accordingly, we performed a minireview of the literature, to unveil the details of the topic with regards to epidemiology, contemporary classification systems as well as the available surgical armamentarium and possible treatment options.

EPIDEMIOLOGY, RISKS AND PREDISPOSING FACTORS

Non-A non-B AAD is an infrequently documented condition, comprising only a small proportion of all AADs. Its comparatively elevated mortality, hinders the ascertainment of its true incidence, since a considerable number of patients die prior to the diagnosis[2]. Regardless of the divergent results across different studies, a recent review exhibited that the incidence of non-A non-B AAD lies between the respective of type A and type B, varying from 2.8% to 16.5%[5]. The affected individuals tend to be 5 to 10 years younger in comparison to patients with other AADs[9], while some disagreement exists as to whether or not there is a prevailing type of location for the entry tear (arch or descending)[10,11].

There are several risk factors associated with non-A non-B AADs, with chronic and mainly poorly controlled hypertension being the most frequently reported. In the majority of the published cases, roughly 80% of the patients have a medical history of hypertension[5,8,10,12,13]. Tobacco addiction, hypercholesterolemia and diabetes mellitus were also found to pose a great risk for AAD. In addition, connective tissue disorders like Ehlers-Danlos and Marfan Syndromes, inflammatory vasculitis, pregnancy, trauma, previous heart surgery, the presence of bicuspid aortic valve, stimulant usage, infections and some very rare genetic disorders are among the predisposing medical conditions linked to AAD[2]. Additionally, a non-A non-B dissection can be attributed to an intramural hematoma and penetration aortic ulceration[1].

Furthermore, the role of other factors has also been investigated. Recent papers have exhibited a correlation between this specific type of AAD and anatomic characteristics of the aortic arch. Rylski *et al*

[12] demonstrated that arch types are distributed variably among different dissections. Type I in which the vertical distance between innominate artery and the top of the aortic arch is less than the diameter of the left common carotid artery (LCCA), was usually seen in type A AADs, while in non-A non-B AADs arch type II (vertical distance between innominate artery and aortic arch is equal or twice the diameter of the LCCA) prevailed (49%). In approximately 1/3 of the non-A non-B patients (28%), two instead of the three branches arise from the arch, since the innominate and the LCCA were found to share a common trunk and in 16% of the cases the left vertebral artery arose directly from the arch[10]. Irrespective of these variations, the aortic arch's curved shape and its branches, form two natural barriers, which can prevent a dissection from spreading further. The origin of the innominate artery serves as the proximal barrier, while the distal barrier is considered to be the LSA. As a result, these margins may be incriminated as the two very distinctive arch and descending entry dissection types[11].

CLINICAL PRESENTATION

In most cases of AAD, the most common symptom is sudden, acute chest pain and/or back discomfort [3]. Nevertheless, in rare cases a subtle or discrete type of AAD[3] has been reported, which is typically detected intraoperatively, despite being misdiagnosed during the patient's initial assessment[14]. Wang *et al*[15] in their retrospective study, stated that all non-A non-B patients reported an abrupt onset of severe chest pain for at least a six-hour duration. Notably, a recent meta-analysis showed that nearly 50% of the patients were admitted with or developed over time, signs of at least one organ malperfusion and that 6% were at risk of an impending rupture[8]. In the same paper, the authors highlighted the surprisingly large proportion of patients (88%), who had a complicated clinical course, as distinct from type B dissections. Hence, cardiogenic shock, cardiac arrest, cardiac tamponade, periaortic hematoma, acute renal failure, stroke/neurologic deficits or even aortic rupture are some of the baseline characteristics of non-A non-B dissection patients[13].

CLASSIFICATION SYSTEM

Over the years and with the exploitation of the emerging imaging modalities, several classification systems have been proposed and deployed to facilitate the triage and enhance the post-treatment clinical outcomes. The two traditional and widely known DeBakey and Stanford classifications were introduced in the 1950s and 1960s, respectively, and are based on the intimal tear's location and extension[16,17]. It is evident, that since the aforementioned systems focus primarily on the ascending and descending part of the aorta, they lack clarity regarding aortic arch involvement[4].

The European Society of Cardiology guidelines about aortic diseases fail to include the arch dissection as a distinct entity. The American Heart Association guidelines propose the term "proximal type B aortic dissection" for patients with entry tears in the arch, expanding antegradely to the descending aorta[18,19]. The 2019 consensus of the European Association for Cardio-Thoracic Surgery and the European Society for Vascular Surgery, referred to non-A non-B AAD, as an arch involvement either by the most proximal tear or by retrograde extension, but sparing the ascending aorta[20].

Since the introduction of the term non-A non-B AAD back in 1994[6], several studies have proposed the modification of the already existing classifications, by adding this type of dissection. Based on the entry tear's location, in 2017, non-A non-B AADs were divided into two distinct groups; arch and descending entry tear[10]. Recently, Qanadli *et al*[4] driven by the Stanford classification, proposed the incorporation of "type C" AAD, referring to the corresponding non-A non-B dissection suggested earlier by Ryłski *et al*[10]. For the first time, they also mention, grades of malperfusion syndrome (MPS grade 0-3). More specifically, the absence of malperfusion is classified as grade 0, compression of the true lumen as grade 1, while the extension of the dissection to renal artery is categorized as grade 2. According to the authors grade 3 incorporates both the absence of malperfusion and the extension of the dissection to the renal artery. Therefore, the MPS grade dictates the need for additional therapy to maintain perfusion of vital organs.

Sievers *et al*[9] extended the Stanford classification by including all types of AAD, the location of primary aortic entry tear and the malperfusion status (TEM). According to their proposal, T refers to type A, type B or non-A non-B dissections, E includes E0: No visible entry site, E1: Entry tear in ascending aorta, E2: Tear in arch, E3: Tear in descending aorta and M includes M0, M1, M2, M3 when no malperfusion, coronary artery, subra-aortic arteries, renal/visceral ± lower extremity arteries were involved, respectively. They also mention the presence (+) and absence (-) of clinical symptoms of organ malperfusion offering a more complete picture of AADs in an attempt to achieve optimal therapeutic planning and outcome[9].

TREATMENT MODALITIES

Decision on optimal medical treatment of AADs is determined based on the dissection's location, extent, the aortic diameter, the accompanying complications, the adjacent anatomy, the patient's status and comorbidities[21]. Stanford type A/DeBakey type I or II dissections, when left untreated, typically have a mortality rate exceeding 50% the first 48 h, so open surgery on emergency basis with replacement of the ascending aorta is highly recommended[3,19]. On the other hand, when the dissection involves solely the descending thoracic aorta (DTA) (Stanford type B/DeBakey type III dissections), the clinical course is usually uncomplicated. When that is the case, the 30-d mortality rate is approximately 10%, thus, conservative medical therapy or interventional, endovascular treatment (for complicated type B dissections) are the most common, yet not exclusive, treatment options[3,19]. However, aortic arch dissections have not been accurately classified, which leads to uncertainty and disagreement on treatment planning[4]. In addition, the contribution of the imaging modalities, towards an accurate diagnosis should not be omitted. The transthoracic echocardiography, although mostly employed in nonemergency cases, could potentially provide useful details regarding the proximal DTA, the aortic arch branches and detect some of the dissection's complications[19]. Yet, the valuable role of the preoperative computed tomography is constantly increasing, as it can sometimes detect the dissection and its extent, delineate the anatomy of the area, and even depict clinically significant incidental findings[22], enhancing the diagnostic accuracy and tailoring the treatment plan[19].

Aiming for the closure of the proximal entry tear, a great number of research papers have suggested the implementation of surgical treatment for non-A non-B AADs, explicitly exhibiting that conservative treatment is inferior to any type of intervention, presenting a 30-d mortality rate of 14% as compared to 3.6% for surgically or endovascularly treated patients[8]. According to recent data, it seems that the clinical manifestation and progression of acute non-A non-B AAD diverge from the typical type A and B dissections and especially from the acute type B AAD, which is confined to the DTA[23]. Valentine *et al* [24] noted that dissections including the arch had a worse outcome than those affecting only the DTA. Equally important results from an expert consensus state that the arch's involvement in the dissecting process has an immense impact on the patients' outcome, including but not limited to the prolonged hospital stay, the increased probability of cardiac and neurologic complications such as rupture, congestive heart failure, MPS, stroke, spinal cord injury (SCI) and the need for reintervention if not addressed betimes[20,25].

Because non-A non-B AADs are associated with an increased likelihood of a complicated course, the optimal management orders early intervention[5]. In spite of the fact that, during the past years, many therapeutic plans have been proposed, there remains a dearth of literature regarding pertinent studies comparing different modalities for the treatment of non-A, non-B AAD. Moreover, the existing studies have limited patient samples and lack long-term follow-up[21]. Therefore, a unanimous consensus defining the gold standard treatment has yet to be reached[5]. Currently, the available treatment options in the surgical armamentarium are conventional open surgery with standard aortic arch replacement or frozen elephant trunk (FET), interventional therapies such as the thoracic endovascular aortic repair (TEVAR) with extra-thoracic surgical transposition or chimney stent graft and hybrid techniques combining TEVAR with debranching of the supra-aortic vessels[8]. Lately, a new hybrid technique was launched by Wang *et al*[15] with satisfactory short-term outcomes, called the "inclusion aortic arch technique", as an alternative to the traditional hybrid surgery, so to avoid endoleaks and retrograde type A dissection, which may complicate the procedure.

According to the International Registry of Acute Aortic Dissection study findings, arch entry and DTA entry type dissections differ from one another in terms of their course. More specifically, a DTA dissection, expanding retrogradely to the arch, has no impact on either early or late mortality or the management plan, with its clinical course resembling that of type B AAD. Whereas complicated arch entry dissections with antegrade expansion to the DTA, were found to have an elevated in-hospital mortality, requiring an even more urgent intervention[13,25]. Trimarchi *et al*[13] also presented data which argue that non-A non-B AAD should perhaps warrant a more aggressive approach. In their analysis, 14% of patients with an "uncomplicated" arch tear had progression of the dissection, which likely contributed to a 30% incidence of lethal stroke. In the same frame, Kosiorowska *et al*[7] stressed/pointed out the contemporary tendency towards an earlier intervention on the altar of a favorable aortic remodeling. In arch entry type patients, open aortic arch repair is preferable compared to endovascular techniques in term of survival and post-operative complications rate[7]. In these cases, there are several arch replacement grafts commercially available (Figures 1 and 2).

The arch entry dissections, can be managed with standard aortic arch replacement combined with FET, as the procedure is associated with low peri and post-operative mortality and complication rates [7]. Hybrid methods have been proposed as an effective alternative, which can prevent the need for cardiopulmonary bypass, hypothermic cardiac arrest and any related problems, but their efficacy has not yet been proven in the long run[26]. However, the study conducted by Tian *et al*[27], employing different hybrid methods (type I-III) to treat 46 patients, has demonstrated promising outcomes with respect to overall mortality and complication rates, in comparison to surgical or endovascular repair. Taking into account the lack of guidelines regarding postoperative thromboprophylaxis, caution must be exerted to avoid the graft's occlusion[28]. Irrespective of the entry type, evidence shows that TEVAR

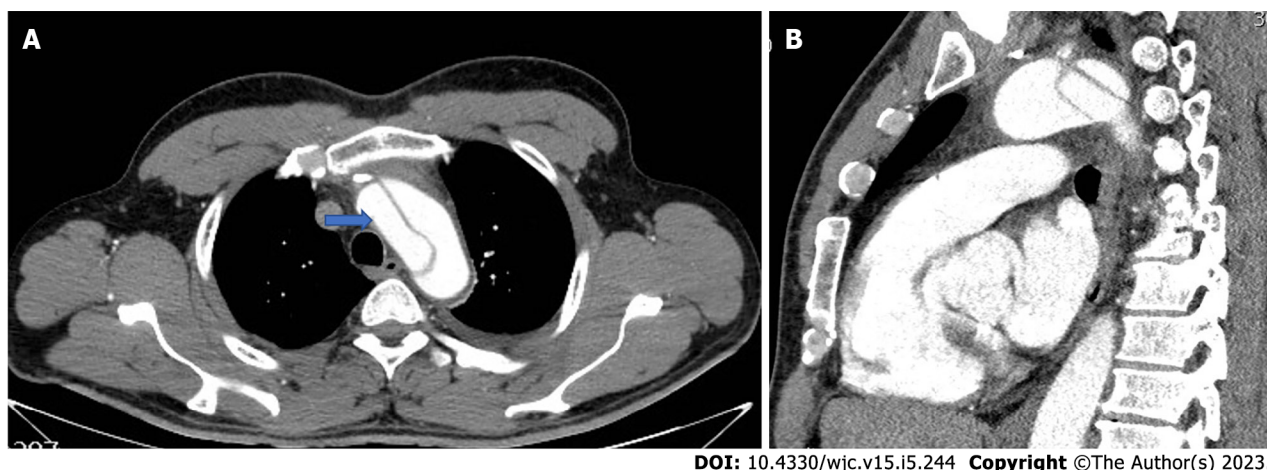


Figure 1 Pre-operative computed tomography images of a non-A non-B aortic dissection case contained in the aortic arch, which was surgically managed in our department. A: Axial view, blue arrow shows the true lumen; B: Sagittal view.

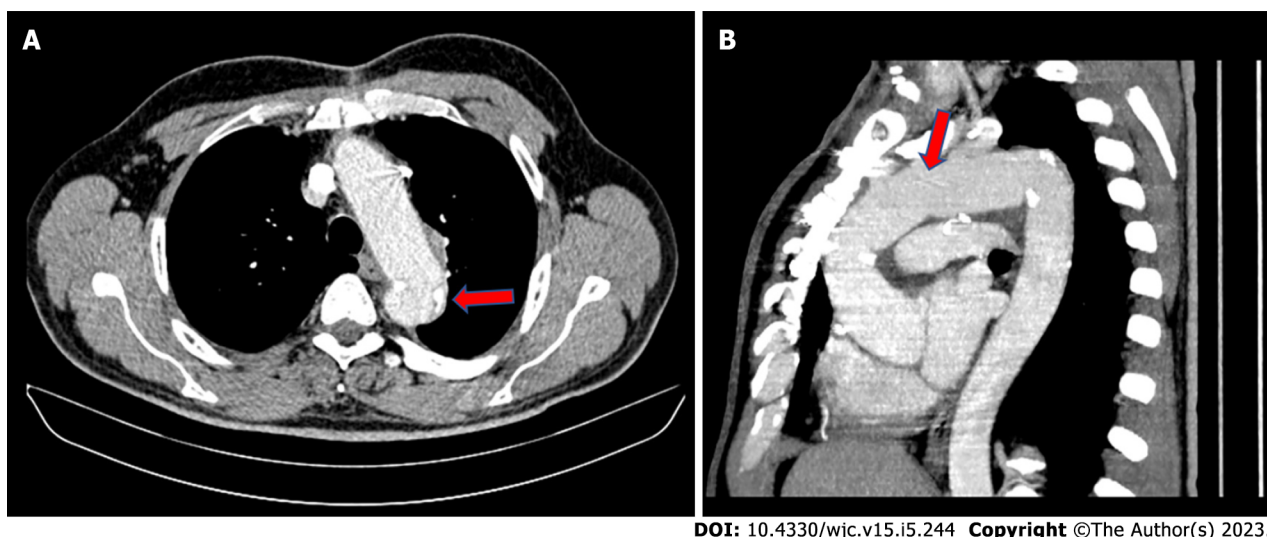


Figure 2 The aortic arch was replaced with a graft (prefabricated aortic branched graft), which contained three pre-attached branches for all three great vessels. A: Axial view, red arrow demarcates distal anastomotic suture line; B: Sagittal view; red arrow the proximal suture line with the ascending aorta.

is a valid treatment option provided that the aortic arch has favorable anatomy[8]. Alternatively, when the entry tear is located in zone 1, a hybrid arch repair, aortic arch replacement or even FET should be given thorough consideration[8]. This minireview focuses primarily on the FET and TEVAR techniques.

ET AND FET

Treatment of non-A non-B AAD can be performed with a two-stage surgical technique called “ET”[29]. The first stage of ET includes a sternotomy and a reconstruction of the ascending aorta and the aortic arch with a graft while in the second stage, the floating extension of the graft (ET) in the descending aorta is utilized in order to extend the repair of the DTA. The second stage *per se* includes a lateral thoracotomy to approach the descending aorta. The evolution of surgical and endovascular techniques has resulted in the development of a composite prosthesis, known as the “Frozen ET”[20]. The use of FET instead of the conventional ET has been increasing over the last years[20].

Combining the benefits of both open and interventional repair, FET is a viable solution in cases of a proximal entry tear as well as for patients with non-A non-B AAD or complicated chronic type B, who are not suitable for TEVAR[30,31]. This one-stage procedure allows a total aortic arch replacement with antegrade delivery of a descending aortic stent-graft[32]. The stent-graft may serve as a proximal landing zone to facilitate future endovascular intervention in the distal aorta[30]. The FET technique has

been extensively applied in cases of acute dissections to restore true lumen patency, seal intimal tears in the descending aorta and promote false lumen thrombosis, as well as repairing chronic degenerative arch aneurysms[19,32]. FET implantation has the potential to prevent secondary thoracic and abdominal aortic replacement by enlarging the true lumen and promoting favorable remodeling of the distal aorta [19,33,34]. Yet, if replacement of the thoracic and abdominal aorta is required, its additional suture margins at each side, facilitate anastomosis[5,30]. The two most common commercially available hybrid FET prostheses namely the Thoraflex hybrid and E-vita open are associated with comparable outcomes [20].

Carino *et al*[8] mention that 7% of the non-A non-B patients underwent the FET procedure, pointing out that it should be considered in complicated cases, since it alleviates the compressed true lumen and covers any newly formed entry tears in the proximal DTA, applying pressure to the false lumen. Zhao *et al*[35] reported the in-hospital mortality rate of their 24 non-A non-B AAD patients treated with FET, to be 4.1%, while the 5-year survival rate was approximately 92%. The authors concluded that, this surgical technique represents a feasible option with acceptable short and long-term outcomes. Another study cohort, whilst exhibiting similar early results, stresses the importance of the continuous monitoring and follow-up, due to the potential need for aortic reintervention[31]; results in accordance with Tian *et al* [27] paper.

Although the technique is more invasive than TEVAR, it minimizes the risk of type Ia endoleaks and retrograde type A dissection[30]. On the other hand, FET's primary disadvantage is the increased risk of surgical trauma brought on by the necessity for extended periods of extracorporeal circulation, circulatory arrest, myocardial ischemia, stroke and SCI, due to the extensive coverage of the descending aorta with the occlusion of intercostal arteries[8]. Additionally, aortic valve insufficiency, bovine aortic arch, the dissection of the LCCA and preoperative cardiopulmonary resuscitation have all been linked to an increased risk for postoperative stroke[36,37]. Notably, in many studies, including a meta-analysis with 3000 "aortic surgical" patients, SCI was documented in 4% of the cases. By diminishing the circulatory arrest time and FET maneuvers above the 8th thoracic vertebra, SCIs could be substantially reduced[38]. Cerebrospinal fluid drainage and neuromonitoring should also be carried out for high-risk patients[39].

TEVAR

TEVAR, given its minimal invasive character, has recently been shown to be the most widely used technique to treat non-A non-B dissections, comprising 55% of the treatment[8]. The aim of the stent-graft's deployment in the thoracic aorta is the successful closure of the primary entry tear. As a result, the false lumen is excluded from the systemic circulation, thrombosed and shrank, thus it no more compresses the true lumen and organ perfusion is maintained. According to the location of the primary entry tear, different TEVAR sealing zones exist (zone 0, 1, 2, 3). Zone 3 TEVAR refers to entry tears located in the DTA with retrograde extension, with the stent-graft deployed distal to the LSA. For more proximal entry tears, zone 2 TEVAR is employed, which includes a sealing zone between the origin of the LCCA and the LSA. TEVAR zone 1 refers to graft apposition between the innominate artery and LCCA, while TEVAR zone 0 includes a sealing zone proximal to the innominate artery[3,5,10,20].

In order to establish a disease-free sealing zone, the sacrifice of important aortic arch branches can be, in some cases, unavoidable. Nonetheless, there are several techniques to maintain perfusion; supra-aortic branch bypass (hybrid technique), apposition of extra stent-grafts (chimney technique) or both [40]. TEVAR zone 2 can be accompanied with carotid-subclavian (CS) bypass/transposition or with chimney graft to the LSA. Similarly, TEVAR zone 1 can be followed by two chimney grafts to the LCCA and LSA, but more frequently, a single chimney graft to the LCCA and a CS bypass/transposition are used. Finally, TEVAR zone 0 can entail two chimney grafts to the innominate artery and LCCA followed by a left CS bypass, or alternatively a chimney graft to the innominate artery, right to left carotid bypass and CS bypass[20]. Compared to more distal landing zones, zone 0 is more likely to be associated with retrograde type A dissection, especially when accompanied by excessive oversizing of the stent-graft [41]. Yet, it has also been demonstrated that the use of chimney grafts in the aortic arch, increases the risk of post-operative complications[40].

Liu *et al*[21] studied 215 patients with a non-A non-B AAD, treated with TEVAR, open surgical techniques or conservatively. TEVAR was used in 127 patients (59.1%) with a success rate of 85.9%. The 30-d mortality rate was 1.6%, compared to 7.1% in patients treated with open techniques. However, during the follow up, 9 deaths occurred in the endovascular group, 5 of which were related to the dissection, while no deaths occurred in the surgical group. Supplementary, following TEVAR, patients had a worse clinical outcome in terms of aortic rupture, retrograde type A dissection, distal stent graft induced new entry, major stroke and the need for reintervention. Likewise, a study published in 2022, observed that 67% of the initial TEVAR cases (10/15), demanded reintervention, with eventually 4 patients deceasing during the first 30 d[7].

CONCLUSION

Management of non-A non-B dissections remains challenging. The paucity of relevant studies reflects the fact that non-A non-B AADs account for a relatively modest percentage of all AADs. Although little is known about their natural history and course of treatment, it has been explicitly shown that surgical intervention surpasses medical treatment in the case of a non-A non-B dissection[5,8,42]. Current data advocate that this clinical entity does not behave like an uncomplicated type B AAD, and perhaps a more aggressive approach is warranted. Open repair is mostly employed in arch entry, while TEVAR with hybrid procedures in descending entry dissections both of which are thought to be preferable as opposed to conservative treatment. Secondary analysis with long-term follow up of the existing studies as well as large prospective clinical trials will enlighten the field around non-A non-B AAD which still remains an obscure and perplexing variation of acute AAD. Future research is anticipated to determine the most optimal surgical method as well as the time to intervene, ultimately helping surgeons to navigate through these uncharted waters.

FOOTNOTES

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Retrospective Cohort Study

Importance of concomitant functional mitral regurgitation on survival in severe aortic stenosis patients undergoing aortic valve replacement

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Abstract

BACKGROUND

Mitral regurgitation (MR) is commonly seen in patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR). But the long-term implications of MR in AS are unknown.

AIM

To investigate MR's impact on survival of patients undergoing surgical AVR for severe AS.

METHODS

Of the 740 consecutive patients with severe AS evaluated between 1993 and 2003, 287 underwent AVR forming the study cohort. They were followed up to death or till the end of 2019. Chart reviews were performed for clinical, echocardiographic, and therapeutic data. MR was graded on a 1-4 scale. Mortality data was obtained from chart review and the Social Security Death Index. Survival was analyzed as a function of degree of MR.

RESULTS

The mean age of the severe AS patients who had AVR ($n = 287$) was 72 ± 13 years, 46% women. Over up to 26 years of follow up, there were 201 (70%) deaths, giving deep insights into the determinants of survival of severe AS who had AVR. The 5, 10 and 20 years survival rates were 75%, 45% and 25% respectively. Presence of MR was associated with higher mortality in a graded fashion ($P = 0.0003$). MR was significantly associated with lower left ventricular (LV) ejection

fraction and larger LV size. Impact of MR on mortality was partially mediated through lower LV ejection fraction and larger LV size. By Cox regression, MR, lower ejection fraction (EF) and larger LV end-systolic dimension were independent predictors of higher mortality ($\chi^2 = 33.2$).

CONCLUSION

Presence of greater than 2+ MR in patients with severe AS is independently associated with reduced survival in surgically managed patients, an effect incremental to reduced EF and larger LV size. We suggest that aortic valve intervention should be considered in severe AS patients when > 2+ MR occurs irrespective of EF or symptoms.

Key Words: Aortic stenosis; Mitral regurgitation; Aortic valve replacement; Long term survival

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Core Tip: This study is unique in several aspects: (1) Shows that mitral regurgitation negatively impacts survival in an independent fashion, an effect incremental to left ventricular size and ejection fraction; (2) Perhaps the longest follow up of severe aortic stenosis (AS) patients undergoing aortic valve replacement (AVR) (till death or 16-26 year follow up in survivors); (3) Gives insights into potential mitral regurgitation (MR) mechanisms; and (4) Validates echocardiographic MR severity against survival in patients with severe AS undergoing AVR.

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INTRODUCTION

Significant mitral regurgitation (MR) is seen in about 20% of patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR) or transcatheter aortic valve replacement (TAVR)[1-3]. Presence of MR is associated with worse symptoms, higher pulmonary artery pressures and higher short-term mortality in TAVR patients[1-5]. However, its impact on long term survival after AVR is not well characterized, especially in those with moderate or severe MR. The recent American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines do not include presence of MR as an indication for AVR or TAVR[6]. We investigated the impact of different grades of MR on long term survival (to death or up to 26 years) in a cohort of patients undergoing surgical AVR for severe AS in period 1993-2003.

MATERIALS AND METHODS

The research project was approved by the institutional review board of Loma Linda University, Loma Linda, California. A need for an informed consent was waived because of its retrospective, observational study design without any intervention.

The data underlying this article will be shared on reasonable request to the corresponding author. This was a retrospective observational study conducted in a large university medical center. The study was approved by the institutional review board, which waived the need for patient consent. Some of the other results of this observational study have been published previously[7,8]. This report includes 15 additional years of follow up. The echocardiographic database was searched for patients with severe AS during the period from 1993 to 2003. Severe AS was diagnosed based on the generally accepted criteria prevalent at that time[9]. The criteria used included aortic valve area ≤ 0.8 cm² or a mean transvalvular gradient of ≥ 40 mmHg or peak gradient of ≥ 64 mmHg. This yielded a total of 740 patients. Complete clinical, echocardiographic, and pharmacological data were compiled on these patients from comprehensive chart review. Of these 287 underwent AVR and formed the study cohort.

Clinical variables

Various clinical comorbidities were defined as follows: Hypertension was defined as a blood pressure > 130/90 mmHg, being on any antihypertensive medication, or a documented history of hypertension. Diabetes mellitus (DM) was defined as a fasting blood sugar of > 126 mg/dL or being on treatment for

diabetes. Renal insufficiency was defined as a creatinine value of ≥ 2 mg/dL. Coronary artery disease (CAD) was defined as angiographic evidence of CAD with lesions $> 50\%$ as all had coronary angiograms before AVR.

All patients had standard 2-dimensional echocardiographic examinations. The left ventricular (LV) ejection fraction (EF) was assessed visually by a Level 3-trained echocardiographer and entered into a database at the time of the examination. This has been proven to be reliable and has been validated against contrast and radionuclide LV angiography[10,11]. Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography prevalent at that time and MR was graded 0-4[12,13].

Pharmacotherapy around the time of initial echo was recorded and placed into broad categories of beta blockers, calcium-channel blockers, digoxin and angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI). Most of the patients continued on the medications for the length of the recorded clinical observation. Patients were on beta blockers, ACEI/ARB only if they had a concomitant indication for their use like hypertension or CAD. Beta blockers and ACEI/ARB are not recommended as primary treatment for severe AS. Hence the low treatment rate with beta blockers and ACEI/ARB.

The end point of the study was all-cause mortality. Mortality data were obtained from clinical records or the Social Security Death Index till the end of 2019.

Statistics analysis

Stat View version 5.01 (SAS Institute, Cary, North Carolina) program was used for statistical analysis. Kaplan-Meier survival curves were computed for patients with severe AS with and without MR and were compared using the log-rank statistic. Characteristics of patients with and without MR were compared using the Student *t* test for continuous variables and the χ^2 test for categorical variables, the largest *P* value for differences between the groups was taken. Cox proportional hazards models was employed to adjust for clinical comorbidities and covariate imbalances. Baron and Kenny method was employed for mediation analysis[14]. *P* < 0.05 was considered significant.

RESULTS

Patient characteristics

The baseline characteristics of the severe AS patients who had AVR were: mean age 72 ± 13 years, 46% women, mean LVEF $57 \pm 19\%$, and DM in 22%, hypertension in 55%, and CAD in 55%. The mean aortic valve area was 0.70 ± 0.17 cm², transvalvular mean systolic gradient 44 ± 16 mmHg and peak gradient 72 ± 24 mmHg. Of the 287 patients, 42% had concomitant coronary artery bypass grafting (CABG) with AVR; 169 (59%) had no or mild (0 or 1+) MR, 63 (22%) had moderate (2+) MR and 55 (19%) had moderate to severe or severe (3 or 4+) MR. Of the 55 patients with 3 or 4+ MR, 18 had mitral valve repair (*n* = 11) or replacement (*n* = 7).

Survival as function of degree of MR

As the survival curves were similar for MR grades 0 and 1+ and very close to 2+ MR, hence these groups were combined. As shown in (Figure 1), there was a graded decrease in survival with increase in MR (*P* = 0.003). The 5, 10 and 20 year survivals for those with 0/1+ MR were 78%, 50% and 33% respectively compared to 78%, 43% and 14% for 2+ MR and 64%, 30% and 15% for 3 or 4+ MR respectively. Comparison between grade 0-1 and 3-4+ MR showed significant difference with *P* < 0.0001. Similarly, comparison between grade 2 and 3-4 +MR showed difference with *P* < 0.0001. Comparison between grades 0-1 and grade 2 showed slight difference with *P* = 0.03.

Correlates of MR

Table 1 shows the comparison of patients with different degrees of MR. As it can be seen from the table, higher degrees of MR correlated strongly with larger LV end-diastolic and end-systolic dimensions (*P* < 0.0001), lower LVEF (*P* < 0.0001) and lower LV relative wall thickness (*P* = 0.0002). There was no relationship with age, gender, hypertension, diabetes, CAD, renal failure or severity of AS. As expected, those with MR had higher mitral E/A velocity ratio (*P* < 0.0001) and shorter E wave deceleration time (*P* < 0.0001) indicating higher left atrial pressure, higher pulmonary artery pressure (*P* < 0.0001) and higher prevalence of heart failure (*P* = 0.0015). It is notable that 38% of patients with 3 or 4+ MR had no dyspnea or heart failure.

Though MR was strongly related to lower EF, 47% of patients with 3 or 4+ MR had an LVEF $\geq 50\%$ (ACC/AHA guidelines use an EF threshold of $< 50\%$ as a class I indication for AVR or TAVR in patients with severe AS).

Mediation analysis and Cox regression analysis

In view of strong correlations between MR grade, EF and LV size and as all these were predictive of

Table 1 Characteristics of aortic stenosis patients with different grades of mitral regurgitation

	0 or 1+ MR	2+ MR	3 or 4+ MR	P value
Age (yr)	70 ± 12	74 ± 9	72 ± 13	< 0.05
Women (%)	44	48	51	0.4
Syncope (%)	3	4	4	0.85
Angina (%)	38	49	47	0.12
Dyspnea (%)	39	38	62	0.002
Atrial fibrillation (%)	24	32	33	0.18
Hypertension (%)	58	57	44	0.06
Diabetes mellitus (%)	24	22	18	0.4
Coronary artery disease (%)	53	60	58	0.3
Renal insufficiency (%)	10	8	13	0.39
LV end-diastolic diameter (mm)	48 ± 7	48 ± 4	56 ± 10	< 0.0001
LV end-diastolic diameter index (mm/m ²)	26 ± 4	27 ± 4	23 ± 6	< 0.0001
Left ventricular end-systolic diameter (mm)	31 ± 9	33 ± 9	41 ± 13	< 0.0001
LV end-systolic diameter index (mm/m ²)	16 ± 4	18 ± 4	41 ± 13	< 0.0001
Ventricular septum (mm)	14 ± 2	14 ± 3	14 ± 3	0.2
Posterior wall (mm)	13 ± 2	13 ± 2	12 ± 2	0.13
Relative wall thickness	0.57 ± 0.15	0.57 ± 0.13	0.48 ± 0.13	0.0006
LV ejection fraction (%)	62 ± 16	54 ± 17	45 ± 21	< 0.0001
Left atrial dimension (mm)	41 ± 9	43 ± 8	48 ± 6	< 0.0001
Aortic valve area (cm ²)	0.72 ± 0.16	0.68 ± 0.16	0.70 ± 0.20	0.18
Aortic valve peak gradient (mmHg)	73 ± 23	71 ± 26	67 ± 22	0.09
Aortic valve mean gradient (mmHg)	45 ± 15	43 ± 17	41 ± 15	0.08
Aortic regurgitation grade	0.65±0.83	1.16±0.91	1.00±1.00	< 0.0001
Mitral E/A velocity ratio	1.00 ± 0.53	1.09 ± 0.64	1.60 ± 0.67	< 0.0001
Mitral E wave deceleration time (ms)	270 ± 105	278 ± 112	194 ± 89	0.0001
Pulmonary artery systolic pressure (mmHg)	40 ± 13	45 ± 20	53 ± 14	< 0.0001
Beta-blocker use (%)	46	46	27	0.02
ACEI or ARB use (%)	25	33	36	0.12
Digoxin use (%)	35	32	38	0.47
Statin use (%)	31	21	35	0.09
Coronary artery bypass grafting (%)	38	49	47	0.12
Mitral valve repair (%)	3	2	20	< 0.0001
Mitral valve replacement (%)	2	10	13	0.06

AS: Aortic stenosis; MR: Mitral regurgitation; LV: Left ventricular; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

survival, we performed mediation analysis described by Baron and Kenny by sequentially adding EF and LV end-systolic dimension to the Cox regression model that included MR severity[14]. Adding EF and LV end diastolic dimension, significantly reduced the χ^2 associated with MR, but MR still remained significant (P values for MR, EF and LV end –diastolic dimension: 0.0049, < 0.0001 and 0.0013 respectively and global $\chi^2 = 34.3$). Addition of pulmonary artery pressure to the model did not improve its predictive value. This indicates that not all negative effects of MR were through increase in LV size and reduction in EF, but MR independently was related to survival as well. The results of Cox regression analysis are shown on Table 2.

Table 2 Results of Cox regression analysis on the effect of mitral regurgitation on survival

Variable	χ^2 value	P value
LV end-diastolic dimension	10.4	< 0.01
LV ejection fraction	23.3	< 0.0001
Mitral regurgitation	7.9	< 0.01

Global $\chi^2 = 34.3$; LV: Left ventricular.

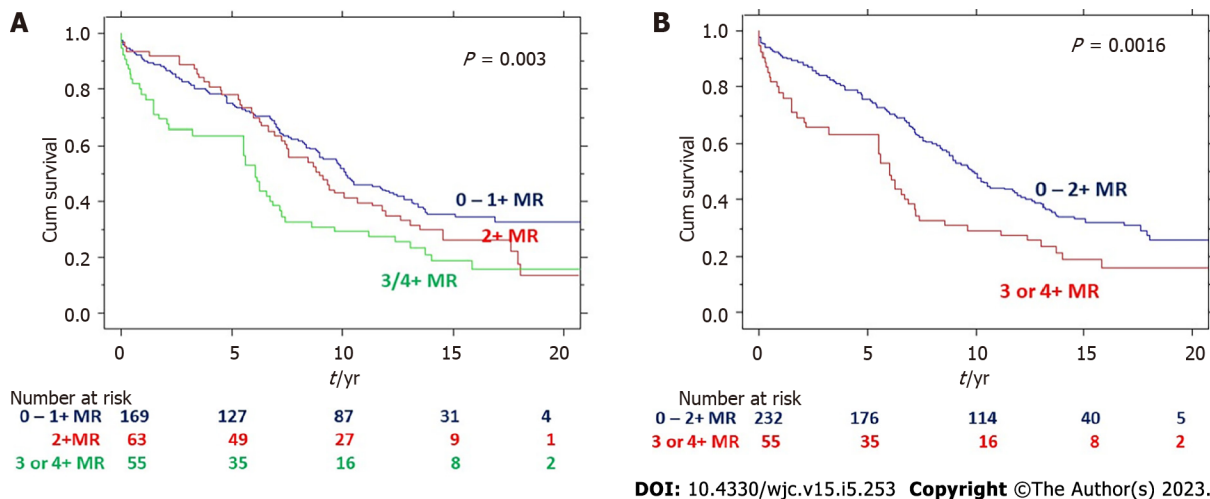


Figure 1 Survival in severe aortic stenosis patients undergoing aortic valve replacement as a function of preoperative severity of mitral regurgitation. A: MR severity split into 3 groups; B: MR severity split into 2 groups. MR: Mitral regurgitation.

Effect of MR on survival stratified by CABG status

Of the 287 patients with severe AS undergoing AVR, 121 had CABG and 166 did not have CABG. As shown in Figure 2, the deleterious effect of MR was seen in both groups of these patients ($P = 0.007$ and $P = 0.05$, respectively).

Mitral valve surgery in 3 or 4+ MR

Mitral valve surgery was performed in 18 of the 55 patients with 3 or 4+ MR at the time of AVR. Of these 12 patients also underwent CABG at the time of mitral valve surgery, was a trend towards better survival with mitral valve surgery with 10- and 20-year survivals being 45% and 37% respectively in those with mitral valve surgery compared to 22% and 8% respectively for those without ($P = 0.08$, Figure 3).

DISCUSSION

Our observational study with very long-term data suggests harm produced by MR in patients with severe AS undergoing AVR. According to ACC/AHA guidelines, MR is not considered an indication for AVR in severe AS patients in the absence of symptoms or $EF < 50\%$ or a need for concomitant cardiac surgery. About 1/3 of our patients even with 3 or 4+ MR had no symptoms and one half of them had an $EF \geq 50\%$ without a traditional indication for AVR. These findings are novel and have major clinical implications in the management of these patients. The other strength of our study is length of follow up – to death or 16-26 years in the long-term survivors.

Presence of MR was also associated with higher left atrial and pulmonary artery pressures and some degree of LV enlargement indicative of adverse LV remodeling and functional impairment. Data from patients undergoing TAVR or AVR for severe AS indicates that MR may regress by one grade in about half the patients, but not full regression in all the patients leaving the patients with significant MR which may have negative impacts in terms of symptoms, heart failure and reduced survival or a need for another procedure to eliminate MR[4,15].

The mechanism of MR seems to be mostly functional because of an increase in LV size leading to mitral leaflet tethering in contemporary series with calcific AS, though older series included rheumatic

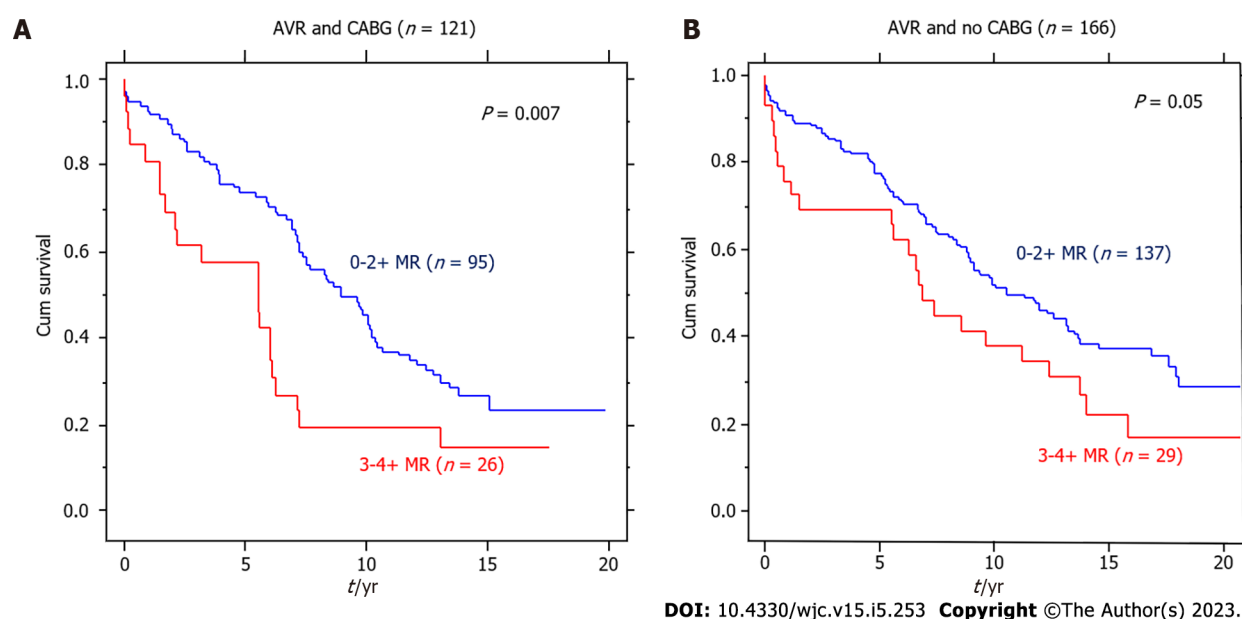


Figure 2 Effect of preoperative mitral regurgitation severity on survival in aortic valve replacement patients stratified by concomitant coronary artery bypass grafting status. A: Patients who had AVR and CABG; B: Patients who had AVR only and no CABG. MR: Mitral regurgitation; AVR: Aortic valve replacement; CABG: Concomitant coronary artery bypass grafting.

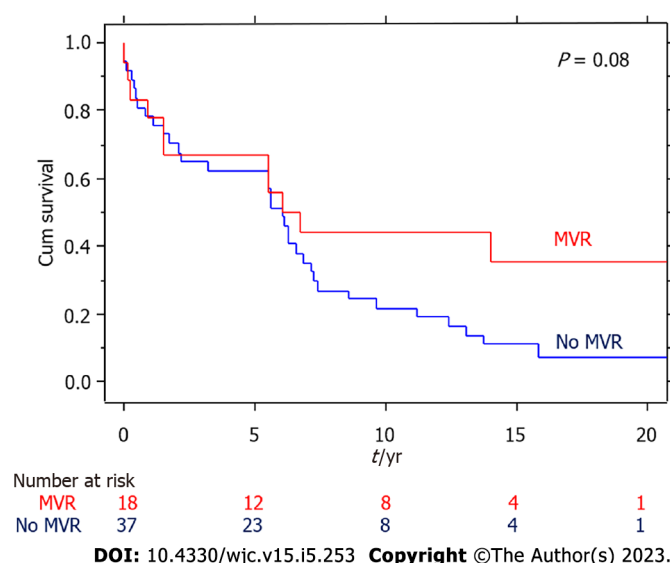


Figure 3 Survival in patients with pre-aortic valve replacement 3 or 4+ mitral regurgitation as a function of mitral valve repair or replacement during aortic valve replacement surgery. MVR: Mitral valve repair or replacement.

valve disease as well[16]. There could also be an atrial mechanism due to atrial enlargement due to LV diastolic dysfunction or atrial fibrillation leading to secondary mitral annular dilatation[17]. Hence, monitoring asymptomatic severe AS patients for increases in LV or left atrial size or onset of atrial fibrillation may be important, besides evaluating for presence, degree and mechanism of MR. Performance of AVR or TAVR will reduce LV systolic pressure that drives MR. In addition, reverse remodeling of the LV and left atrium may occur as well and this will help in MR regression. One should also consider restoration of sinus rhythm to reduce the risk of genesis or progression of MR as atrial fibrillation may produce MR and even tricuspid regurgitation through atrial and annular dilation. Patients undergoing TAVR may introduce another issue of production of left bundle branch block or complete heart block needing a pacemaker. Both of these electrical disturbances may impair LV function and produce or worsen MR. These mechanistic factors should be kept in mind in patients with severe AS.

There are some limitations to this retrospective observational study. We do not have follow up echocardiographic data as the images are generally archived only for 7 years and many patients had these studies outside our healthcare system. Also, surgery for MR was at the discretion of the operating

surgeon.

CONCLUSION

In summary, 3 or 4+ MR is present in about 20% of patients undergoing AVR for severe AS and negatively impacts hemodynamics, symptoms and survival. We suggest that one should be vigilant for any MR in patients with severe AS and also the potential mechanisms that may lead to MR such as progressive LV or left atrial dilation or onset of atrial fibrillation. We also suggest that presence of $\geq 3+$ MR in patients severe AS should be considered as a potential indication for AVR or TAVR as appropriate.

ARTICLE HIGHLIGHTS

Research background

Severe aortic stenosis (AR) and concomitant mitral regurgitation (MR) are common. But the impact of MR in those with severe AS on outcomes and management are unknown.

Research motivation

To study the impact of concomitant MR on outcomes in severe AS.

Research objectives

Does MR affect prognosis and decision making in severe AS patients.

Research methods

Of the 740 consecutive patients with severe AS evaluated between 1993 and 2003, 287 underwent AVR forming the study cohort. They were followed up to death or till the end of 2019. Chart reviews were performed for clinical, echocardiographic, and therapeutic data. MR was graded on a 1-4 scale. Mortality data was obtained from chart review and the Social Security Death Index. Survival was analyzed as a function of degree of MR.

Research results

Presence of MR was associated with higher mortality in a graded fashion. MR was significantly associated with lower left ventricular (LV) ejection fraction and larger LV size. Impact of MR on mortality was partially mediated through lower LV ejection fraction and larger LV size. By Cox regression, MR, lower ejection fraction (EF) and larger LV end-systolic dimension were independent predictors of higher mortality.

Research conclusions

Presence of greater than 2+ MR in patients with severe AS is independently associated with reduced survival in surgically managed patients, an effect incremental to reduced EF and larger LV size. We suggest that aortic valve intervention should be considered in severe AS patients when $> 2+$ MR occurs irrespective of EF or symptoms.

Research perspectives

More studies are needed to study the mechanisms of MR and its prevention in severe AS patients.

FOOTNOTES

Author contributions: Pai RG and Varadarajan P designed the study, analyzed the data, wrote the manuscript and revised the final form.

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Informed consent statement: A need for an informed consent was waived because of its retrospective, observational study design without any intervention.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Observational Study

Pharmacoepidemiologic study of association between apparent treatment resistant hypertension, cardiovascular disease and interaction effect by sex and age

Julianne Theresa Nelson, Longjian Liu

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Abstract

BACKGROUND

A limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

AIM

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

METHODS

We applied an observational analysis study design using data from the United States Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT recruited participants ($n = 25516$) from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: Fatal or non-fatal myocardial infarction, coronary revascularization, angina, stroke, heart failure, or peripheral artery disease. Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction.

RESULTS

Of the total study participants ($n = 25516$), 5030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH [hazards ratio (HR) = 1.3, 95%CI: 1.19-1.42]. Sex and

age modified this relationship on both multiplicative and additive scales independently. Stratified by sex, aTRH was associated with a 64% increase in risk of CVD (HR = 1.64, 95%CI: 1.43–1.88) in women, and a 13% increase in risk of CVD (HR = 1.13, 95%CI: 1.01–1.27) in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged < 65 (HR = 1.53, 95%CI: 1.32–1.77) than it did in those aged ≥ 65 (HR = 1.18, 95%CI: 1.05–1.32). Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed ($P < 0.05$). The observed joint effect of aTRH and ages ≥ 65 years (HR = 1.85, 95%CI: 1.22–2.48) in males was less than what was expected for both additive and multiplicative models (HR = 4.10, 95%CI: 3.63–4.57 and 4.88, 95%CI: 3.66–6.31), although three-way interaction of sex, age, and aTRH on the risk of CVD and coronary heart disease did not reach a statistical significance ($P > 0.05$).

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

Key Words: Apparent treatment resistant hypertension; Cardiovascular disease outcomes; Chronic kidney disease; Sex; Age

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Core Tip: Apparent treatment resistant hypertension (aTRH) increased the risk of a cardiovascular event by 30%. This association varied by sex and age, with a stronger impact in women and in younger adults. These findings highlight the importance of controlling aTRH among those with excess risk of cardiovascular disease.

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INTRODUCTION

Hypertension has long been a serious public health concern. Its impact on cardiovascular health and long-term outcomes has been well studied[1]. In the United States approximately 121.5 million (47.3%) adults suffer from hypertension leading to an added economic burden costing up to \$51.1 billion per year[2]. One of the significant challenges in control of hypertension is the appearance of treatment resistant hypertension.

Treatment resistant hypertension is defined as having blood pressure (BP) that remains uncontrolled [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] while a patient is on ≥ 3 different antihypertensive medications. Additionally, those who are on 4 or more different classes of antihypertensive medications, regardless of BP are also classified as treatment resistant hypertension. Individuals with diabetes or chronic kidney disease (CKD) have an altered definition, these patients with SBP/DBP ≥ 130/80 mmHg are classified as treatment resistant hypertension[3-5]. In addition to the number of antihypertensive medications and BP readings, ideally at least one of the medications should be a diuretic[6]. Apparent treatment resistant hypertension (aTRH) is used to define observed treatment resistant hypertension when factors relating to pseudoresistance (adherence to regimen, sufficient dose for therapy, etc.) are unknown[7].

It is estimated that 19.7% of patients on antihypertensive medication have aTRH, a 2% increase within the recent decade[3-5]. While it is known that treatment of hypertension can reduce the risk of cardiovascular events and mortality, little research has been done on outcomes of those with resistant hypertension[3,8]. Several cross-sectional studies have found relationships between aTRH and cardiovascular disease (CVD), however, longitudinal studies remain sparse[3,9]. What has been observed is that aTRH is associated with higher rates of cardiovascular and renal diseases, including: Coronary heart disease (CHD), peripheral artery disease (PAD), stroke, heart failure (HF), end-stage renal disease, and all-cause mortality. Of particular note is that aTRH increased the risk of CHD by 44% and the risk of death by 30% compared to non-aTRH[9,10].

Men and women experience differing rates of hypertension and CVD[11,12]. However, findings of sex-specific aTRH studies remain inconsistent[3,5,13-15]. Women experience an increase in risk of hypertension post-menopause indicating a possible impact of sex and age on the risk of aTRH and CVD

outcomes[12].

Of the many risk factors for CVD, age is one of the most important factors as age is an independent risk factor for the development of atherosclerosis[5,11,16,17]. However, the degree of this effect does not impact men and women in the same way neither in the risk of incident hypertension nor in the progress of hypertension in clinical treatment[11,18]. Several studies have observed that age is significantly and independently associated with risk of aTRH[3-5,14]. However, studies of the potential modification effects of sex and age on the association between aTRH and risk of CVD are limited. In this study, we hypothesized that sex and age play an important role both independently and together in the risk of aTRH for CVD outcomes. To test this hypothesis, we examined the independent and additive effects of sex and age on aTRH and risk of CVD, and whether sex and age modify the association between aTRH and CVD risk.

MATERIALS AND METHODS

Study sample

We analyzed data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In ALLHAT, a total of 42418 participants aged 55 and older were recruited from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands. Participants were randomly assigned into four groups and then received one of four antihypertensive treatment arms: Chlorthalidone, amlodipine, lisinopril, and doxazosin. Participants who received doxazosin are excluded in the analysis because this group was discontinued early. All participants had hypertension and at least one additional risk factor for CHD. Participants were followed for an average of 6 years[19-21]. The study design and process of ALLHAT have been published in detail elsewhere[21].

This study, using de-identified data from the National Heart, Lung, and Blood Institute, has been approved by Drexel University Institutional Review Board (# 1608004781).

Measures

Exposure (aTRH): In ALLHAT the recruited participants were initially randomized to one of 4 first-line antihypertensive drugs. Additional anti-hypertensive medications were added on to therapy over the course of follow-up visits, thus, aTRH was determined at the year 2 visit to allow time for additional medications to be added, consistent with follow-up studies[10,21]. aTRH was defined as BP $\geq$ 140/90 while on 3 antihypertensive medications, or being on 4 antihypertensive medications regardless of BP at the year 2 visit. For subjects with either type II diabetes or CKD (assessed by glomerular filtration rate, epidermal growth factor receptor (eGFR) $<$ 60 mL/min), the cut-offs of SBP/DBP were set at $\geq$ 130/80 mmHg. Due to subjects being randomized to first-line anti-hypersensitive treatment, the condition that one medication be a diuretic for aTRH classification could not be applicable in the study.

Outcome (CVD): Subjects were classified as having had a CVD event if they experienced one of the following after the year 2 follow-up visit: Fatal or non-fatal myocardial infarction (MI), coronary revascularization, angina, stroke, HF, or PAD. These events were ascertained from follow-up visits and medical recording during the course of the trial[10].

Covariates: Covariates were selected based on their independent associations with both the exposure (aTRH) and outcome (CVD), existing literature, and use of a directed acyclic graph[10]. All covariates were measured at baseline of ALLHAT. They included: Race (white, African American, American Indian/Alaskan Native, Asian/Pacific Islander, other), ethnicity (Hispanic), geographic region (East, Midwest, South, West, Canada, Puerto Rico/Virgin Islands), measures of GFR, SBP and DBP at baseline, and history of CHD, history of MI or stroke, history of coronary revascularization, previous use of BP medication, smoking status (current, former, never), history of left ventricular hypertrophy, estrogen use (in women subgroup analysis only), aspirin use, and enrollment in concurrent lipid lowering trial.

Statistics

Univariate analysis was conducted to describe the baseline characteristics of participants by aTRH status. Student's *t* test was used to examine mean difference in continuous variables, and Chi-square tests to examine rate and proportion differences in categorical variables. We used Cox Proportional Hazards regression models to examine the association between aTRH and CVD risk with adjusting covariates. Assumptions of the proportional hazards in Cox model were tested graphically by log-log survival curves. To test potential modification effects of sex (men *vs* women) and age ($<$ 65 *vs* $\geq$ 65) on the association between aTRH and CVD risk, we assessed potential multiplicative interaction (*e.g.*, aTRH*modifier) on CVD risk. We also assessed potential additive interaction effects on CVD risk by estimating the joint effects and calculating the relative excess risk for interaction (RERI)[22]. If the RERI $\neq$ 0 then there is evidence that the observed additive risk of our exposures is different (more or less depending on the direction of the RERI) than what was expected. The methods of the calculations and hypothesis tests for the RERI have been discussed and published in detail elsewhere[23]. To test the overall interaction effect of sex and age and aTRH on CVD risk, we tested three-way interaction through

a product interaction term (*e.g.*, aTRH*sex*age) in Cox models. Observed joint effects were compared to expected for both additive and multiplicative models to determine presence of effect modification and subgroup analyses were performed.

Sensitivity analyses: To avoid overfitting attributable to multiple control covariates, we applied a propensity score analysis technique[24]. A propensity score for the probability of aTRH was estimated utilizing all confounders and created using the boosted CART method in the “twang” package in R software[25–27]. Extreme weights were trimmed and inverse probability weighting was used to weight observations by the propensity score[24,28]. Second, in the ALLHAT study, missing data in BP measures occurred at year 2 visit. We conducted a sensitivity analysis using Markov Chain Monte Carlo method for multiple imputation based on the randomness of the missing values[29]. Third, because of the pathophysiologic differences between hemorrhagic and ischemic stroke, we conducted a subgroup of CVD analysis by strokes and CHD (fatal CHD or nonfatal MI, coronary revascularization, or hospitalized angina). Fourth, to control the effects attributable to the conclusion of patients who had uncontrolled hypertension (BP $\geq 140/90$) but with < 3 medications ($n = 11223$), on the estimate of hazards ratio (HR) for CVD risk, we excluded this group of patients in the final sensitivity analysis.

Data analyses were conducted using SAS software (Version 9.4, SAS Institute Inc., Cary, NC, United States). Statistical significance as set up at a two-sided $P < 0.05$.

RESULTS

From the original sample of 42418 subjects in ALLHAT, those on the doxazosin treatment arm (9061) were removed early for safety reasons. After excluding subjects with CVD events or death prior to year 2, and those missing year 2 visit information we had an analytic study sample of 25516. During the follow-up (average 4.7 years), 5030 (19.7%) participants had a CVD event. Table 1 shows baseline characteristics of the participants.

Overall subjects were more likely male (53.3%), from the South (41.6%), white (60.3%), and previously treated for hypertension (90.3%). Over a third (35.2%) had type 2 diabetes (T2DM), and 40.7% were former smokers. While over 40% of subjects were obese, the average body mass index (BMI) was 29.7 (SD 5.92). The average age was 66 years, and average GFR 78 mL/min. The rate of aTRH was 9.1% ($n = 2329$) in the total sample, 9.8% in men, 8.4% in women, and 9.1% in those aged 65 and older. Subjects with aTRH were predominantly more likely to be African American, male, BMI ≥ 30 kg/m², and T2DM than their corresponding counterparts.

Table 2 shows that after adjustment for covariates, aTRH remained significantly associated with risk of CVD (HR = 1.30, 95%CI: 1.19–1.42, $P < 0.0001$).

Sensitivity analyses of propensity score for adjusting multi-covariates and multiple imputation for estimates of missing values produced similar results as did the analysis involving exclusion of participants with uncontrolled BP on < 3 medications. When CHD was examined as the endpoint instead of CVD, the overall risk associated with aTRH was stronger (HR = 1.56, 95%CI: 1.29–1.89).

Table 3 shows individual and joint effects. Among women, aTRH was associated with a 64% increase in risk of CVD event (95%CI: 1.43–1.88), and a 13% increase in risk of CVD (95%CI: 1.01–1.27) among men. aTRH had a stronger impact on risk of CVD among younger subjects than it did among older (HR = 1.53, 95%CI: 1.32–1.77 In those aged < 65 , and HR = 1.18, 95%CI: 1.05–1.32 in those aged 65 and older). All HRs were statistically significant and the two-way multiplicative interaction terms of sex*aTRH, and age*aTRH and RERIs on risk of CVD were statistically significant ($P < 0.05$).

Results stratified by aTRH, age, and sex can be found in Table 4 and Figure 1. Females aged 65 and older with aTRH had the highest risk of CVD (HR = 2.61, 95%CI 2.20–3.01), followed by men < 65 years with aTRH (HR = 2.17, 95%CI: 1.76–2.58). The observed joint effect (HR = 1.85, 95%CI: 1.22–2.48) was less than expected for both additive and multiplicative models (HR = 4.10, 95%CI: 3.63–4.57 and HR = 4.88, 95%CI: 3.66–6.31 respectively). However, the three-way interaction term for sex, age and aTRH was not significant for CVD ($P = 0.28$), and CHD ($P = 0.42$).

DISCUSSION

The overall findings of the present study indicate that there is a positive association between aTRH and risk of CVD. Based on statistically significant two-way interactions of sex with aTRH, and age with aTRH, heterogeneous strata results, statistically significant RERIs, and differing observed and expected joint effects, this study highlights that the association between aTRH and risk of CVD is modified independently by sex and age on both the additive and multiplicative scales.

Although it appeared there was a potential three-way interaction such that sex may modify the interaction of age and aTRH, and vice versa that age may modify the interaction of sex and aTRH on CVD risk, testing for these three-way interactions were not statistically significant. The results suggest that the interaction of sex and aTRH, or of age and aTRH did not depend on the third factor. This finding adds new insights into the body of the literature, that sex and age independently modify the

Table 1 Baseline characteristics overall and by apparent treatment resistant hypertension status, *n* (%)

	Overall	Resistant hypertension		<i>P</i> value
		Yes	No	
Total	25516	2329 (9.1)	23187 (90.9)	
Treatment group				< 0.001
Chlorthalidone	11808 (46.3)	853 (36.6)	10955 (47.3)	
Amlodipine	6955 (27.3)	554 (23.8)	6401 (27.6)	
Lisinopril	6753 (26.5)	922 (39.6)	5831 (25.2)	
Race				< 0.001
White	15397 (60.3)	1272 (54.6)	14125 (60.9)	
African American	8808 (34.5)	953 (40.9)	7855 (33.9)	
Am. Indian/Alaskan Native	58 (0.2)	3 (0.1)	55 (0.2)	
Asian/Pacific Islander	312 (1.2)	26 (1.1)	286 (1.2)	
Other	941 (3.7)	75 (3.2)	866 (3.7)	
Hispanic	4485 (17.6)	204 (8.8)	4281 (18.5)	< 0.001
Sex				< 0.001
Male	13597 (53.3)	1333 (57.2)	12264 (52.9)	
Female	11919 (46.7)	996 (42.8)	10923 (47.1)	
Geographic region				< 0.001
East	3917 (15.4)	337 (14.5)	3580 (15.4)	
Midwest	4736 (18.6)	449 (19.3)	4287 (18.5)	
South	10603 (41.6)	1165 (50.0)	9438 (40.7)	
West	2635 (10.3)	254 (10.9)	2381 (10.3)	
Canada	461 (1.8)	33 (1.4)	428 (1.9)	
PR/VI	3164 (12.4)	91 (3.9)	3073 (13.3)	
Preventive HTN treat	23033 (90.3)	2242 (96.3)	20791 (89.7)	< 0.001
Obese	10604 (41.6)	1085 (46.6)	9519 (41.1)	< 0.001
History of MI or stroke	5499 (21.6)	498 (21.4)	5001 (21.6)	0.84
History of coronary revascularization	3016 (11.8)	327 (14.0)	2689 (11.6)	< 0.001
Type 2 diabetes	8975 (35.2)	1061 (45.6)	7914 (34.1)	< 0.001
left ventricular hypertrophy	5110 (20.0)	551 (23.7)	4559 (19.7)	< 0.001
History of CHD	5981 (23.6)	534 (23.2)	5447 (23.7)	0.61
Smoking status				< 0.001
Current	5491 (21.5)	423 (18.2)	5068 (21.9)	
Past	10394 (40.7)	992 (42.6)	9402 (40.6)	
Never	9631 (37.7)	914 (39.2)	8717 (37.6)	
Aspirin use	9084 (35.6)	922 (39.6)	8162 (35.2)	< 0.001
Estrogen use (in women)	2230 (18.7)	182 (18.3)	2048 (18.8)	0.84
Age (years) (mean ± SD)	66.6 ± 7.5	67 ± 7.5	67 ± 7.5	0.78
BMI (kg/m²) (mean ± SD)	29.7 ± 5.9	30 ± 5.9	30 ± 5.9	< 0.001
SBP (mm Hg) (mean ± SD)	146.0 ± 15.6	152 ± 15.1	145 ± 15.5	< 0.001
DBP (mm Hg) (mean ± SD)	84.0 ± 10.0	85 ± 10.6	84 ± 9.9	0.001
Cholesterol (mean ± SD)	215.7 ± 42.5	216 ± 44.8	216 ± 42.2	0.79

GFR	78.0 ± 19.3	75 ± 20.6	78 ± 19.2	< 0.001
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HTN: Hypertension; MI: Myocardial infarction; CHD: Coronary heart disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GFR: Growth factor receptor; PR: Puerto Rico; VI: United States Virgin Islands.

Table 2 Hazard ratios of apparent treatment resistant hypertension for cardiovascular disease risk and sensitivity analyses

	Model 1			Model 2			Model 3		
	HR	95%CI		HR	95%CI		HR	95%CI	
aTRH	1.51	1.39	1.64	1.49	1.37	1.62	1.3	1.19	1.42
Sensitivity analyses									
Propensity score							1.33	1.20	1.48
Multiple imputation sensitivity analysis							1.24	1.16	1.33
CHD							1.56	1.29	1.89
Without uncontrolled on < 3 drugs							1.3	1.18	1.44

aTRH: Apparent treatment resistant hypertension; HR: Hazards ratio; Model 1: Crude; Model 2: Adjusted for age and sex; Model 3: Adjusted for age, sex, region, race, body mass index, diabetes; GFR: Growth factor receptor, history of CHD, history of myocardial infarction (MI)/Stroke, history of coronary revascularization, baseline systolic blood pressure (BP), baseline diastolic BP, left ventricular hypertrophy, smoking status, baseline BP medication use, aspirin, lipid lowering trial. Propensity score weighting sensitivity analysis (model 3). Multiple imputation sensitivity analysis (model 3); CHD: Coronary heart disease-outcome CHD (fatal CHD or nonfatal MI, coronary revascularization, or hospitalized angina) (model 3).

Table 3 Joint effects for interaction of sex and apparent treatment resistant hypertension, and age and apparent treatment resistant hypertension on cardiovascular disease risk

		aTRH (No)		aTRH (Yes)		HR (95%CI) by sex
		HR	(95%CI)	HR	(95%CI)	
Sex	Female	Reference		1.67	(1.45, 1.91)	1.64 (1.43, 1.88)
	Male	1.25	(1.16, 1.34)	1.39	(1.12, 1.56)	1.13 (1.01, 1.27)
HR (95%CI) (M vs F)		1.25	(1.16, 1.35)	0.80	(0.66, 0.97)	
RERI (95%CI)		-0.52	(-0.75, 0.25)			
Interaction of sex and aTRH on CVD: $P < 0.0001$						HR (95%CI) by age
Age	< 65	Reference		1.56	(1.42, 1.71)	1.53 (1.32, 1.77)
	≥ 65	1.38	(1.31, 1.45)	1.61	(1.48, 1.73)	1.18 (1.05, 1.32)
	≥ 65 vs < 65	1.37	(1.28, 1.47)	1.05	(0.87, 1.27)	
RERI (95%CI)		-0.339	(-0.61, 0.06)			
Interaction of age and aTRH on CVD: $P = 0.0326$						

CVD: Cardiovascular disease; HR: Hazards ratio; aTRH: Apparent treatment resistant hypertension; F: Female; M: Male; RERI: Relative excess risk for interaction.

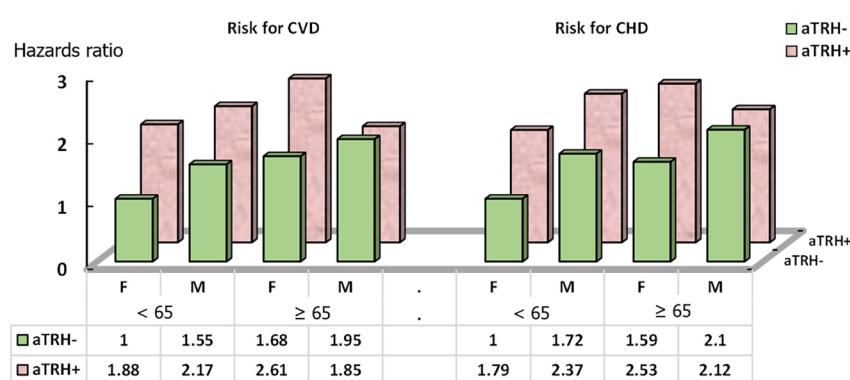
association between aTRH and CVD.

Treating BP becomes more difficult as a patient ages and is complicated by differing BP goals by age and a possible U-shaped relationship between BP and mortality among the elderly. Among this population also exists the risk of over-correcting and lowering BP too much which can cause other health concerns including dizziness and falls[2,30,31]. However, 2017 ACC/AHA changes to the guidelines no longer specify a different target BP for those ≥ 60 and the SPRINT study of older Americans indicated better health outcomes among those with more aggressive BP lowering targets (SBP 120 vs 140 mmHg)[32,33]. This area remains a topic of debate with more research needed on this

Table 4 Joint impact of age, sex, and apparent treatment resistant hypertension on cardiovascular disease and coronary heart disease risk

	Sex	Age	HR	(95%CI)
Risk for CVD				
aTRH				
No	Female	< 65	Reference	
No	Male	< 65	1.55	(1.43-1.67)
No	Female	65+	1.68	(1.56-1.79)
No	Male	65+	1.95	(1.70-2.20)
Yes	Male	65+	1.85	(1.22-2.48)
Yes	Female	< 65	1.88	(1.64-2.11)
Yes	Male	< 65	2.17	(1.76-2.58)
Yes	Female	65+	2.61	(2.20-3.01)
Three-way interaction of sex, age, and aTRH on CVD, $P = 0.2841$				
Risk for CHD				
aTRH				
No	Female	< 65	Reference	
No	Male	< 65	1.72	(1.57-1.86)
No	Female	65+	1.59	(1.44-1.74)
No	Male	65+	2.1	(1.77-2.42)
Yes	Male	65+	2.12	(1.28-2.97)
Yes	Female	< 65	1.79	(1.47-2.11)
Yes	Male	< 65	2.37	(1.82-2.92)
Yes	Female	65+	2.53	(1.98-3.08)
Three-way interaction of sex, age, and aTRH on CHD, $P = 0.4246$				

CVD: Cardiovascular disease; HR: Hazards ratio; aTRH: Apparent treatment resistant hypertension; CHD: Coronary heart disease.



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Figure 1 Joint effects of sex and age on the risk of cardiovascular disease and coronary heart disease by apparent treatment resistant hypertension status. CVD: Cardiovascular disease; CHD: Coronary heart disease; aTRH: Apparent treatment resistant hypertension; F: Female; M: Male.

unique population.

Research has shown that older women are more likely to adhere to medications and more likely to have their BP taken regularly, yet they appear to experience higher rates of uncontrolled hypertension [15]. Multiple mechanisms are believed to contribute to this increase in hypertension and uncontrolled hypertension in aging women including: Activation of the renin angiotensin system, obesity, activation

of sympathetic nervous system, and decline in estrogen levels[15,17,34]. Stress on the body due to hypertension is believed to be more severe in women than in men[35]. Coupled with gender biases in treatment and management of CVD symptoms and events, we can envision how uncontrolled hypertension and aTRH would lead to more adverse health outcomes in women than men, especially in an aging population[36,37]. The pathophysiology of aTRH is believed to be linked to blood volume and salt, and salt-sensitive hypertension increases in women post-menopause thus we would expect aTRH to be more prevalent among post-menopausal women[18,38,39].

Very few studies have examined potential effect modifiers on the relationship between aTRH and CVD. Our findings are consistent with existing research in that aTRH is positively associated with CVD and both sex and age independently can modify the association between aTRH and CVD[3-5,9,10]. However, these studies only examined relative measures of association. Our study both confirmed presence of two-way interaction on the multiplicative scale and also identified that this modification is present on the additive scale. Epidemiologists have noted that additive interaction is most important for public health as it indicates an absolute number of cases which would be prevented if the modifier were removed[22,40].

No study to date has examined potential three-way interaction with aTRH. With health effects of sex and age linked it is important to examine how these gender disparities in cardiovascular outcomes of patients with aTRH differ between subgroups of age[11,12]. Public health programs aimed at improving awareness of aTRH should make specific effort to target women and informing them of the dangerous health consequences associated. This study suggests that physicians should take special note in their treatment considerations when female patients are experiencing uncontrolled hypertension and understand the serious cardiovascular risks associated with developing aTRH. For example, because the interaction of age and aTRH on CVD did not change by sex, we would still endorse applying these recommendations to vigorously control aTRH in women of all ages instead of focusing on the older group only.

This study has several strengths. ALLHAT provides us with one of the largest datasets to test the impact of aTRH on CVD risk. Sample size is particularly important when analyzing effect modification as it utilizes subgroup analyses. We also deployed two methods (propensity score weighting and multiple imputation) to conserve power in our analyses. Similar findings from our original analysis and both sensitivity analyses indicate our study is adequately powered. Another strength provided by use of ALLHAT is in our classification of aTRH. BP was taken twice from a seated position and averaged for each study visit, medication adherence was maintained through pill counts at each study visit, and doses of antihypertensive medications were appropriately titrated up to the maximum tolerated dose prior to adding on an additional medication. All of these factors allow for accurate ascertainment of aTRH status and reduce the likelihood of false positives due to pseudoresistance[2-5].

While a strong study, there are also several limitations. As this study is limited to its analysis of variables collected in ALLHAT only, additional data could be included in the analysis. For example, dietary salt intake was not measured in ALLHAT, thus we could not adjust for this in multivariate models as it is suggested that aTRH is influenced by blood volume and salt intake[38,39]. However, because ALLHAT is a randomized clinical trial, potential unmeasured factors are balanced among the participants. The clinical trial nature of our data source, while a strength for validity of aTRH classification, is also a limitation as subjects were selected based on pre-determined criteria best fit for the goals of ALLHAT and thus further studies are needed to confirm the results among different study populations. The study participants consisted of older adults (≥ 55) and thus findings of the study in women should also be evaluated in women aged 55 and older, instead of interpreting the results to those aged < 55 . Additionally, the impact of pseudoresistance can never be completely removed and “white coat” effect is always a possibility when examining BP readings.

aTRH increases the risk of CVD in patients with hypertension and this relationship is modified by age and sex independently on both the relative (multiplicative) and absolute (additive) scales. More research is needed to shed further light on these gender differences, especially with regard to women both pre and post menopause. Future research should focus on these sex and age differences and how it might impact treatment and control of aTRH as there is still much unknown about this specific relationship. Management of aTRH should take a patient’s age and sex into consideration and more preventive interventions should be aimed at aging women as they represent the subgroup of aTRH patients with the highest combined risk of CVD.

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

ARTICLE HIGHLIGHTS

Research background

A Limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

Research motivation

aTRH is significantly associated with the risk of CVD. It is important to understand whether age and sex significantly modify this association. Findings of the study could add new evidence to the body of literature, and provide new insights into further mechanism studies.

Research objectives

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

Research methods

We applied an observational analysis study design using data from the United States Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT recruited participants ($n = 25516$) from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: Fatal or non-fatal myocardial infarction, coronary revascularization, angina, stroke, heart failure, or peripheral artery disease. Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction.

Research results

Of the total study participants, 5030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH [hazards ratio (HR) = 1.3]. Sex and age modified this relationship on both multiplicative and additive scales independently. Stratified by sex, aTRH was associated with a 64% increase in risk of CVD in women, and a 13% increase in risk of CVD in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged < 65 than it did in those aged ≥ 65 . Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed ($P < 0.05$). The observed joint effect of aTRH and ages ≥ 65 years in males was less than what was expected for both additive and multiplicative models, although three-way interaction of sex, age, and aTRH on the risk of CVD and CHD did not reach a statistical significance ($P > 0.05$).

Research conclusions

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age.

Research perspectives

Further studies are warranted to test these mechanisms.

FOOTNOTES

Author contributions: Nelson JT and Liu L contributed to the design and analysis of the study; Nelson JT prepared the written manuscript; Liu L critically reviewed and edited the manuscript.

Institutional review board statement: This study, using de-identified data from the National Heart, Lung, and Blood Institute, has been approved by Drexel University Institutional Review Board, No. 1608004781 (Principal Investigator: Longjian Liu).

Informed consent statement: This ALLHAT data is de-identified and publicly available for investigators to obtain through an IRB application process. Signed Informed Consent Forms are unavailable for the investigators conducting a secondary data analysis project.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The manuscript was prepared using ALLHAT Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI). We are not allowed to share this dataset. For those who are

interested in using this dataset, they need to apply for it from the NHLBI directly.

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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Impact of erythropoietin therapy on cardiorenal syndrome: A systematic review with meta-analysis

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Abstract

BACKGROUND

Heart and kidney dysfunction frequently coexist in patients with acute heart failure due to the overlap between these two organ systems. Cardiorenal syndrome (CRS) results from pathology occurring in the heart and kidneys along with the consequences of dysfunction in one organ contributing to dysfunction in the other and vice versa.

AIM

To evaluate the use of erythropoietin (EPO) in patients with CRS and its effects on hemoglobin (Hb), major cardiovascular (CV) events, and hospitalization rates.

METHODS

On February 24, 2022, searches were conducted using PubMed, MEDLINE, and EMBASE, and 148 articles were identified. A total of nine studies were considered in this systematic review. We assessed the included articles based on the National Heart, Lung, and Blood Institute quality assessment tools for controlled intervention and observational cohort or cross-sectional studies. An assessment of bias risk was conducted on the chosen studies, and data relevant to our review was extracted.

RESULTS

The systematic review of these studies concluded that most existing literature indicates that EPO improves baseline Hb levels and decreases myocardial remodeling and left ventricular dysfunction without reducing CV mortality. In addition, the effect of EPO on the hospitalization rate of patients with CRS needs

to be further studied since this relationship is unknown. Future studies, such as randomized controlled clinical trials and prospective cohort studies, should be conducted to enhance the literature on the potential of EPO therapy in patients with CRS.

CONCLUSION

Our systematic review suggests that EPO therapy may have a significant role in managing CRS. The review highlights the potential benefits of EPO in improving baseline Hb levels, reducing the risk of major CV events, improving cardiac remodeling, myocardial function, New York Heart Association class, and B-type natriuretic peptide levels. However, the effect of EPO treatment on hospitalization remains unclear and needs further exploration.

Key Words: Cardiorenal syndrome; Anemia; Cardiovascular disease; End-stage renal disease; Erythropoietin; Congestive heart failure

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Core Tip: Erythropoietin improves baseline hemoglobin levels and decreases the risk of major cardiovascular.

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INTRODUCTION

Many patients with heart failure also experience kidney dysfunction and vice versa, as these two organs are closely related in their functions. Cardiorenal syndrome (CRS) describes a pathophysiological disorder of the heart and kidneys, whereby dysfunction of one system may contribute to dysfunction of another[1]. An estimated 50% of patients with congestive heart failure (CHF), who have both reduced and preserved left ventricular ejection fraction, have an estimated glomerular filtrate rate (eGFR) of less than 60 mL/min/1.73 m²[2]. Even moderate renal insufficiency, defined as an eGFR less than 60 mL/min/1.73 m², is associated with an increased risk of cardiac failure, hospitalization, and all-cause mortality[2]. CRS was previously considered to indicate acute kidney injury resulting from acute cardiac disease; however, more recent research suggests that the relationship between these two organs is bi-directional, meaning either organ could be the primary culprit[1,3]. CRS is categorized into five categories: acute and chronic cardiorenal, acute and chronic nephrocardiac, and secondary cardiorenal syndrome[1,3]. Essentially, each sub-category of CRS describes the acuity and pathophysiology of cardiac and kidney dysfunction, how the two overlap, and the presence of other systemic disorders[3]. The most common subtype of CRS is type one (acute cardiorenal), with approximately 50% of patients diagnosed with this condition[4]. The risk factors associated with worsening renal function in CRS include existing chronic kidney disease, hypertension, history of heart failure, diabetes mellitus, coronary artery disease, ischemic cardiomyopathy, and history of acute kidney injury[4].

In addition, many studies have shown that kidney dysfunction in CHF is caused by poor renal plasma flow, which leads the kidneys to retain water and sodium, which in turn, allows for improved perfusion of all essential organs[1]. The presence of anemia can result in tissue hypoxia and peripheral vasodilation, resulting in lower blood pressure and renal blood flow, increased heart rate, stroke volume, renal vasoconstriction, and sodium and water reabsorption[5]. Poor renal blood flow causes increased release of renin, angiotensin, aldosterone, and antidiuretic hormone (ADH), further increasing renal vasoconstriction and sodium and water reabsorption[5]. Renin, angiotensin, aldosterone, and ADH are toxic to cardiac, renal, and endothelial cells, which results in dysfunction in these tissues[5].

Nevertheless, recent studies have revealed that kidney hemodynamic changes can occur independently of the heart's hemodynamic changes[1]. An initial response of the kidneys to CHF is to reduce renal plasma flow and eGFR, which results in a higher filtration fraction[1]. To maintain eGFR, both efferent arteriolar resistance and glomerular capillary hydrostatic pressure must be increased, severely impairing overall cardiac function[1]. Additionally, there is evidence of increased sodium reabsorption, specifically in the Loop of Henle, as well as activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) all play a role in the development of CRS[1,3]. Overactivation of the RAAS increases both preload and afterload, leading in the long-term to cardiac dysfunction.

The presence of anemia with kidney dysfunction has also been shown to exacerbate CHF's progression and increase the risk of morbidity and mortality[6]. Besides contributing to tissue dysfunction by potentiating hypoxia, anemia can also increase oxidative stress, which contributes to increased hyperdynamic blood circulation and heart failure development[6]. Hemoglobin (Hb) levels are less than or equal to 12 g/dL in approximately 40% of patients with CHF[5]. Moreover, anemia is more common in the elderly, diabetics, and patients with poor baseline cardiac and/or renal function [5]. Increasing Hb levels can limit the detrimental effects of oxidative stress on the kidney and cardiac function. In a study by Pagourelas *et al*[6], for every 1 g/dL increase in Hb, there was a 15.8% reduction in mortality and a 14.2% reduction in mortality plus hospitalization in patients with CHF[6]. Erythropoietin (EPO) is a hematopoietic growth factor, the major function of which is to stimulate the proliferation and differentiation of erythropoiesis. EPO treatment is an efficient approach to increase Hb levels in patients with CHF whose anemia is caused by reduced EPO production. EPO can also influence other cellular processes, such as cell integrity and angiogenesis[7]. EPO has been demonstrated to improve both renal and cardiac function. EPO can decrease marrow inflammation, which can reverse the myelosuppressive effects of cardiac dysfunction and coexisting uremia[6]. Furthermore, EPO may prevent myocardial ischemic injury in CHF patients by inhibiting the apoptosis of cardiac myocytes[6]. Iron therapy is unable to provide such effects on hematopoiesis due to the lack of hematological and immunological regulatory ability and its limited bioavailability[6].

It is of great significance to investigate the role of EPO in treating patients with CRS. Recombinant human EPO (rhEPO) is a drug routinely prescribed to treat anemia in patients with end-stage renal disease (ESRD), and rhEPO treatment has been demonstrated to be beneficial for improving patients' life quality and survival. It is reasonable to assume that rhEPO treatment is beneficial for patients with CRS. Given the high prevalence of CRS, searching for a treatment modality that can improve therapeutic responses is of high significance in clinical practice and will significantly decrease the mortality and hospitalization of CRS patients. Fewer hospitalizations would likely result in lower healthcare costs as well. Several studies are ongoing to examine the benefits of rhEPO treatment in patients with CRS. A two-part clinical trial conducted by the University of Alberta is currently examining whether treatment with EPO will increase cardiac performance and decrease renal disease progression in patients with CRS[8]. The failure to further investigate EPO for use in the treatment of CRS will result in the deprivation of a promising treatment option for many patients.

Through this systematic review, we aim to deepen our understanding of the role of EPO in managing CRS.

MATERIALS AND METHODS

Our article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9]. It was not registered as a systematic review and no separate protocol was written. On February 24, 2022, a literature search was conducted on PubMed, MEDLINE, and EMBASE databases. The literature search was conducted using the following search strategy consisting of medical subject headings (MeSH) terms and regular keywords: ("Cardio-Renal Syndrome"[Mesh] OR "cardio-renal syndrome" OR "cardiorenal" OR "cardiorenal syndrome" OR "CRS" OR "reno-cardiac syndrome" OR "renocardiac syndrome") AND ("Erythropoietin"[Mesh] OR "erythropoietin" OR "EPO" OR "epoetin alfa" OR "darbepoetin alfa" OR "colony-stimulating factors").

Subsequently, the search results were imported into the Covidence platform, which automatically removed duplicate articles. Two reviewers independently examined titles and abstracts as part of an initial screening, followed by a second screening of full-length articles. Conflicts in the selected articles were discussed directly between the two reviewers, and a conclusion was drawn after each conflict article's discussion. In the event that a conclusion could not be reached, a third reviewer was consulted to vote on the final decision. We included randomized controlled clinical trials, cross-sectional studies, prospective and retrospective case-control, and cohort studies exploring the use of erythropoietin in CRS management. The articles published up to February 24, 2022, were included. We excluded *in vitro* studies, animal studies, abstracts, case reports, case series, systematic reviews, and meta-analyses. Furthermore, we excluded articles in languages other than English.

Following this, a quality assessment was performed using the 2013 National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for controlled intervention studies and observational cohort or cross-sectional studies[10]. We included studies that scored 11 or higher on each quality assessment tool. Each study was then analyzed for obvious biases and confounding variables. Extrapolation of data was performed by one reviewer and displayed in a table (shown below). A qualitative analysis of the data was conducted following data extraction for the systematic review.

We performed a meta-analysis since there were a number of eligible studies. For studies included in the meta-analysis, an odds ratio (OR) was calculated. Due to the substantial heterogeneity in the concluded study, a random effects model was used for the meta-analysis. Meta-analysis was conducted using Review Manager 5.4.1 software. Meta-analysis studies with forest plots were included for the outcomes.

RESULTS

We selected 148 relevant articles from PubMed, MEDLINE, and EMBASE using an advanced search strategy combining MeSH terms and common keywords. We removed 11 duplicate articles. We screened 137 titles and abstracts before selecting 43 articles for full-text review. Of the 43 articles assessed for eligibility, 34 articles were excluded (7 were incorrect study designs, 3 were not retrievable, and 1 was an abstract). A total of nine studies were evaluated using the NHLBI quality assessment tools for controlled intervention studies and observational cohort studies or cross-sectional studies. Of the nine studies, six were randomized controlled trials, two were retrospective cohort studies, and one was a prospective cohort study. Articles that scored 11 or higher out of 14 on the assessment scale were considered high-quality articles, and therefore were included in the systematic review. Eight studies scored 11 points out of 14, whereas one study scored 12 points out of 14. A PRISMA flowchart of the reviewed literature and search strategies can be found in [Figure 1](#). [Table 1](#) summarizes the included studies and their statistical significance[11-19]. In addition, [Table 1](#) illustrates how each study was scored according to the NHLBI quality assessment tools.

There were two studies included in the meta-analysis[11,12]. Study results showed a nonsignificant decrease in all causes of hospitalization (OR = 0.93 [95% confidence interval (CI), 0.23, 3.72]; $P = 0.92$). There was a high level of heterogeneity among the included studies ($I^2 = 76\%$) ([Figure 2](#)). The asymmetry in the funnel plot indicates the existence of publication or selective reporting bias ([Figure 3](#)).

Elevated serum neutrophil-gelatinase-associated lipocalin (NGAL) is inversely correlated with baseline EPO levels, independent of renal function. Low-dose EPO treatment caused a moderate decrease in serum NGAL levels, therefore reflecting potential improvement in renal tubular damage.

DISCUSSION

Effects of EPO on Hb levels and predictors of EPO use

As expected, the majority of studies concluded that EPO therapy increased Hb levels in patients with CRS. Furthermore, it would be expected that lower Hb levels would be associated with a higher rate of EPO prescription. This was confirmed in a study by Jackevicius *et al*[12] that found EPO therapy to be inversely related to Hb levels, such that patients with lower Hb levels are more likely to be prescribed EPO. On average, Hb levels are found to increase approximately 6 wk after EPO treatment, at which point most patients experience symptomatic improvement[20]. The need for prolonged treatment was confirmed by Jie *et al*[16], who found that short-term EPO use (3 wk) did not result in any change in Hb levels in patients with CRS, whereas long-term EPO therapy (52 wk) resulted in a significant increase in both Hb and reticulocyte count. Further, the strongest predictors of EPO use include iron supplementation, markers of declining renal function, and patients taking hydralazine, nitrates, angiotensin II receptor blockers (ARBs), and/or aspirin concurrently[12]. Hydralazine and nitrates are typically prescribed to patients with heart failure once patients' renal function no longer permits RAAS inhibitor usage, at which point they are also far more likely to be prescribed EPO for advanced chronic kidney disease[12]. The temporal relationship is also important because hydralazine is a drug used to treat hypertension, and hypertension is a known side effect of EPO. No clear conclusions regarding aspirin or ARBs were drawn.

Likewise, in another study by Jie *et al*[18], EPO not only provided a significant rise in Hb levels compared to the non-EPO therapy but more interestingly, altered the monocyte transcriptomes that played a role in inflammation and oxidative stress. The increase in oxidative stress, in turn, increased the risk of cardiovascular (CV) events[18]. In this study, EPO's role in oxidative stress was found to be associated with improving Hb level and alterations in gene expression directly involved in the inflammatory response. The effects were, however, very variable and inconsistent between individuals. The authors were unable to demonstrate a beneficial non-hematopoietic effect of EPO, although no harmful effects were found[18].

Several studies have shown that Hb levels improve after sufficient treatment with EPO. Exogenous EPO stimulates erythropoiesis, which increases red blood cell production and Hb levels. By reducing the degree of anemia among patients with CRS, oxidative stress and inflammatory response can be reduced. As a result, anemia symptoms such as fatigue, malaise, weakness, and dizziness are also improved, thus enhancing patients' overall quality of life. Similarly, since the data presented clearly points towards increasing Hb levels, it is reasonable to expect that those suffering from symptomatic anemia would experience clinical improvement, likely prompting them to be compliant with EPO therapy. In our review, the degree of Hb improvement varied significantly between the studies that were analyzed, and it was highly dependent on the dose of EPO given and the frequency of EPO administration. There is still insufficient data to predict an individual's response to therapy.

EPO's effect on significant CV risk and mortality

The effect of EPO on CV mortality is at this time difficult to establish, considering the differences in outcomes reported by currently available studies[11,13-15]. The results of a randomized study by

Table 1 Summary of included studies

Ref.	Study design	No. of Patients	EPO dosage and treatment duration	Average Hb level (g/dL)			EPO's effect on			Other findings
				Before EPO therapy	After EPO therapy	Without EPO treatment	Hb level	Major CV event	Hospitalization rate	
Jackevicius <i>et al</i> [12], 2015	Retrospective cohort	2058	N/A	N/A	10.5	11.1	Inverse relationship between EPO therapy and Hb levels	N/A	N/A	The strongest predictors of EPO use include iron supplementation, markers of declining renal function, and patients concurrently taking hydralazine, nitrates, ARBs, and/or aspirin
Eisenga <i>et al</i> [13], 2019	Open-label, prospective, randomized trial	56	N/A	11.7	13.2	11.8	Increased Hb levels	Increased cFGFR23 and iFGFR23, increased risk of CV events and mortality	N/A	N/A
McMurray <i>et al</i> [14], 2011	Randomized trial	3847	N/A	N/A	N/A	N/A	N/A	Patients with CKD and anemia have an 11.2% higher risk for a major CV event. History of CHF was the highest-ranked predictor of future CV events, followed by age (hazard increase by 74% and 27%, respectively)	N/A	N/A
Fazlibegović <i>et al</i> [15], 2006	Prospective cohort	90	2000 to 6000 international units (I.U.) for 1-3 times per week, depending on the Hb level	8.7	10.1	N/A	Increased Hb levels	Improved functional ability of the myocardium, LV function, and quality of life	N/A	The average NYHA class before treatment with EPO was class II, with a range of I-IV; after treatment, the average class was I, with a range of I-II
Palazzuoli <i>et al</i> [11], 2007	A randomized, double-blind controlled study	51	6000 I.U. twice weekly	10.4	11.2	10.6	Increased Hb levels	Improved LV systolic function, LV remodeling, NYHA class, BNP levels, and quality of life compared to control group	N/A	N/A
Jie <i>et al</i> [16], 2011	Open-label randomized trial	65	N/A	7.5	8.4	6.9	Increased Hb levels with long term use	N/A	N/A	Reduced CD34+ KRD-EPC levels, which was associated with decreased vascular regenerative potential
Jackevicius <i>et al</i> [17], 2014	Retrospective cohort study	2058		10.5		11.1	Increased Hb levels	Increased risk of major CV and acute coronary syndrome events	Increased risk of an all-cause hospitalization rate	EPO use increases the risk of mortality
Jie <i>et al</i> [18], 2012	Randomized trial	30	50 I.U./kg once weekly	11.8	12.3	N/A	Increased Hb levels	Modest alteration in monocyte transcriptomes, indicating imprints of inflammation and oxidative stress. The increase in oxidative stress, in turn, increased the risk of CV events	N/A	Variable response in gene expression. Unable to conclude whether EPO improved hematopoietic effects in CRS patients with such gene mutations
Emans <i>et al</i> [19], 2013	Open-label prospective	62	50 I.U./kg once weekly		13.7	11.8	Increased Hb levels	N/A	N/A	Elevated serum NGAL is inversely correlated with baseline EPO levels,

randomized trial

independent of renal function. Low-dose EPO treatment caused a moderate decrease in serum NGAL levels, therefore reflecting potential improvement in renal tubular damage

ARB: Angiotensin II receptor blocker; BNP: B-type natriuretic peptide; cFGF: C-terminal fibroblast growth factor; CKD: Chronic kidney disease; CHF: Congestive heart failure; CRS: Cardiorenal syndrome; CV: Cardiovascular; EPO: Erythropoietin; EPC: Endothelial progenitor cell; Hb: Hemoglobin; iFGFR: Intracellular fibroblast growth factor receptor; LV: Left ventricular; N/A: Not applicable; NGAL: Neutrophil-gelatinase-associated lipocalin; NYHA: New York Heart Association.

McMurray *et al*[14] revealed that patients with both chronic kidney disease and anemia are at an increased risk of major CV events by 11.2%. In addition, a history of CHF was the strongest predictor of CV events in the future (hazard increased by 74%), followed by age (hazard increased by 27%)[14]. Moreover, a prospective cohort study involving EPO therapy ranging from 2000 to 6000 international units (I.U.) for 1-3 times per week found that EPO treatment concurrently with iron supplementation improved the functional ability of the myocardium, left ventricular (LV) function, and overall quality of life among patients with chronic forms of the cardiorenal syndrome[15]. Palazzuoli *et al*[11] also compared the efficacy of combination therapy with EPO and iron to iron alone in patients with cardiorenal syndrome with anemia. They found that concurrent EPO and iron supplementation improved LV systolic function, LV remodeling, New York Heart Association (NYHA) class, B-type natriuretic peptide (BNP) levels, and quality of life compared to a control group that took only oral iron [11]. Eisenga *et al*[13] found that EPO caused a significant increase in C-terminal FGF23 (cFGF23) and a smaller increase in intact FGF23 (iFGF23). A higher level of cFGF23 has been associated with increased risk of CV events and mortality; however, the underlying mechanism remains unknown[13].

As demonstrated in this review, the exact effects of EPO supplementation, with or without iron supplementation, are difficult to determine. Some studies have even suggested worse CV outcomes, whereas others did not show statistically significant differences in CV mortality. The effects on myocardial function and the reported quality of life appear more promising.

EPO's effect on hospitalization rates

Our review included studies on the effects of EPO therapy on hospitalization rates in patients with CRS. For example, a study by Jackevicius *et al*[17] found that EPO use was associated with an increased risk of all-cause hospitalization, major CV events, acute coronary syndrome, and mortality. The risk of hospitalization may be due in part to patients receiving EPO having a poor renal function and/or myocardial dysfunction, which places them at an increased risk of hospitalization even before receiving EPO. However, a study by Emans *et al*[19] showed that baseline EPO levels inversely correlated with serum neutrophil gelatinase-associated lipocalin (NGAL) levels, regardless of renal function, and that low-dose EPO treatment caused a moderate decrease in serum NGAL levels, reflecting a potential improvement in renal tubular damage. NGAL is a protein from the lipocalin family that inhibits bacterial uptake of iron and is a biomarker reflective of tubular damage as it can detect early-stage acute kidney injury[19].

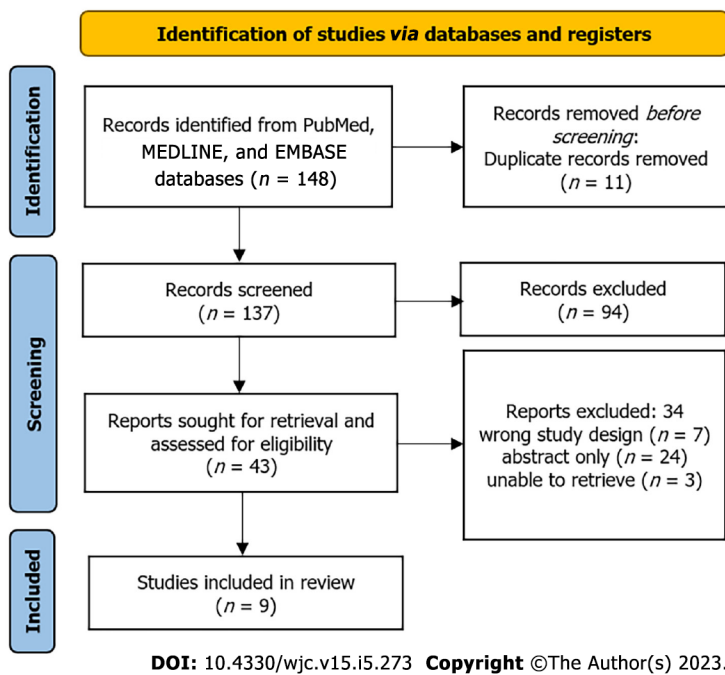


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for new systematic reviews, which included searches of databases and registers only.

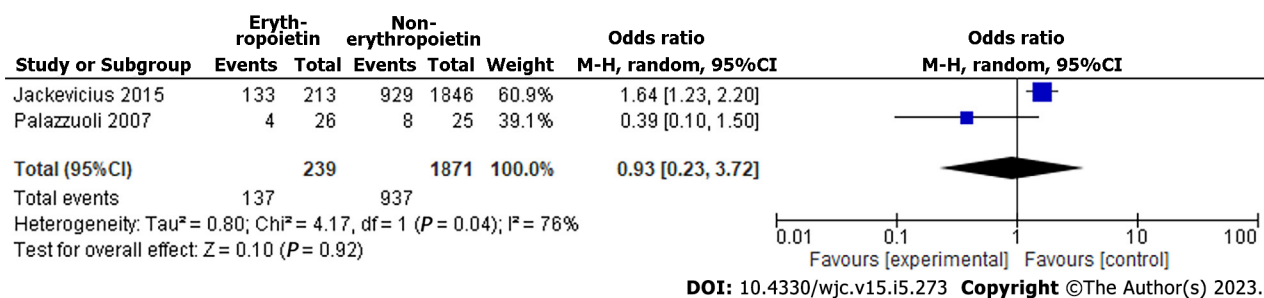


Figure 2 Forest plot of all causes of hospitalization of erythropoietin vs non-erythropoietin.

The effects of EPO treatment on the hospitalization rates of patients with CRS remain variable and should therefore be further investigated. Interestingly, EPO reduces NGAL levels, thereby minimizing renal tubular destruction and increasing iron availability. Therefore, this is likely to minimize hospitalization rates as well. The effect of EPO on renal tubular function should be further explored, as this is a potentially significant benefit of EPO therapy in patients with CRS and other renal conditions. For the time being, physicians should determine whether the potential benefits of EPO use in patients with CRS outweigh the risks.

In summary, this systematic review studied the overall significance of EPO when managing patients with CRS. The literature demonstrates that not only does EPO increase patients baseline Hb levels but it also lowers the risk of major CV events from occurring in patients with CRS. EPO improves the heart failure aspect of CRS by both improving cardiac remodeling and overall myocardial function, and by doing so, EPO is able to minimize the CV mortality as well. Moreover, the reviewed literature does not demonstrate a clear effect of EPO on hospitalization rates and hence this effect should be further analyzed in future studies. Lowering hospitalization rates would potentially decrease healthcare expenses and, more importantly, improve the quality of life of patients with this condition. In conclusion, the literature included in this review clearly demonstrates how EPO has several significant benefits when used to treat patients with CRS.

Strengths

The strongest aspect of this systematic review is that it primarily focused on randomized controlled clinical trials and cohort studies, which provide a more accurate description of the temporal sequence among exposure, EPO treatment, and CRS effects.

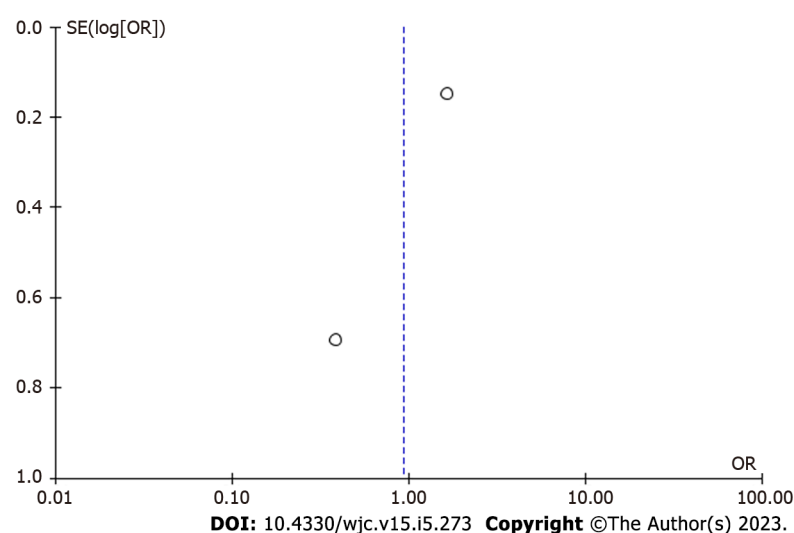


Figure 3 Funnel plot of all causes of hospitalization of erythropoietin vs non-erythropoietin.

Limitations

This systematic review had some limitations that should be highlighted. A limited amount of total data available regarding this topic increased the risk of publication bias. In addition, some articles discussing this topic had small sample sizes, raising the possibility of cognitive bias. Moreover, the articles were selected from three separate databases with a constriction of only selecting articles written in English.

Future directions

The literature regarding patients with CRS and the use of EPO therapy should be expanded with more randomized controlled clinical trials and prospective cohort studies. Moreover, since the protocols used for EPO administration varied significantly between studies, further research should be conducted regarding EPO's most optimal dosage and treatment duration. The effect on mortality does not appear to reach statistical significance at this time, which may change with a larger sample size. It is also important for further research to be performed examining the effects of EPO treatment on hospitalization rates, as this association remains unknown at this time due to insufficient data.

CONCLUSION

We conducted a systematic review to investigate the role of EPO in CRS management. The benefits of EPO therapy in patients with ESRD and CHF are well-established. Thus, it is highly likely that EPO would also be beneficial for patients with CRS. The literature review indicates that EPO improves baseline Hb levels and decreases the risk of major CV events in patients with CRS. The ability of EPO to improve cardiac remodeling, myocardial function, NYHA class, and BNP levels is significant since this will improve the heart failure aspect of CRS and, more importantly, lower the likelihood of death for patients who have this condition. Additionally, the effect of EPO treatment on hospitalization remains unclear and should be further explored as it would benefit patients and potentially reduce healthcare costs. Our review had a few limitations, including the possibility of publication bias, cognitive bias, and the possibility of missing some studies due to the criteria used for selecting articles. Additionally, future randomized controlled clinical trials would benefit the medical community in assessing the use of EPO in treating patients with CRS and specifically examine different EPO dosages and their effects on CV risk, mortality risk, and hospitalization rates. Since CRS is a prevalent condition, the discovery of an effective adjunctive treatment option will significantly affect the clinical outcome of patients with this condition.

ARTICLE HIGHLIGHTS

Research background

Cardiorenal syndrome (CRS) describes a pathophysiological disorder of the heart and kidneys, whereby dysfunction of one system may contribute to dysfunction of another. Many patients with heart failure also experience kidney dysfunction and vice versa, as these two organs are closely related in their functions. Poor renal plasma flow in congestive heart failure (CHF) causes the kidneys to retain water

and sodium, which allows for improved perfusion of all essential organs, leading to kidney dysfunction.

Research motivation

Anemia exacerbates CHF's progression and increases the risk of morbidity and mortality, and increasing hemoglobin (Hb) levels can limit the detrimental effects of oxidative stress on the kidney and cardiac function. Erythropoietin (EPO) treatment is an efficient approach to increase Hb levels in patients with CHF whose anemia is caused by reduced EPO production. Investigating the role of EPO in treating patients with CRS is of great significance as it could significantly decrease the mortality and hospitalization of CRS patients and lead to lower healthcare costs.

Research objectives

This systematic review evaluated the use of erythropoietin (EPO) in patients with CRS and its effects on Hb, major cardiovascular (CV) events, and hospitalization rates. The study aimed to deepen our understanding of the role of EPO in managing CRS and whether it can be a promising treatment option for many patients. The primary objective was to assess the efficacy of EPO therapy in improving cardiac and renal function in CRS patients.

Research methods

The article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The literature search was conducted on PubMed, MEDLINE, and EMBASE databases using a search strategy consisting of medical subject headings terms and regular keywords. Two reviewers independently examined titles and abstracts, followed by a second screening of full-length articles. Quality assessment was performed using the 2013 National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for controlled intervention studies and observational cohort or cross-sectional studies. A meta-analysis was performed using Review Manager 5.4.1 software, and meta-analysis studies with forest plots were included for the outcomes. *In vitro* studies, animal studies, abstracts, case reports, case series, systematic reviews, and meta-analyses were excluded. Furthermore, articles in languages other than English were excluded.

Research results

This study selected 148 relevant articles and narrowed them down to nine studies that were evaluated using the NHLBI quality assessment tools. The majority of the studies concluded that EPO therapy increased Hb levels in patients with CRS and reduced anemia symptoms such as fatigue, malaise, weakness, and dizziness. However, the degree of Hb improvement varied significantly between the studies and was highly dependent on the dose and frequency of EPO administration. The effect of EPO on CV mortality is difficult to establish as different studies have reported varying outcomes. EPO use was associated with an increased risk of hospitalization, major CV events, acute coronary syndrome, and mortality in some studies. However, other studies found potential benefits of EPO on myocardial function and quality of life. The study's strength lies in its focus on randomized controlled clinical trials and cohort studies, while its limitations include publication bias and small sample sizes.

Research conclusions

The literature review provides evidence supporting the use of EPO therapy as a potential treatment option for patients with CRS. The benefits of EPO treatment in improving Hb levels, reducing major CV events, and improving cardiac remodeling, myocardial function, NYHA class, and BNP levels are significant, indicating a positive impact on the heart failure aspect of CRS and lowering the likelihood of death for patients. However, further studies are needed to investigate the effect of EPO treatment on hospitalization rates and potential side effects. Overall, the findings of this review suggest that EPO therapy may be a promising adjunctive treatment option for CRS, and more research is needed to confirm its effectiveness and optimize its use in clinical practice.

Research perspectives

In terms of future research perspectives, it is crucial to investigate the potential long-term effects of EPO therapy in patients with CRS. Since CRS is a chronic condition, examining the long-term effects of EPO treatment will provide valuable insights into its efficacy and safety. Additionally, future studies should explore the potential of combining EPO therapy with other treatments for CRS, such as angiotensin-converting enzyme inhibitors and beta blockers, to determine if combination therapy could improve clinical outcomes. Finally, future research should also aim to identify biomarkers that can predict a patient's response to EPO therapy, which would allow for more personalized treatment approaches.

FOOTNOTES

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Current role and future perspectives of artificial intelligence in echocardiography

Rafael Vidal-Perez, Julia Grapsa, Alberto Bouzas-Mosquera, Ricardo Fontes-Carvalho, Jose Manuel Vazquez-Rodriguez

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Abstract

Echocardiography is an essential tool in diagnostic cardiology and is fundamental to clinical care. Artificial intelligence (AI) can help health care providers serving as a valuable diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and interpretation of results. In addition, it can help expand the capabilities of research and discover alternative pathways in medical management specially on prognostication. In this review article, we describe the current role and future perspectives of AI in echocardiography.

Key Words: Echocardiography; Artificial intelligence; Machine learning; Deep learning; Prognosis

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Core Tip: Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence (*e.g.*, pattern recognition) by mimicking human thought processes. Echocardiography is an essential tool in diagnostic cardiology and is fundamental to clinical care. AI could help the health care providers by one side serving as a valuable diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and by the other side helping on the interpretation of results. The current role of this technique is described in this review and its future perspectives are covered through the text highlighting the obstacles and advantages expected on this implementation.

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INTRODUCTION

Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence by mimicking human thought processes[1]. The AI applications in cardiology are showing that not complex devices like electrocardiography (ECG) machine could generate big amounts of potential data transforming the ECG into a powerful tool for prediction[2].

On the same side, the use of AI techniques in cardiovascular imaging into the process of daily decision-making will enhance the delivery of care, and AI has been influencing in the last years every field of cardiac imaging in all phases from the beginning with acquisition to the last step of reporting[3-5]. But for sure it will be basic for the specialty that cardiologists retain the final step in the control of the system, take care of the decisions, and have the authority to amend algorithms in the cases that these get mistaken.

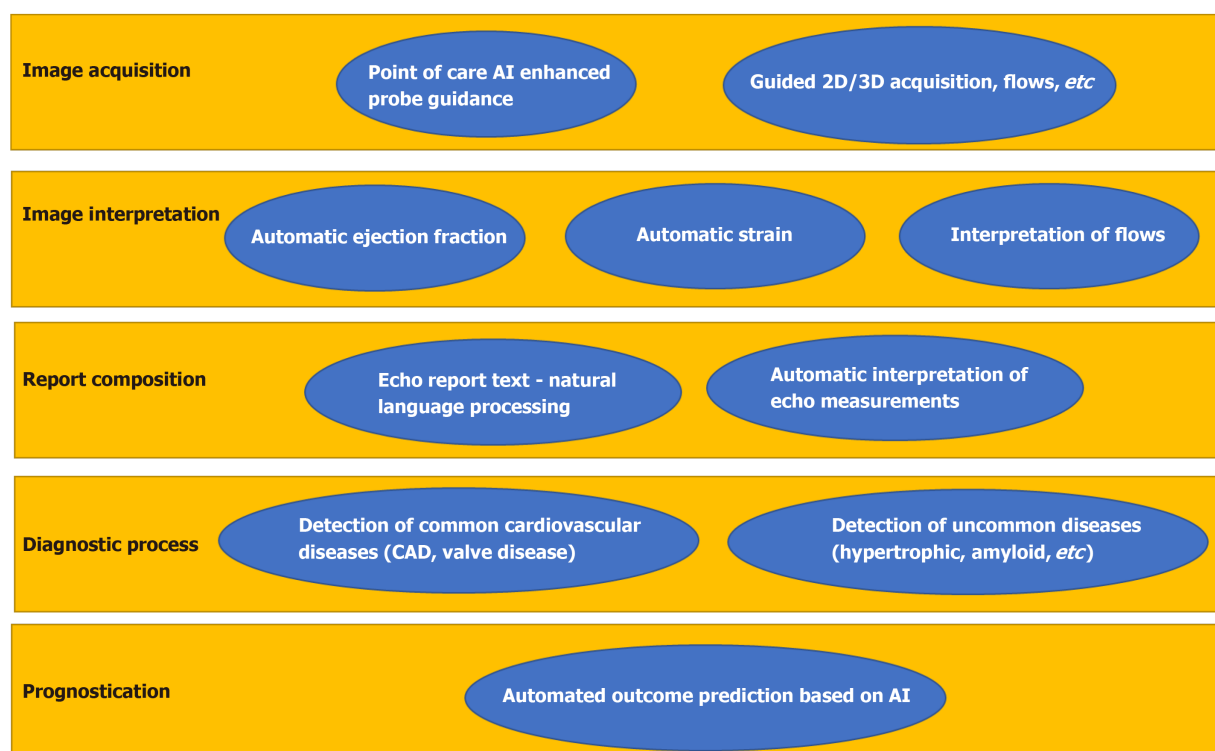
In radiology departments, the likely influence of AI on the imminent advance of this area of medical specialization is crystal clear. The use of computers to assist with radiologic image interpretation tasks is a practice that will endure for a considerable period, one example of this that we could see it on cardiothoracic imaging where the subset most commonly utilized in medical imaging is machine learning (ML) and the more complex deep learning (DL). Much scientific research has been done focusing on the use of ML for pattern recognition to identify and diagnose potentially a great amount of pathologies[6].

ML models based on AI are being applied quickly to the assessment of magnetic resonance or cardiac computed tomography (CT) as it is an independent tool completely different from the manual approach that the echocardiography needs. For echocardiography, the quality of the imaging obtained during the study is the most critical element for a good interpretation; however, for cardiac imaging with magnetic resonance or CT, the obtained imaging quality is seldom an issue as it is not obtained manually. The workforce for performing echocardiography will prevail for a long period of time as is needed to obtain good quality imaging in patients with adequate acoustic windows.

Echocardiography has a critical role in the diagnosis and management of patients that develop a cardiovascular disease. It allows for real-time imaging of the cardiac structures and fast detection of various anomalies[7]. Despite the large amount of echocardiographic interpretation and evaluation guidelines, the quantification and diagnosis are mainly based on a subjective review of the images obtained by 2- and 3-dimensional (3D) echocardiography, and due to this, we could say that echocardiography is still an error-prone and imperfect technique. Another element is that there exists a high level of inter-operator variation in the interpretation of echocardiography findings, which has been for ages a long-standing problem[8]. This inter-operator variation can lead to incorrect interpretations and diagnoses, especially when the poor-quality images obtained previously are interpreted. Furthermore, critical care specialists (cardiologist, intensivists, and anaesthesiologists) frequently have limited time to improve echocardiographic images and measurements in the critical care patients and have to make analyses quickly in unstable patients due to hemodynamic reasons. The need for fast, automated analysis of echocardiography data that are less dependent on operator effort is crucial for critical care scenarios.

Although the application of AI in echocardiography is still in its first steps to greater implementation, the use of this technology in the future has great potential and is presumed to support the improvement of the efficiency and accuracy of the manual tracing. The technology based on AI can help in a more standardized evaluation of echocardiographic images/videos to decrease human errors by producing automated, consistent, and accurate interpretations.

Current and future applications of AI in echocardiography are shown in Figure 1, and these applications of the AI technology in echocardiography go through multiple areas, including the process of image acquisition, the image interpretation tasks, text interpretation, performing diagnosis, and



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Figure 1 Current and future applications of artificial intelligence in echocardiography. AI: Artificial intelligence; CAD: Cardiovascular diseases; 2D/3D: 2 dimensional/3 dimensional.

prognosis evaluation.

CURRENT ROLE OF AI IN ECHOCARDIOGRAPHY

Imaging techniques like echocardiography have many advantages in relation with other techniques, and the main advantages of echocardiography include a wide availability, the potential portability, and nowadays the affordability that was not real before. However, when it comes to interpreting echocardiographic images, there is a notable level of variability among observers compared to other cardiovascular imaging techniques. In this regard, AI has the potential to play a valuable role by not only reducing observer variability but also enhancing diagnostic accuracy[9].

On the other hand, the utilization of AI in this field has been constrained by the intricate multi-view format of echocardiography and the indispensable requirement for human expertise in both image acquisition and interpretation. In daily clinical practice, this is mostly evident, as happened for new multidimensional imaging technologies that are not easily adopted, such as 3D echocardiography and speckle-tracking[1,5,10-17].

Image acquisition

In numerous clinical settings, echocardiography is not available because of an absence of qualified workforce. In these locations, nonexpert operators may perform limited exams [point-of-care ultrasound (POCUS)] using portable or handheld machines, but quality is no homogeneous, with risks for misleading and nondiagnostic imaging[18]. POCUS is commonly utilized in intensive care units; emergency departments; preoperative and outpatient clinics; and areas medically underserved, from rural areas of US to low- and middle-income countries to man operated space flights. POCUS also enabled frontline clinicians to acquire echocardiograms in patients with coronavirus disease 2019 during the pandemic, restricting the exposure of sonographers[19]. During this period, technology based on AI allowed acquisition of diagnostic-quality ultrasonographic studies by users with a minimal training in these locations, and data from one study showed this recently with novice users, demonstrating that they could obtain 10-view transthoracic echocardiographic studies of diagnostic quality using DL-based software[20] approved by the United States Food and Drug Administration[21], that guides the operator on the recording of the right views.

Image interpretation

In comparison with image acquisition technology, echocardiographic interpretation using AI has evolved in recent years based on a correct automated image interpretation and classification[22,23]. Several studies have confirmed and validated the use of AI for automated quantification of left ventricle and right ventricle volumes or ejection fraction, global longitudinal strain, and atrial size or function from both 2D and 3D acquisitions[23-31].

One of the notable applications of AI in the field of echocardiography is the assessment of myocardial thickening and endocardial excursion, which enables the detection of regional wall motion abnormalities (RWMA). This application holds great significance, particularly in managing ischemic coronary artery disease[9]. The assessment of RWMA typically relies on the visual interpretation of the operator, which is subjective and experience-dependent. This evaluation holds great importance, especially when assessing patients with chest pain in the emergency room. To mitigate the possibility of incorrect interpretations, AI models have been developed to detect and quantify RWMA, providing a more objective approach[3]. These ML and DL models exist, designed to evaluate RWMA and diagnose ischemic cardiomyopathy[32,33]. The sensitivity of RWMA evaluation models for automated diagnosis of ischemic heart disease is related to the area under the receiver-operating characteristic curve by AI algorithm. It should be remarked that AI algorithm "experience and expertise" are based on the available real-world datasets, that will have the same limits, such as the relatively higher ratios of wrong classification of the left anterior descending coronary artery perfusion territory described in the latest publications[33].

Report composition

The natural language processing algorithms have been created for large-scale extraction of the text data from echocardiographic reports; however, the widespread application has been limited due to the portability of each algorithm, with a potential degradation of algorithm performance when it is applied to an external data set[34,35].

Another step is the automatic interpretation of echo measurements that for sure is the next step for the automation of the echocardiography workflow. One good example of this strategy is the screening for valvular heart diseases (VHDs) using the data obtained through Doppler echocardiography video recordings automatically analyzed; the research of this interesting investigation created a three-step DL framework for the automatic screening of the echocardiographic videos for the detection of mitral regurgitation (MR) and stenosis (MS), and the detection of aortic regurgitation (AR) and stenosis (AS), and this DL algorithm categorizes the echocardiographic views, detects the presence of VHDs, and, when present, measures essential metrics related with the valvular severities. The DL algorithm was trained initially with 1335 exams, then was validated with 311, and finally was tested in 434 individuals using retrospectively selected studies from five hospitals. A prospectively collected set of 1374 consecutive echocardiograms was used later as the real-world data set for testing the algorithm. Disease categorization accuracy obtained was high, showing the following areas under the curve: 0.88 (95% confidence interval: 0.86-0.90) for MR; 0.99 (95% confidence interval: 0.97-0.99) for MS; 0.90 (95% confidence interval: 0.88-0.92) for AR; and 0.97 (95% confidence interval: 0.95-0.99) for AS in the prospective test data set[36].

Diagnostic process

In this aspect, a continuous progress has been made, and one of the first successful approaches was published by Zhang *et al*[23] that used a model based on DL to create a fully automated echocardiogram interpretation program, that included view identification (a kind of chamber view detection), image segmentation (detection of the different parts of the image), quantification of structure and function (automatic measurements), and disease detection (after the integration of prior data). By analyzing over 14000 echocardiographic studies, the algorithm achieved an impressive 96% accuracy in recognizing and distinguishing between various echocardiographic view classifications, such as parasternal long-axis and short-axis views. Furthermore, it demonstrated an accuracy ranging from 72% to 90% in accurately segmenting the image.

Additionally, the authors of the research presented that the algorithm for automated quantification of cardiac structure and function was similar to or even superior to the manual measurements across 11 internal consistency metrics, and that unexpectedly the convolutional neural networks were also successfully trained to detect hypertrophic cardiomyopathy, cardiac amyloidosis, and pulmonary artery hypertension, with a high accuracy. Even though the accuracy has not reached the level of the experts, the potential application of the DL models to echocardiography interpretation is a very promising tool for the detection of uncommon diseases.

Another important research is the one centered on common diseases like the potential automation of the detection of severe coronary artery disease with an echocardiographic system using AI. This innovation demonstrates the potential of validating an AI system for automating the analysis of stress echocardiography, thereby assisting clinicians in their interpretation. To achieve this, an automated image processing pipeline was developed to extract new geometric and kinematic features from a dataset of stress echocardiograms. The dataset was collected as part of a large, prospective, multicenter,

multivendor study conducted in the United Kingdom. Using the extracted features, a ML algorithm was trained to identify patients with severe coronary artery disease based on invasive coronary angiography. Through cross-fold validation, the algorithm achieved a satisfactory classification accuracy in identifying patients with severe coronary artery disease in the training dataset. It utilized 31 unique geometric and kinematic features and demonstrated a sensitivity of 84.4% and specificity of 92.7%. Importantly, this accuracy was also observed in the independent validation dataset from the United States. By providing automated classifications to clinicians during the interpretation of stress echocardiograms, this method has the potential to enhance accuracy, improve inter-reader agreement, and boost reader confidence in the near future[37]. Another area of research of great interest is the VHD for the acceleration of echocardiography workflows[36,38-40].

Prognostication

In the scientific literature, we could find nonrandomized studies on the use of AI in echocardiography to predict outcomes, going from the response to cardiac resynchronization therapy to in-hospital mortality[41-43]. Samad *et al*[44] employed an ML framework for the prediction of all-cause mortality combining the information from echocardiographic measurements and electronic medical information of 171510 patients. A random forest model was compared with a logistic regression model based on a range of analytic approaches employing echocardiographic and clinical variables to predict outcomes. The random forest models had a superior prediction accuracy (all areas under the curve > 0.82) over common clinical risk scores (areas under the curve = 0.69-0.79) and did better than logistic regression models ($P < 0.001$) on all survival durations[44].

FUTURE PERSPECTIVES OF AI IN ECHOCARDIOGRAPHY

For the prediction of the future, probably we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come.

The utilization of automated tracing and recognition of structures faces several limitations, as outlined in Table 1. However, ongoing advancements in this technology aim to address these limitations and enhance reproducibility and user experience. It is important to note that most studies have primarily focused on patients in sinus rhythm, with limited knowledge regarding the application of automation in patients with arrhythmia, significant conduction disease, and paced rhythm. Erroneous border tracings by the computer were found to be more prevalent in poor and fair-quality images, and the automated software did not function effectively in numerous cases. This poses a significant obstacle to the further development of this software. On the other hand, contour corrections appear to enhance the accuracy of automated analysis, resulting in a stronger correlation with cardiac MRI. However, this does increase the analysis time and may reduce workflow efficiency. In conclusion, the automation processes have demonstrated a favorable correlation with cardiac MRI volumes, as traditional 2D measurements have been shown to potentially underestimate chamber volumes[13].

Nowadays, most of the studies of AI in echocardiography are constructed with retrospective data and centered largely on the performance of AI in specific diagnostic tasks. These studies cover from small exploratory studies (like the 2017 study made by Sanchez-Martinez *et al*[45] with 55 patients) to larger studies (like the 2018 study created by Madani *et al*[22] evaluating > 200000 images or the 2021 study by Solomon *et al*[46] evaluating > 900000 echocardiography reports). There is a need for prospective studies to show the feasibility of the AI algorithms in the cardiovascular field[47], and the first AI-ECG prospective study based on DL (unsupervised system) has been recently published[48] showing that the study arm had increased diagnostic accuracy.

Nowadays, the utilization of AI in the field of echocardiography is characterized by a scarcity of randomized control trials. The objective of the Prospective Randomized Controlled Trial Evaluating the Use of Artificial Intelligence in Stress Echocardiography (ISRCTN15113915) trial is to evaluate the benefit of using an AI model for a complex modality like stress echocardiography. If we think how the upcoming studies in AI in echocardiography look like, we could affirm that it is likely that AI will be used for the assessment of diagnostic test performance in the field of the automatization of measurements and automatic interpretations of the set of images obtained during the echocardiographic studies. Nevertheless, future studies in the field of echocardiography will explore the capability of AI to identify diagnostic or prognostic insights that may elude human comprehension, as has been done for ECG exams, and AI has the potential to transform ECG into a tool that can accurately detect conditions that were previously undetectable using conventional methods[48].

As fresh data emerges in this field, it becomes crucial, without any hesitation, to establish a comprehensive plan and framework for integrating AI into daily clinical practice, including its incorporation into clinical practice guidelines. These guidelines should encompass various domains, undoubtedly encompassing the utilization of AI for diagnosis assistance as well as clinical management and prognostication. One indispensable aspect of these clinical guidelines is to provide clinicians with a curated body of evidence that they can be relied upon for patient care. This evidence must possess the following attributes: Validity, accuracy, generalizability, safety, and fairness. The initial step involves

Table 1 Current applications, strengths, and limitations of artificial intelligence in echocardiography

Applications of AI in echocardiography	Strengths	Limitations
View interpretation and classification	View identification and classification among thousands of images. Possibility of quantification of both structure and function. Possibility of disease diagnosis	Lack of learning process clarification. Possibility of imperfect classification. Image quality is often suboptimal, and nonstructural echocardiographic data need careful preprocessing by the specialist to build the definitive model. Non-standardized intermediate off-axis and continuously rotational and sweeping views, which can be clinically very helpful, even though of low technical quality, are difficult to be managed by AI models
Measuring anatomy and morphofunctional structure	Building a patient similarity model (<i>e.g.</i> , for predicting major cardiac events). Comparing automatic analysis between echocardiography and other imaging modalities	Possibility of suboptimal image quality. Possibility of limited number and representativeness of datasets. Current inferiority of automatic compared to semi-automatic software. Frequently inadequate standardization
Wall motion abnormalities detection	Reducing the potential operator-dependent misreading. Detecting different patterns of responses to stress. Possibility of integration with other technologies (<i>e.g.</i> , strain technology)	AI algorithms are based on the existing real world datasets, that bring with them the same limits and misclassification risks. Possibility of suboptimal images quality (which implies the exclusion of some acquisitions, hence limited authenticity). Presence of arrhythmias (difficult to be managed by AI models)

AI: Artificial intelligence.

promoting the standardization of study design and reporting when utilizing AI in conjunction with echocardiography. The CONSORT-AI initiative has already taken a pivotal stride in this direction, and it is recommended that this or similar standardized reporting formats be endorsed in all future studies [49].

ML has given us a greater ability to build predictive models, and now we are facing due to these advances a translational crisis[50]. Two studies found four essential stages in the process of creating a predictive model that could advance to a practical use: Development, validation, association with actual patient outcomes, and knowledge transition to a wide applicability[51,52]. They revised more than 800 predictive models for cardiovascular diseases previously published and found that a great part of them were improperly validated and only 0.1% were widely used finally in clinical practice.

One open question needs to be answered: Will the use of AI replace echocardiographers? Probably we could answer that not anytime soon. When considering the outcomes generated by AI, it is essential to interpret them in conjunction with the additional information obtained from echocardiography and stress testing. Nonetheless, AI holds promising potential for enhancing the reproducibility and efficiency of echocardiography. Cardiologists should make an effort to comprehend the AI tools and be ready to validate their effectiveness. For instance, the integration of AI into stress echocardiography should not be perceived as a threat but rather as an exceptional opportunity to further amplify the advantages of an already highly valuable test[53].

Considering the multitude of encouraging and promising outcomes, it begs the question why we have not implemented them in clinical practice. Should not our ethical obligation be to utilize every available resource to provide the best patient care? Or perhaps we doubt the authenticity of these findings? Alternatively, could it be that we are simply apprehensive about the potential threat to our roles if AI technology starts assuming some of our current tasks? Throughout human history, it has been demonstrated that our opinions hold little significance in the grand scheme of things. We may disagree with or even resist these technological advancements, but ultimately, they will prevail. Why? Because, in the long run, they prove to be beneficial for everyone involved[54].

Another concern that arises is how to address situations when there is a discrepancy between the machine and human opinions. As the accurate validation of algorithms holds immense importance, it is vital to underscore the necessity for it. While utilizing AI to supplement clinical decision-making, it is imperative for the physician to exercise their judgment while maintaining a degree of modesty. Unsupervised ML, specifically the advanced methods used in DL, may have limitations in terms of explanation ability (the ability to clarify how the algorithm produced its results). Despite these challenges, the potential of AI applications in healthcare is promising, and its capacity to enhance medical practices is remarkable.

CONCLUSION

Echocardiography is an essential asset in diagnostic cardiology and is really necessary to clinical care. AI is helping healthcare providers as a worthy diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and interpretation of results. Furthermore, it will help to expand the abilities of research and find alternative pathways in medical management specially

on prognostication. For sure many obstacles or barriers need to be broken to reach a whole integration of AI in the echocardiography lab workflow.

FOOTNOTES

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Basic Study

Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of *TDO2* as a potential therapeutic target

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Abstract

BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a high mortality rate. On this basis, exploring potential therapeutic targets to meet the unmet needs of IPF patients is important.

AIM

To explore novel hub genes for IPF therapy.

METHODS

Here, we used public datasets to identify differentially expressed genes between IPF patients and healthy donors. Potential targets were considered based on multiple bioinformatics analyses, especially the correlation between hub genes and carbon monoxide diffusing capacity of carbon monoxide, forced vital capacity, and patient survival rate. The mRNA levels of the hub genes were determined through quantitative real-time polymerase chain reaction.

RESULTS

We found that *TDO2* was upregulated in IPF patients and predicted poor prognosis. Surprisingly, single-cell RNA sequencing data analysis revealed significant enrichment of *TDO2* in alveolar fibroblasts, indicating that *TDO2* may participate in the regulation of proliferation and survival. Therefore, we verified the upregulated expression of *TDO2* in an experimental mouse model of transforming growth factor- β (TGF- β)-induced pulmonary fibrosis. Furthermore, the results showed that a *TDO2* inhibitor effectively suppressed TGF- β -induced fibroblast activation. These findings suggest that *TDO2* may be a potential target for IPF treatment. Based on transcription factors-microRNA prediction and scRNA-seq analysis, elevated *TDO2* promoted the IPF proliferation of fibroblasts

and may be involved in the P53 pathway and aggravate ageing and persistent pulmonary fibrosis.

CONCLUSION

We provided new target genes prediction and proposed blocking TGF- β production as a potential treatment for IPF.

Key Words: Idiopathic pulmonary fibrosis; Lung function; Overall survival; Transforming growth factor- β ; *TDO2* inhibitor

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Core Tip: This study is unique in several aspects: (1) We identified six hub genes for idiopathic pulmonary fibrosis (IPF) and determined through quantitative real-time polymerase chain reaction; (2) Multi-omics analysis proved that *TDO2* was upregulated in IPF patients and promoted the IPF proliferation of fibroblasts; (3) *TDO2* may be involved in P53 pathway and aggravate aging and persistent pulmonary fibrosis; and (4) *TDO2* inhibitor effectively suppressed transforming growth factor- β -induced fibroblast activation.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease characterized by exertional dyspnoea and diminished lung function. Its progression seriously affects the quality of life of patients, leading to respiratory failure and death in severe cases. In addition, IPF is a fatal disease characterized by abnormal lung epithelial cells and excessive accumulation of lung interstitial matrix [1]. Clinical symptoms are usually progressive and manifest as shortness of breath, dry cough, and dyspnoea. Smoking exacerbates the loss of lung function in patients with IPF [2]. In addition to smoking, other factors, including viral and bacterial infections, genetic factors, age and sex, have different effects on IPF patients [3-7]. IPF mainly occurs in male patients and may develop earlier in men than in women for various biological reasons [8]. In terms of age, IPF predominantly affects elderly individuals, and its prevalence increases with age [9]. These microinjuries induce abnormal epithelial-fibroblast communication [10,11]. Moreover, slight injuries induce matrix-producing myofibroblasts and the accumulation of extensive extracellular matrix (ECM) with remodelling in the lung interstitium [12].

The median annual survival after the diagnosis of IPF is 2 to 3 years [13]. Although two antifibrotic drugs (pirfenidone and nintedanib) are currently available, they can only slow the progression of the disease instead of curing IPF [14]. There is no effective treatment for the illness, and a major need for new therapies has not been satisfied [15]. Therefore, identifying and intervening in key genes of IPF and exploring new therapeutic approaches are essential. The diagnosis of IPF usually requires respiratory physicians, radiologists, and pathologists to review various clinical features, imaging results, and biopsy results of patients in a group discussion to arrive at the final diagnosis. Standard imaging assessment of IPF with high-resolution computed tomography provides diagnostic and predictive information [16]. The degree of fibrosis and cellularity correlated with forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO), as well as predicted mortality, can be observed. The most common indicators of lung function associated with prognosis are total vital capacity, FVC, and DLCO [17,18]. The decreases in FVC and DLCO in IPF patients reflect disease progression and predict mortality [19,20].

Previous studies on IPF still need to be extended, and further identification of additional gene-targeted therapies for IPF remains challenging. In this study, several novel genes were investigated to explore the treatment of IPF. We adopted quantitative real-time polymerase chain reaction (qRT-PCR) to identify common hub genes in multiple sets of IPF data and discussed the correlation between these genes and lung function and the overall survival rate. Afterwards, a hub gene, *TDO2*, was used as an example to demonstrate the expression level. This gene was increased in IPF and validated by western blotting. After inhibitor treatment, transforming growth factor- β (TGF- β)-induced fibroblast activation was effectively inhibited.

MATERIALS AND METHODS

Data collection and preprocessing

All raw data in this study were retrieved from the Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>). GSE53845 (platform: Agilent microarray GPL6480) consists of lung tissues from 8 healthy subjects and 40 IPF patients[21]. In GSE47460[22], only samples with IPF from the interstitial lung disease population were included. The Agilent GPL14550 platform consists of 91 normal and 122 IPF samples, and the Agilent GPL6480 platform consists of 17 normal and 38 IPF samples. There were 110 men and 50 women with IPF, of whom 58 had never smoked, 96 had smoked, 2 were current smokers and 4 had an unclear smoking status. The age range of individuals with these IPF data was 37 to 82 years. GSE24206 (platform: Affymetrix GPL570) consists of 6 healthy and 17 IPF samples[23]. GSE110147 (platform: Affymetrix GPL6244) consists of 11 normal and 22 IPF samples[24]. The GEOquery package[25] was used to download the series matrix files of the databases above in R (v4.0.2). Soft formatted family files were downloaded to correctly map the probe ID to the gene symbol. GSE136831 contains lung tissue from 32 IPF and 28 control patients.

Differentially expressed gene screening

We screened differentially expressed genes (DEGs) between IPF patients and controls using the R package of the Microarray Data Linear Model (limma, version 3.50.3)[26]. The significant DEGs were identified according to the thresholds of adjusted $P < 0.05$ and fold change (FC) > 1.5 . The common DEGs in the datasets were visualized by ggVennDiagram[27].

Functional and pathway enrichment analyses

Gene Ontology (GO) enrichment analyses of hub genes were performed by the clusterProfiler package with a background set of all Entrez IDs mapped to a GO pathway[28]. There are three functional categories, specifically biological processes (BPs), cell components (CCs), and molecular functions (MFs). Because GO is organized in a parent-child structure, a parent term can have a large percentage of overlap with its child terms. Concerning this problem, a simplified approach in the clusterProfiler implements was used. The organism reference was set as "org.Hs.eg.db". The terms meeting $P < 0.05$, p AdjustMethod = "BH" and P adjust < 0.05 were selected. Enrichment analyses of the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome were performed using Database for Annotation, Visualization and Integrated Discovery (DAVID)[29]. After Benjamini-Hochberg adjustment, terms meeting $P < 0.01$ were selected.

Protein-protein interaction network establishment and hub gene exploration

The protein-protein interaction (PPI) network of identified DEGs was built using the Search Tool for the Retrieval of Interacting Genes (STRING, <https://string-db.org>, v11.5) to determine the functional interactions between the products of the key genes. The condition for constructing the PPI network was an interaction combined score > 0.4 . The interaction information network was downloaded and visualized through Cytoscape software (v3.9.1). The Molecular Complex Detection (MCODE) plugin was applied to select the significant subnetworks from the PPI network (degree cut-off ≥ 2 , node score cut-off ≥ 0.2 , K-core ≥ 2 , and max depth = 100, score ≥ 3)[30]. The hub genes were identified through a plugin from Cytoscape named cytoHubba[31]. The cytoHubba plugin quantifies the importance of nodes in biological interaction networks through 11 node ranking methods. Five of these methods were adopted in this study: Degree, maximum neighbourhood component (MNC), density of maximum neighbourhood component (DMNC), maximal clique centrality (MCC), and edge percolated component (EPC). The top 30 Hubba nodes were ranked by these methods, and common hub genes were taken as the true final hub genes.

Overall survival analyses

Disease status, survival days, age, and survival status were extracted from GSE70866[32]. Clinical data from 176 IPF-diagnosed cases were used to analyse survival changes in specific genes in IPF. According to the mRNA expression from one of the hub genes, IPF patients were divided into high-expression (upper tertile) and low-expression (lower tertile) groups. The survival analysis of hub genes was performed in R using the functions "survfit" and "coxph" of the "survival" package. Survival curves were generated using the "ggsurvplot" function of the "survminer" package. The final results were visualized by ggplot2[33].

Clinical correlation

Several factors, including age, sex, smoking history, carbon monoxide diffusion capacity (DLCO), and FVC, have been identified as predictors of poor survival in IPF patients[34]. Varying degrees of decline in FVC and DLCO predict higher mortality in patients with IPF[35]. In this study, clinical metadata were analysed using clinical datasets of GEO accession No. GSE47460[22]. Linear models were created for selected gene expression and clinical variables such as DLCO and FVC percentage using the lm function in the R stats package. Scatterplots were made using the ggscatter function in the ggpubr package. The

Pearson correlation coefficient and significance were calculated in R using the `stat_cor` function in the `ggpubr` package.

Prediction of target microRNAs

We used three online microRNA (miRNA) databases (miRWalk, DIANATools, and miRDB) to predict miRNAs of hub genes with the default parameters. The miRNA was selected if it targeted a gene in all three databases. Subsequently, Cytoscape was used to construct the mRNA-miRNA coexpression network.

Transcription factors-miRNA prediction

Both miRNAs and transcription factors (TFs) are important in gene transcription and expression. Thus, clarifying the regulatory relationship between miRNAs and mRNAs and discovering key TFs can provide more insight into the pathological mechanisms of IPF. The "Enrichment analysis" module in TransmiR v2.0[36] was used to identify significant TFs that may regulate the list of miRNAs targeting TDO2.

Mouse model of Bleomycin-induced pulmonary fibrosis

SPF C57/6J mice were purchased from Beijing Weitonglihua Experimental Animal Co., Ltd. This experiment was approved by the Experimental Animal Welfare Ethics Review Committee of Henan University of Traditional Chinese Medicine (Review No. DWLL202110014). Mice were fed for one week in an SPF barrier environment in the Animal Experimental Center of Henan University of Chinese Medicine. Mice were randomly divided into two groups. For the phosphate-buffered saline (PBS) group, mice were intratracheally administered 50 μ L of saline at Day 0. All mice were subjected to an anaesthesia experiment with a small animal anaesthesia machine (Ruiwode Life Technology Co., Ltd., Shenzhen, China). The light source was fixed at the pharyngeal skin, and the surgical instrument was fully exposed to the pharynx. At this time, a bright spot could be observed to open and close continuously with the spontaneous respiration of mice, and a tracheal intubation was inserted into the bright spot. For the Bleo group, mice were given intratracheal instillation of 50 μ L of bleomycin (5 mg/kg). On Day 21, mice were euthanized by intraperitoneal injection of excessive pentobarbital sodium. Lung tissue was homogenized in TRIzol (Invitrogen) and stored at -80 °C for subsequent RNA isolation.

Cell culture and treatment

The A549 cell line and IMR-90 cell line were purchased from ATCC. A549 cells were cultured in F-12K medium (Boster Biological Technology) containing 10% foetal bovine serum (FBS), 100 U/mL penicillin, and 100 μ g/mL streptomycin. IMR-90 cells were cultured in DMEM (Biological Industries) containing 10% FBS, 100 U/mL penicillin, and 100 μ g/mL streptomycin. The MLE-12 cell line was purchased from the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). MLE-12 cells were cultured in DMEM/F-12 medium (Corning) containing 10% FBS, 100 U/mL penicillin, and 100 μ g/mL streptomycin. A549, MLE-12, and IMR-90 cells were incubated in a humidified incubator with 95% air and 5% CO₂ at 37 °C. A549 cells, MLE-12 cells, and IMR-90 cells were seeded in six-well plates and cultured overnight. Cells were treated with TGF- β (10 ng/mL) for 24 h[37] and then exposed to 680C91 (20 μ m) for 24 h.

Quantitative real-time polymerase chain reaction assay

Primers were designed using PrimerBank (<https://pga.mgh.harvard.edu/primerbank/index.html>) and synthesized by Sangon Biotech Co., Ltd. (Shanghai, China). Total RNA was extracted using RNAiso Plus (TaKaRa) according to the manufacturer's instructions. Reverse transcription (RT) was performed using HiScript® II Q RT SuperMix for qPCR (Vazyme, Nanjing, China). The reactions were performed using a QuantStudio 6 real-time fluorescence quantitative PCR System (Life Technologies, Singapore). The procedure was detailed as follows: Lung tissue was homogenized on ice with TRIzol. After complete homogenization, the homogenized solution was allowed to settle at room temperature for 5 min. The homogenate was then mixed with 200 μ L/mL chloroform, allowed to stand at room temperature for 3 min and then centrifuged at 12000 $\times$ g for 15 min at 4 °C to separate the phases. The aqueous RNA phase was removed and dispensed into a new 2 mL microcentrifuge tube. The upper aqueous phase (RNA solution) was transferred to a new EP tube, mixed with isopropyl alcohol equal to the supernatant, and placed at 12000 $\times$ g for 10 min at 4 °C, and the supernatant was discarded. Then, 75% ethanol was added to 1 mL/mL TRIzol and gently shocked at 4 °C and 12000 $\times$ g for 10 min, and the supernatant was discarded. The pellets were allowed to air dry for approximately 5 min and then dissolved in DEPC water to measure the RNA concentration. The TOYOBO ReverTra Ace qPCR RT Kit was used for RT. RNA was incubated for 10 min at 65 °C and immediately placed on ice. The RT reaction contained 1 μ g of RNA, 2 μ L of 5 $\times$ RT Buffer, 0.5 μ L of RT Enzyme Mix, 0.5 μ L of Primer Mix, and up to 10 μ L of DEPC water and was subsequently incubated at 37 °C for 15 min and 98 °C for 5 min. The values of the target genes were normalized using the 2^{- $\Delta\Delta$ CT} method with the values of the housekeeping gene 18S. Technical repeats were performed three times. Notably, all mRNA levels are expressed as the mean $\pm$ SD.

Western blot assay

After treatment with TGF- β and 680C91, cells were lysed with RIPA buffer in ice. Protein samples of equal concentrations were separated using a 10% SDS-PAGE gel and electrotransferred onto PVDF membranes. Membranes with proteins were blocked with 5% skim milk, followed by incubation with primary and secondary antibodies. *TDO2* (Cat No.:15880-1-AP), α -smooth muscle actin (α -SMA) (Cat No.:14395-1-AP), COL-I (Cat No.:14695-1-AP), and GAPDH (Cat No.:10494-1-AP) were detected using the Bio-Rad Imaging System. These antibodies were purchased from Proteintech Group, Inc.

Statistical analysis

Independent-samples t tests were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, United States), and $P < 0.05$ was considered significant. Pearson's correlation coefficient r was calculated using the R function `stat_cor`.

RESULTS

Identification and enrichment analysis of DEGs

Four sets of raw GEO data (GSE53845, GSE47460, GSE24206, and GSE110147) from five platforms were used to analyze the DEGs between the normal and IPF groups. Data sources are summarized in [Supplementary Table 1](#). After background correction and data standardization, DEGs were determined between IPF and normal lung tissues. DEG analysis was performed by the R package "limma". Based on the threshold of adjusted $P < 0.05$ and $FC > 1.5$, 2157 DEGs were identified in GSE53845, 2861 DEGs were screened out from GSE47460 under the GPL6480 platform, 2113 DEGs were obtained in GSE47460 under the GPL14550 platform, 2525 DEGs were detected in GSE24206, and 7146 DEGs were selected in GSE110147. Venn analysis showed that the DEGs of GSE110147 had less than 50% consistency with other datasets ([Supplementary Figure 1](#)). Therefore, GSE110147 was discarded in subsequent analyses. A total of 254 common genes were screened by intersecting the remaining four DEG datasets ([Figure 1A](#)).

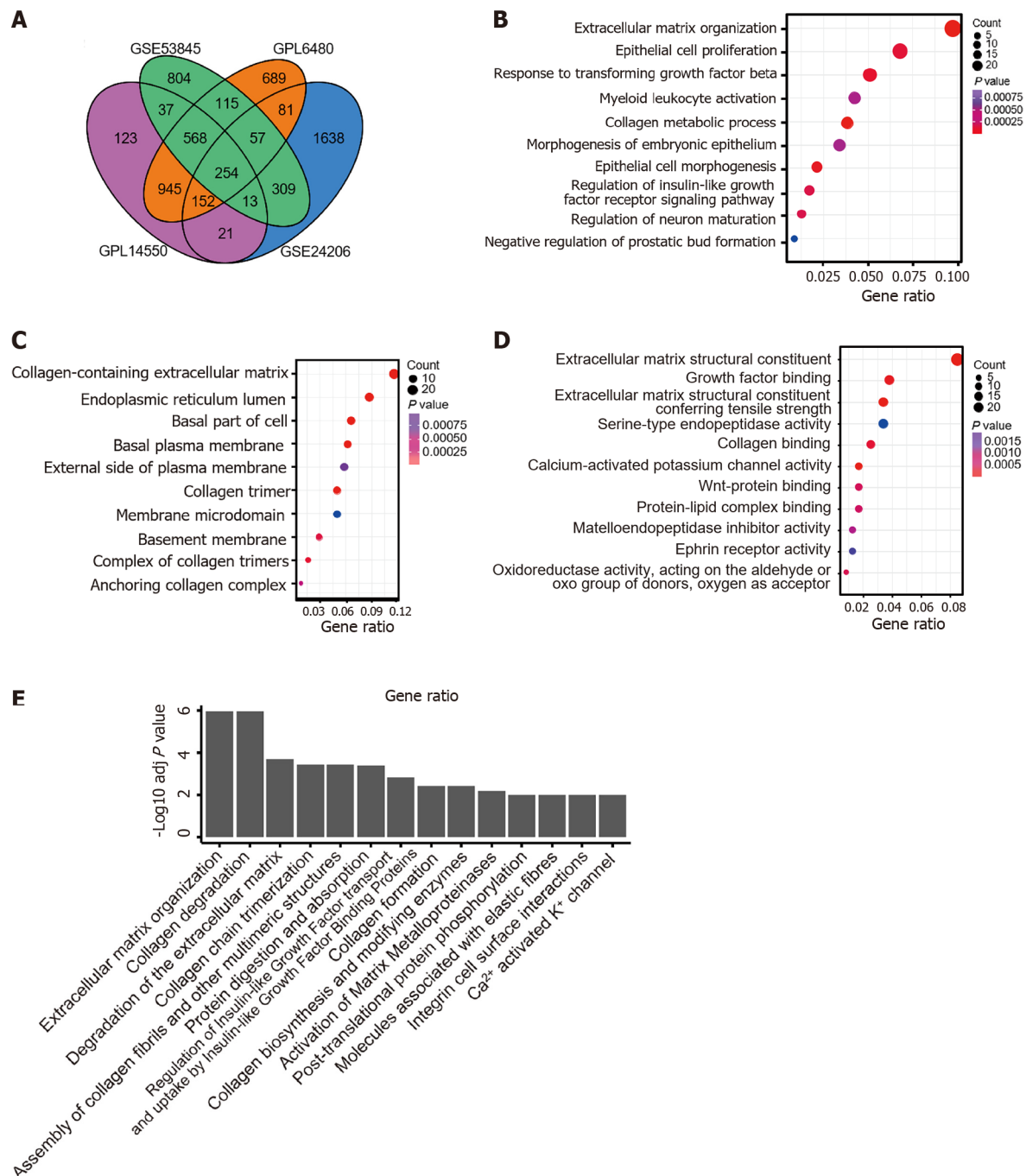
The biological roles and functional pathways of the 254 DEGs were revealed by GO enrichment analysis. The three functional categories were BPs ([Figure 1B](#)), CCs ([Figure 1C](#)), and MFs ([Figure 1D](#)). The results showed that DEGs were significantly involved in "extracellular matrix organization", "response to transforming growth factor beta", "regulation of insulin-like growth factor receptor signalling pathway", "regulation of neuron maturation", "collagen-containing extracellular matrix", "extracellular matrix structural constituent", "serine-type endopeptidase activity", "calcium-activated potassium channel activity", and "Wnt-protein binding". The results of the KEGG and Reactome pathway analyses ([Figure 1E](#)) identified by DAVID showed that the DEGs were significantly correlated with "extracellular matrix organization", "collagen degradation", "regulation of insulin-like growth factor transport and uptake by insulin-like growth factor proteins", and "molecules associated with elastic fibres".

PPI network analysis and identified hub genes

For further elucidation of the interaction of common DEGs, interaction networks were constructed using STRING (STRING v11.5, <https://string-db.org/>). The TSV file containing information on PPI network interactions was downloaded and visualized by Cytoscape (V3.9.1). The network included 69 nodes and 59 edges, with an average number of neighbours of 2.0. The MCODE plugin in Cytoscape was used to detect the most significant hub gene modules and cluster scores under the default parameters. Three modules were identified with the MCODE plugin ([Supplementary Figure 2](#)) according to the following filter criteria: Cluster 1 (score: 4.000, 4 nodes and 6 edges), Cluster 2 (score: 4.000, 4 nodes and 6 edges), and Cluster 3 (score: 3.000, 3 nodes, and 3 edges). Afterwards, five algorithms (MCC, DMNC, MNC, Degree, and EPC) were used to identify hub genes in the cytoHubba plugin ([Figure 2A-E](#)). The top 30 genes in each algorithm were considered hub genes ([Supplementary Tables 2-6](#)). Finally, 15 genes were detected in all five algorithms: *RET*, *TGFB3*, *HSD17B6*, *SULF1*, *ASPN*, *SDR16C5*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNMB4*, *AOX1*, *KCNN3*, and *KCNN4* ([Figure 2F](#)).

Correlation between gene expression and lung functions

The above analysis showed significant enrichment of genes in epithelial cell proliferation. We expect a variety of candidate targets that can be used to treat IPF. Combined with the results of GO molecular functional enrichment analysis, these findings showed that tryptophan 2,3-dioxygenase activity and amino acid binding were significantly enriched ($P < 0.05$), and *TDO2* was involved in these pathways. [Figure 1D](#) does not show this pathway because it was not ranked high enough. Moreover, in conjunction with the query results from DGIdb (https://dgidb.org/search_categories), which indicated that *TDO2* has a potential drug effect, these data were added to the downstream analysis. Moreover, *TDO2* has been confirmed to promote tumour cell proliferation and differentiation in the progression of oesophageal squamous cell carcinoma[38]. No relevant studies have been reported on the role of *TDO2*

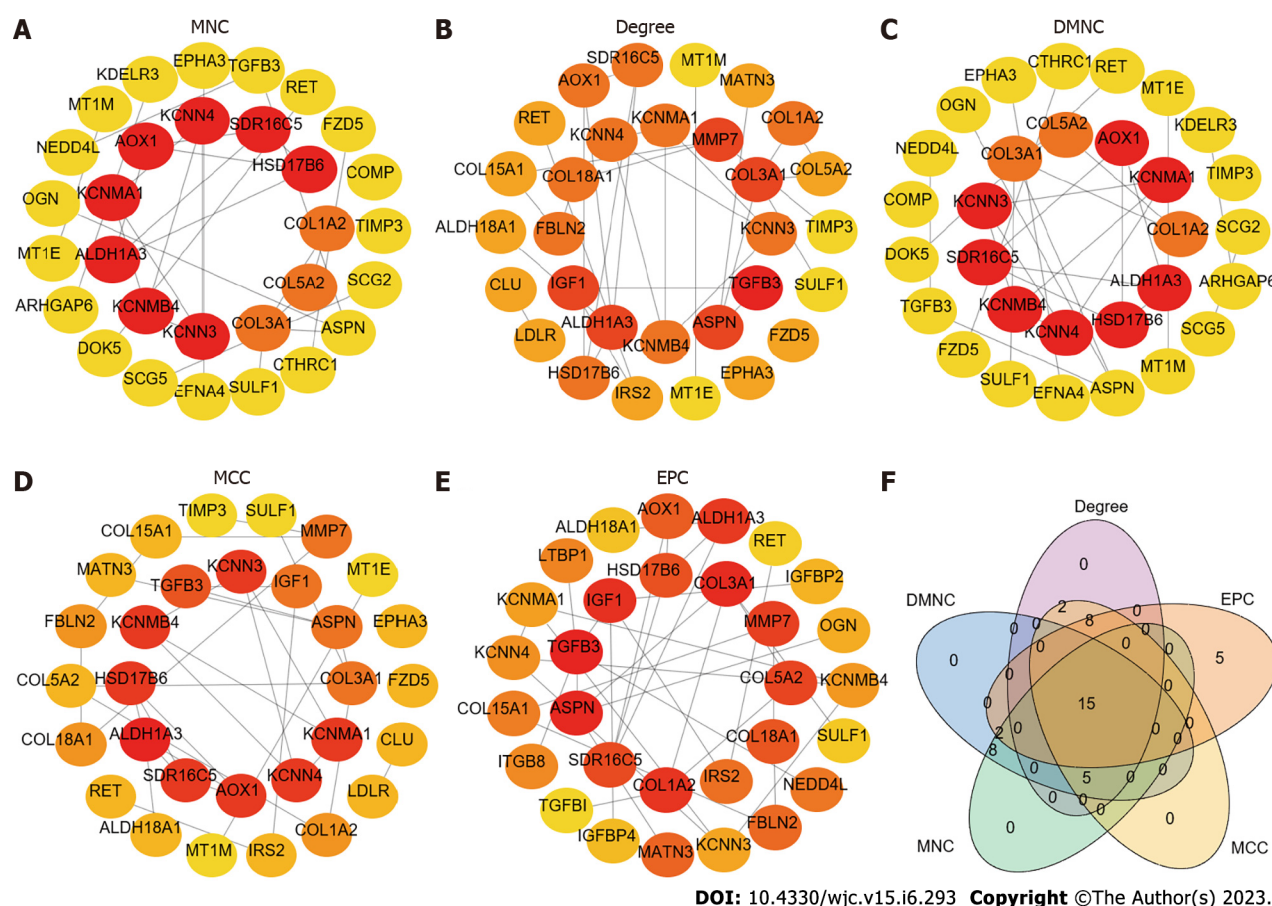


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Figure 1 Identification and enrichment analysis of differentially expressed genes in idiopathic pulmonary fibrosis data compared with control data. A: Analysis of common differentially expressed genes was performed between idiopathic pulmonary fibrosis and normal lung tissues with thresholds of $P < 0.05$ and fold change > 1.5 based on GSE53845, GSE47460 (GPL14550 and GPL6480), and GSE24206; B-D: Three categories of Gene Ontology analysis: Biological processes, cell components, and molecular functions; E: Kyoto Encyclopedia of Genes and Genomes and Reactome pathway analysis.

in IPF. Therefore, 15 genes identified by PPI and *TDO2* were included in the subsequent analysis.

The potential role of these genes in IPF development was examined by tracking expression changes in public datasets. We used linear models to assess changes in gene expression and lung function. The results showed that changes in 16 genes were directly associated with lung function. Twelve (*TDO2*, *RET*, *TGFB3*, *SULF1*, *ASPN*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNN3*, *KCNN4*) of the 16 genes were upregulated in IPF patients in all datasets. Additionally, these 12 genes significantly decreased in terms of lung function (decrease in DLCO and FVC, as shown in Figure 3A-L and Supplementary Figure 3A-L respectively). The changes in *AOX1* expression were conflicting. We observed a downregulation in IPF in the GSE53845 and GSE24206 data (logFC of -0.94 and logFC of -1.27, respectively) and an upregulation in IPF in the GSE47460 data (logFC of 0.9). Therefore, although *AOX1* is negatively correlated with DLCO and FVC (Figure 3M and Supplementary Figure 3M), we



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Figure 2 Hub genes identified by maximum neighbourhood component, Degree, density of maximum neighbourhood component, maximal clique centrality, edge percolated component, venn diagram of hub genes. A: Maximum neighbourhood component; B: Degree; C: Density of maximum neighbourhood component; D: Maximal clique centrality; E: Edge percolated component; F: Venn diagram. The 15 hub genes were *RET*, *TGFβ3*, *HSD17B6*, *SULF1*, *ASPN*, *SDR16C5*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNMB4*, *AOX1*, *KCNN3*, and *KCNN4*.

have excluded this gene from the subsequent analysis. Three (*HSD17B6*, *SDR16C5*, *KCNMB4*) of 16 genes were downregulated in IPF patients in all datasets, revealing a decrease in lung function (decreased DLCO and FVC, as shown in [Figure 3N-P](#) and [Supplementary Figure 3N-P](#) respectively).

Survival analysis

To explore the prognostic value of hub genes in IPF, we performed a survival analysis by Cox models. The data were from GSE70866[32]. Sample grouping information and the average expression and difference statistics of hub genes in each group are shown in [Table 1](#). Survival analysis showed that *TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4*, and *ALDH1A3* were independent prognostic factors for poor survival in IPF ([Figure 4](#)). Patients with high expression of these genes are likely to suffer unfavourable outcomes. There was no significant difference between the expression of other hub genes and survival in IPF patients.

Validation of hub gene expression by qRT-PCR

The mRNA expression levels of the hub genes associated with low survival rates were detected through qRT-PCR. The sequences of the primers are shown in [Table 1](#). The results showed that the mRNA expression levels of six genes (*TDO2*, *COL3A1*, *KCNN4*, *SULF1*, *KCNMA1*, *ALDH1A3*) were significantly increased in the bleomycin-induced pulmonary fibrosis group compared with the control group ($P < 0.01$, [Figure 5](#)). The direction of gene dysregulation was consistent with the test data analysis. These results demonstrate the validity of these genes for further analysis.

Prediction of target miRNAs and identifying genes of interest

Previous studies have shown that miRNAs are widely involved in disease regulation by targeting key genes[39]. The typical function of miRNAs is to bind to their 3' untranslated regions to regulate various target genes. TFs can upregulate or downregulate miRNAs, corresponding to positive and negative feedback phenomena. Identification of the TF-miRNA-mRNA coregulatory network can help determine which miRNAs play a crucial role in the pathogenesis of hub genes involved in IPF and how they interact with TFs to regulate IPF-related genes. We used three online miRNA databases (miRWalk,

Table 1 Primer sequences

Gene name	Forward	Reverse
<i>TDO2</i>	AACATGCTCAAGGTGATAGCTC	GAACCGAGAACTGCTGTACCA
<i>SULF1</i>	TGTGTTCACCGTTCGGTC	CACATCCTGGTCGTCAGTGAG
<i>KCNN4</i>	GCTCAACCAAGTCCGCTTC	GTGATCGGAATCAGCCACAGT
<i>COL3A1</i>	CTGTAACATGGAACTGGGGAAA	CCATAGCTGAACTGAAAACCACC
<i>HSD17B6</i>	GGAGCGTGTGGAGACAGAG	GAGGTTCACTTGAAAGATAGGCA
<i>KCNMA1</i>	TCACGGAATCGCTAAGCC	AATGTGCGTCCCACTGTTTTT
<i>KCNMB4</i>	ACCAACCCCAAGTGCTCCTAT	GAATGGCTGGGAACCGATCTC
<i>ALDH1A3</i>	ATCAACAACGACTGGCACGAA	CACATCGGGCTTATCTCCTTC
<i>SDR16C5</i>	TTGAGTGTTTTGAGAGGCCCTA	AACTGCAATGCTAAGAGCCTT
<i>18S</i>	GTAACCCGTTGAACCCATT	CCATCCAATCGGTAGTAGCG

DIANATools, and miRDB) to predict miRNAs targeting the above nine hub genes. The targeted miRNA was selected when it targeted a gene in all three databases. Finally, 367 miRNAs were selected, and 401 mRNA-miRNA pairs were obtained (Supplementary Table 7). The interaction network of mRNAs and miRNAs, comprising 376 nodes and 401 edges, was constructed by Cytoscape (Supplementary Figure 4). Finally, *TDO2* was selected to further explore the regulatory network.

TFs and miRNAs regulate each other to form feed-forward loops or feedback loops, where a TF regulates a miRNA or a miRNA inhibits a TF[40,41]. In this study, TransmiR was adopted to predict a list of significant TFs that may regulate miRNAs, and it provided 3730 highly reliable TF-miRNA regulations[36]. *TDO2* was regulated by seven miRNAs (hsa-let-7g, hsa-mir-6878, hsa-mir-4270, hsa-mir-4441, hsa-mir-7974, hsa-let-7a-2, hsa-mir-6754). Based on the TFs in TransmiR prediction with a threshold of $P < 0.05$, the number of targeted miRNAs for regulation was 7. Nine molecules corresponding to this condition were *TCF12*, *SPI1*, *HIF1A*, *RUNX1*, ETS-related gene (*ERG*), *MYC*, *EP300*, *RELA*, and *STAT1*. On this basis, the TF-miRNA-mRNA network of *TDO2* was constructed by Cytoscape (Figure 6).

***TDO2* in IPF and alveolar fibroblasts**

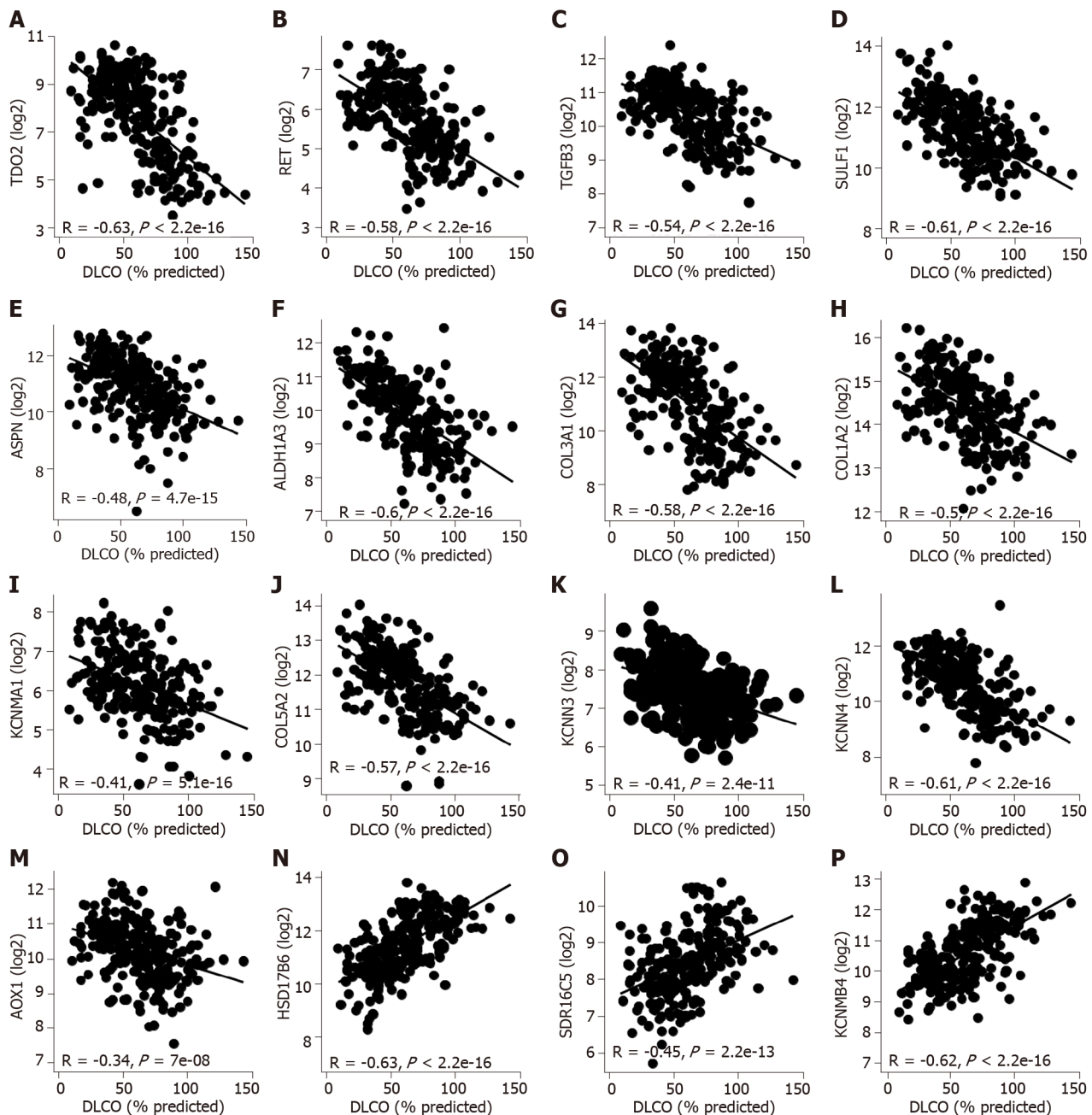
TDO2 was upregulated in IPF in all trained datasets, as shown in Figure 7A. *TDO2* expression was upregulated in IPF, while lung function was decreased (decreased DLCO and FVC, Figure 7B and C and Supplementary Figure 5A). In addition, single-cell RNA-seq data containing 32 IPF and 28 control lung tissues (GSE136831)[42] were used to validate *TDO2* expression between IPF and normal lung tissues of patients. The parameters and cell type identification in UMAP were consistent with those in a study of CD38-mediated pulmonary fibrosis[42]. In addition, *TDO2* expression was significantly enriched in alveolar fibroblasts (Figure 7D-F). This result is consistent with the proliferation of fibroblasts and myofibroblast accumulation in IPF. The above results were also supported by GSE135893 and GSE122960 (Supplementary Figure 5B-E). A UMAP plot with cells labeled by disease identity in GSE136831 has been added to Supplementary Figure 5F.

Reduction of TGF- β -induced fibrosis by *TDO2* deficiency

To identify the effect of altered *TDO2* gene expression on fibrosis, we treated cells with *TDO2* inhibitors. Cells treated with TGF- β were the pulmonary fibrosis model group. After 24 h of TGF- β treatment, cells were treated with the *TDO2* inhibitor 680c91 to explore fibrotic changes. The same experiments were performed in three cell lines, including fibroblasts (IMR-90) and epithelial cells (A549 and MLE-12). The attenuated fibrosis was supported by the decrease in α -SMA and COL-I expression (Figure 8). These *in vitro* data reveal that decreased *TDO2* expression inhibited TGF- β -induced fibroblast activation, indicating that *TDO2* is a potential therapeutic target for fibrosis.

DISCUSSION

The progression of IPF seriously affects the lives of patients, while effective treatments are limited. To address the shortage of IPF-targeted therapeutic candidate genes, this study collected four sets of GEO public data to find common DEGs between IPF and normal lung tissues. Information on the common DEGs has been added to Supplementary Table 8. Since screening large public data ensures more accurate and generally applicable hub genes, data containing extensive IPF and control samples were selected for screening. For more robust data results, further screening was performed with clinical lung



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Figure 3 Correlations between lung gene expression and forced vital capacity and diffusing capacity. A-M: *TDO2*, *RET*, *TGFB3*, *SULF1*, *ASPN*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNN3*, *KCNN4* and *AOX1* expression was negatively correlated with diffusing capacity of carbon monoxide (DLCO); N-P: *HSD17B6*, *SDR16C5*, and *KCNMB4* were significantly positively correlated with DLCO. The Pearson correlation metric was computed by using the 'stat_cor' function in R. DLCO: Diffusing capacity of carbon monoxide.

function indicators and survival analyses. Based on the PPI network and five cytoHubba algorithms, 15 hub genes were identified for the analysis. The relationship of these genes with lung function (such as DLCO and FVC) and overall survival was examined. Nine genes (*TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4*, and *ALDH1A3*) significantly decreased lung function in IPF and caused poor survival. The selected genes were validated by scRNA-seq data, qRT-PCR and western blotting in three cell lines, indicating these results are consistent with the actual situation. Compared with the validation in a single cell line, the results in multiple cell lines provide better support for the therapeutic function of *TDO2* inhibitors.

GO analysis showed that the common DEGs were primarily enriched in extracellular matrix organization (BP), collagen-containing extracellular matrix (CC), and extracellular structure constituent (MF). These biological pathways are involved in the degradation, regeneration, and remodelling of fibrosis[43]. IPF is the most common idiopathic interstitial pneumonia. However, nothing, other than a lung transplant, has thus far increased survival[44]. The antifibrotic drugs on the market are pirfenidone and nintedanib, which are used to slow the progression of the disease. Thus, further exploration of other

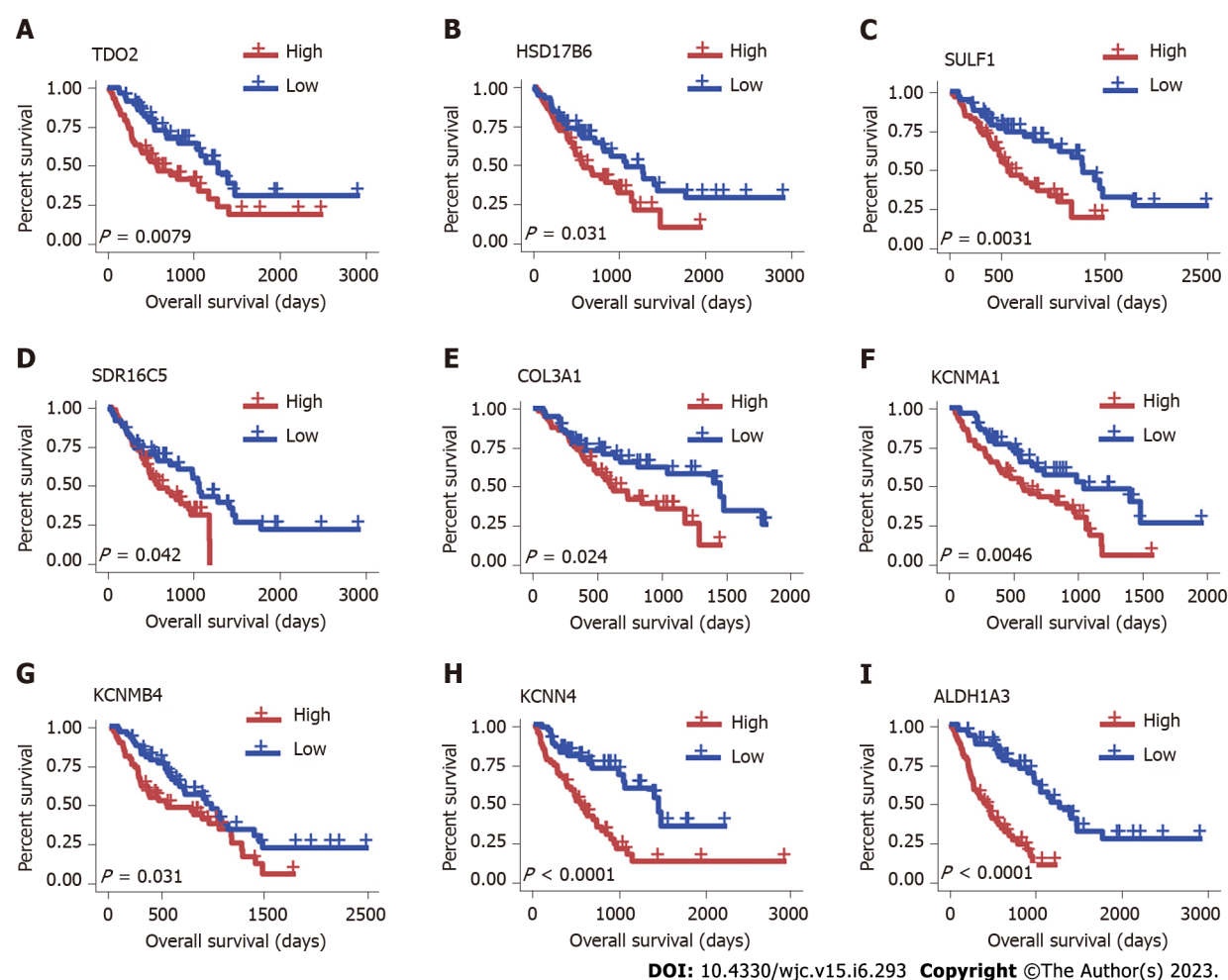


Figure 4 Survival analysis of overlapping hub genes. Overall survival curves show that higher expression of *TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4* and *ALDH1A3* is associated with a worse survival rate. A: *TDO2*; B: *HSD17B6*; C: *SULF1*; D: *SDR16C5*; E: *COL3A1*; F: *KCNMA1*; G: *KCNMB4*; H: *KCNN4*; I: *ALDH1A3*.

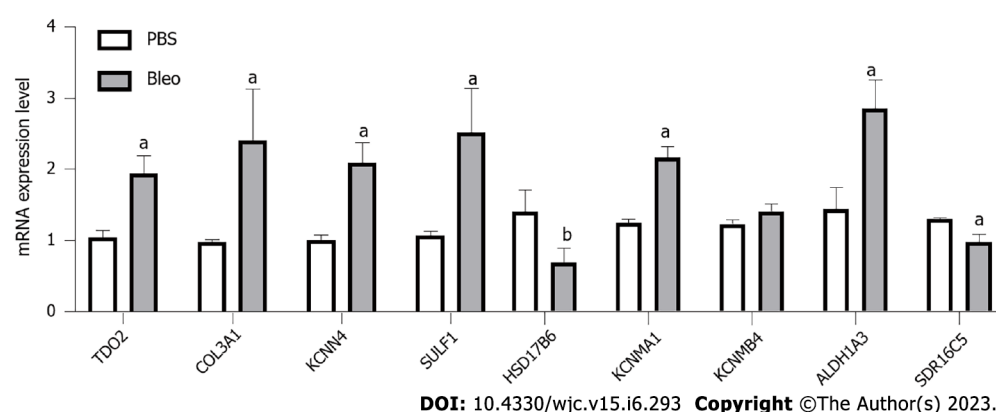
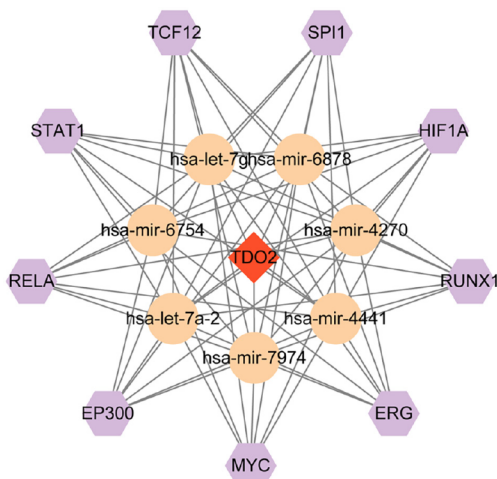


Figure 5 mRNA expression levels of *TDO2*, *COL3A1*, *KCNN4*, *SULF1*, *HSD17B6*, *KCNMA1*, *KCNMB4*, *ALDH1A3*, and *SDR16C5* in the lung tissue vs PBS ($n = 5$ for PBS group, $n = 5$ for Bleo group). The statistical test used was the t test. Data are expressed as the mean with SD. ^a $P < 0.01$, ^b $P < 0.05$.

therapeutic drugs is warranted. Among the screened genes, *SULF1* promotes histone H4 acetylation, enhances the effects of HDAC inhibitors, and inhibits tumorigenesis in hepatocellular carcinoma[45]. HDAC inhibitors can downregulate *COL3A1* expression in primary IPF lung fibroblasts[46]. Therefore, targeting histone deacetylases in IPF may also be a future therapeutic approach[15].

MiRNAs are endogenous noncoding RNAs with regulatory functions and a length of approximately 22 nt[47]. These molecules play important roles in regulating the expression of genes related to the



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Figure 6 Transcription factors-miRNA-mRNA regulatory network. Transcription factors, miRNA, and mRNA are represented by hexagons, circles, and diamonds, respectively.

growth and development of organisms and the occurrence of diseases. Studies have shown that each miRNA may have dozens or hundreds of target genes[48]. With the continuous discovery of specific miRNAs, the study of target genes in some disease pathways may lead to the discovery of new therapeutic methods. In this study, a regulatory pathway that may have the potential to regulate the expression of *TDO2* was identified through the TF-miRNA-mRNA network. In this way, the underlying molecular mechanisms of IPF were revealed, providing potential targets for developing new therapeutic agents to treat IPF patients. The results showed nine TFs targeting seven miRNAs to coregulate *TDO2*. Among them, HIF1A induced overexpression of the p53/hypoxia pathway in the tissues of IPF patients [49]; EP300 was highly enriched at enhancers of several genes in multiple profibrotic pathways[50]; immunostaining of RELA (v-rel reticuloendotheliosis viral oncogene homologue A) was increased in type 2 alveolar epithelial cells of mice treated with bleomycin[51]. The function of the TF ERG is dysregulated in ageing. A previous study showed that ERG dysfunction exacerbated pulmonary vascular ageing and persistent fibrosis[52]. We speculated that the disorder of ERG caused positive feedback, such as mechanisms involving miR-4270 and miR-4441 to regulate the expression of *TDO2*, so specific inhibition of ERG could be assessed in follow-up research, and combined treatment may be the future direction of pulmonary fibrosis treatment.

This study also has some limitations. We used five common sets from IPF data, but the intersection of common DEGs between one group of datasets (GSE110147) and the other groups was less than 50%. This group was removed in subsequent analysis, and the DEGs in the remaining groups were screened using thresholds of adjusted $P < 0.05$ and $FC > 1.5$. The selected common DEGs had identical direction of dysregulation, indicating that the validity of the thresholds and the data are reasonable. With the progress of scientific research, more IPF-related data can be generated, and additional datasets or novel computing methods can be adopted to find relevant genes affecting IPF. In addition to human lung tissue data, mouse data can be analysed and verified. With the diversification of sequencing technologies, multiomics data analysis can be adopted to validate genes. For example, single-cell RNA sequencing technology can examine the expression of specific genes in different cell populations and the existence of tissue preferences. Some genes were differentially expressed in at least one cell type, while some genes related to ECM were largely expressed in fibroblast subpopulations[53]. By investigating the expression of *TDO2* in each cell cluster in scRNA-seq data (GEO series accession No. GSE135893 and GSE122960[54]), we found higher expression in fibroblasts than in other cell clusters. The specific mechanism of *TDO2* in fibroblasts should be further investigated.

Moreover, when using STRING to construct PPI networks, we used different interaction score thresholds to obtain different network structures. Important candidate genes in common DEGs might be missed, and these genes would not appear in the network due to insufficient research. We reviewed these genes again and found that *TDO2* has potential drug effects. Previous research has shown that *TDO2* knockdown inhibits colorectal cancer progression[55]. In vitro experiments have shown that knocking down or blocking *TDO2* expression in myofibroblast subsets can effectively reverse T-cell immunosuppression in oral squamous cell carcinoma[56]. No relevant studies have been reported on the role of *TDO2* in IPF. Therefore, we included *TDO2* for follow-up analysis. Fortunately, the results of the network analysis in this study validated independent data from public databases and qRT-PCR data from our laboratory. However, the disadvantage is that we performed the experiment once, and there is a lack of repeated experiments to prove the repeatability of these findings. Additionally, it is important to explore whether the other group receiving more or less bleomycin has any effect on the reprodu-

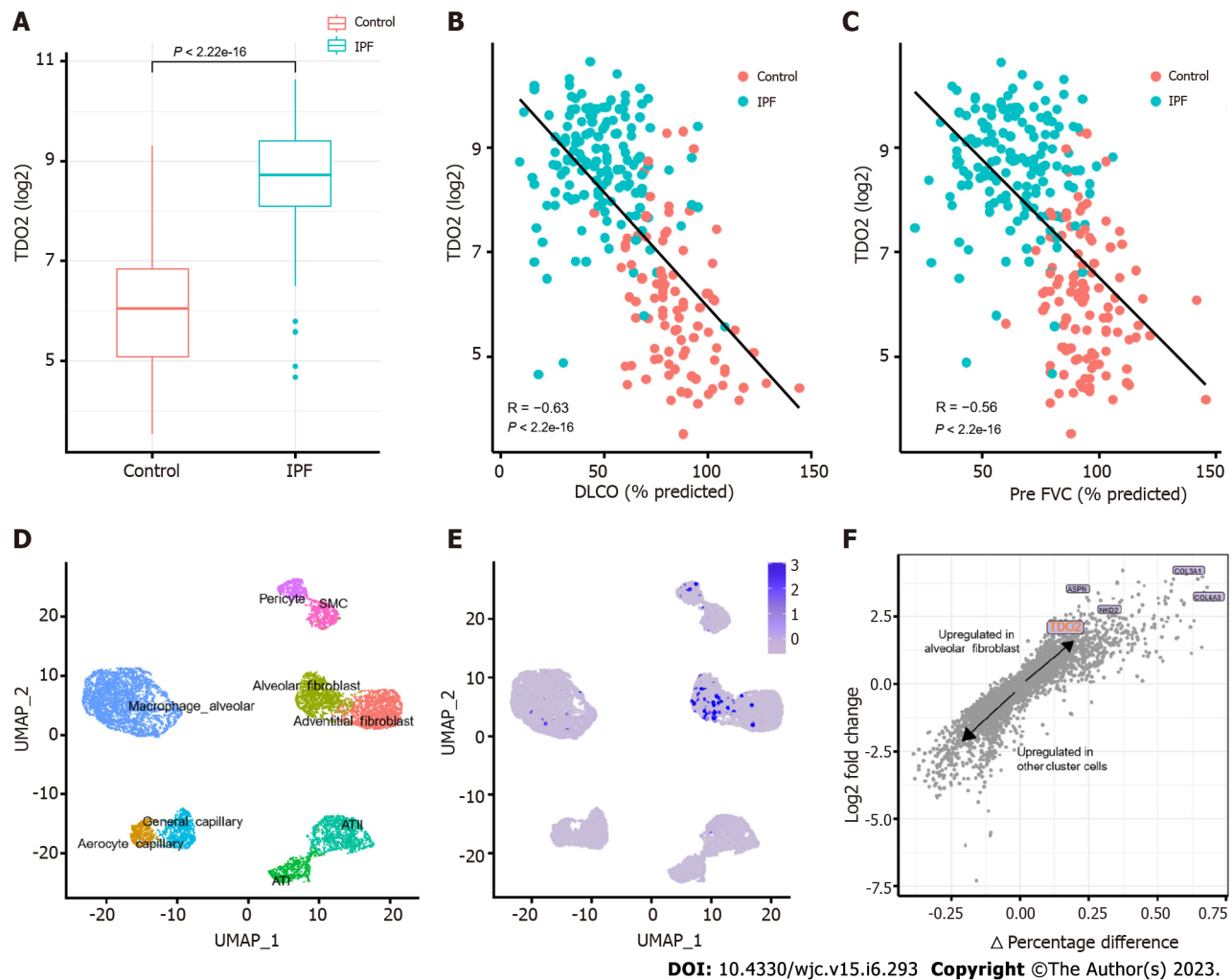
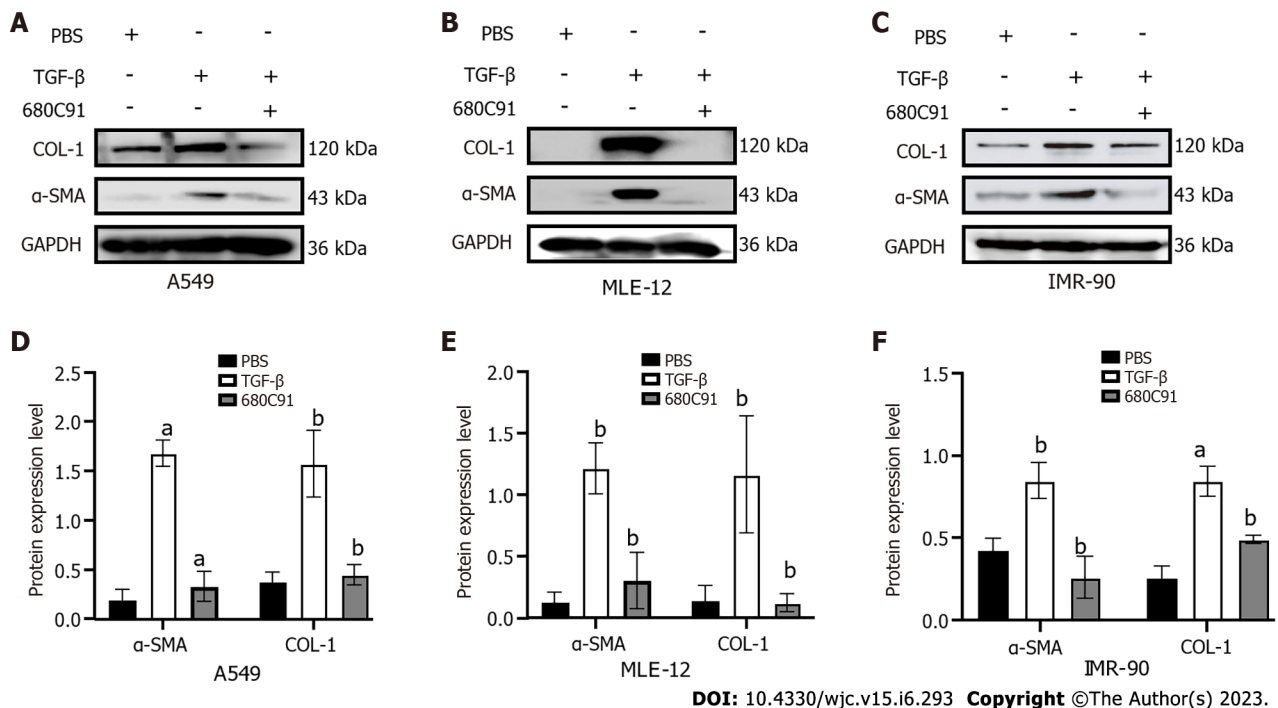


Figure 7 *TDO2* increased in Idiopathic pulmonary fibrosis and was validated in scRNA-seq data. A: Upregulation of *TDO2* in Idiopathic pulmonary fibrosis of trained data (e.g., in GSE47460). The statistical test used was the t test; B and C: Correlations between lung *TDO2* expression and diffusing capacity of carbon monoxide (B) and forced vital capacity (C) in GSE47460. The Pearson correlation metric was computed by using the 'stat_cor' function in R; D: UMAP of 8,942 randomly selected resident lung parenchymal cells from GSE136831; E: UMAP with cells labelled by normalized *TDO2* expression; F: Differential gene expression analysis using the log-fold change expression vs the difference in the percentage of cells expressing the gene comparing alveolar fibroblast cluster vs other cluster cells (Δ Percentage Difference). Labelled genes have a log₂-fold change > 1, Δ Percentage Difference > 20% and adjusted *P* value from Wilcoxon rank sum test < 0.05. DLCO: Diffusing capacity of carbon monoxide; IPF: Idiopathic pulmonary fibrosis; FVC: Forced vital capacity.

cibility of the results. Representative images of rat body weight, survival rate, lung wet-to-dry weight ratio, lung hydroxyproline content, mouse hematoxylin and eosin staining and Masson's trichrome staining of lung sections are more conducive to increasing the persuasiveness of our results, which will be further studied in the future. In summary, we demonstrated that the *TDO2* gene is significantly upregulated after bleomycin treatment and proposed blocking TGF- β production as a potential treatment for IPF. A more comprehensive study of *TDO2* in animal models would be worthwhile.

CONCLUSION

This study identified novel hub genes to explore the treatment of IPF, examined the upregulated expression of *TDO2*, and investigated the TF-miRNA-gene regulatory network of *TDO2*. After inhibitor treatment, TGF- β -induced fibroblast activation was effectively inhibited. *TDO2* appears to be an effective treatment for IPF. Therefore, the molecular mechanisms of these TFs and *TDO2* deserve further exploration. The findings provide new target gene prediction, and we propose blocking TGF- β production as a potential treatment for IPF.



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Figure 8 Western blot analysis of α -smooth muscle actin and COL-1 in A549, MLE-12, and IMR-90 cells. Western blot quantification results in A549, MLE-12 and IMR-90 cells. A and D: A549; B and E: MLE-12; C and F: IMR-90. In line with the homogeneity of variance, the least significance difference method was used when assuming homogeneity of variance. ^a $P < 0.01$ vs phosphate-buffered saline; ^b $P < 0.05$ vs transforming growth factor- β . PBS: Phosphate-buffered saline; α -SMA: α -smooth muscle actin; TGF- β : Transforming growth factor- β .

ARTICLE HIGHLIGHTS

Research background

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with high mortality rate. Therefore, exploring potential therapeutic targets to meet the unmet needs of IPF patients is of great significance.

Research motivation

To explore potential targets for IPF treatment, as well as potential pathways and therapeutic methods.

Research objectives

Explore novel hub genes for IPF therapy. Whether *TDO2* can be a therapeutic target for IPF.

Research methods

We used public datasets (GSE53845, GSE47460, GSE24206, and GSE110147) to identify differentially expressed genes between IPF patients and healthy donors. Potential targets were considered based on multiple bioinformatics conditions, especially the correlation between hub genes and carbon monoxide diffusing capacity, forced vital capacity, and patient survival rate. The mRNA levels of the hub genes were determined through quantitative real-time polymerase chain reaction. Transforming growth factor- β (TGF- β) induced pulmonary fibrosis mouse model and the expression of *TDO2* was observed before and after the addition of inhibitor.

Research results

This study identifies novel hub genes to explore for IPF treatment. *TDO2* was upregulated in an experimental mouse model of TGF- β -induced pulmonary fibrosis and a *TDO2* inhibitor effectively suppressed TGF- β -induced fibroblast activation.

Research conclusions

TDO2 could be a potential target for treatment of IPF.

Research perspectives

More complete work with animal models is needed, as the *TDO2* gene is apparently upregulated by bleomycin treatment.

FOOTNOTES

Author contributions: Yang YM designed the research study; Wang R and Yang YM performed the research; Yang YM analysed the data and wrote the manuscript; Wang R performed the experiment research; all authors have read and approved the final manuscript.

Institutional review board statement: Our manuscript involves experiments on mice, as well as the A549 and IMR-90 cell lines, but does not involve any human experimentation.

Institutional animal care and use committee statement: The study was reviewed and approved by the Experimental Animal Ethics Committee of Henan University of Chinese Medicine, No. DWLLGZR202202036.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available.

ARRIVE guidelines 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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Effect of fibrinolytic therapy on ST-elevation myocardial infarction clinical outcomes during the COVID-19 pandemic: A systematic review and meta-analysis

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Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) is the result of transmural ischemia of the myocardium and is associated with a high mortality rate. Primary percutaneous coronary intervention (PPCI) is the recommended first-line treatment strategy for patients with STEMI. The timely delivery of PPCI became extremely challenging for STEMI patients during the coronavirus disease 2019 (COVID-19) pandemic, leading to a projected steep rise in mortality. These delays were overcome by the shift from first-line therapy and the development of modern fibrinolytic-based reperfusion. It is unclear whether fibrinolytic-based reperfusion therapy is effective in improving STEMI endpoints.

AIM

To determine the incidence of fibrinolytic therapy during the COVID-19 pandemic and its effects on STEMI clinical outcomes.

METHODS

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were queried from January 2020 up to February 2022 to identify studies investigating the effect of fibrinolytic therapy on the prognostic outcome of STEMI patients during the pandemic. Primary outcomes were the incidence of fibrinolysis and the risk of all-cause mortality. Data were meta-analyzed using the random effects model to derive odds ratios (OR) and 95% confidence intervals. Quality assessment was carried out using the Newcastle-Ottawa scale.

RESULTS

Fourteen studies including 50136 STEMI patients ($n = 15142$ in the pandemic arm; $n = 34994$ in the pre-pandemic arm) were included. The mean age was 61 years; 79% were male, 27% had type 2 diabetes, and 47% were smokers. Compared with the pre-pandemic period, there was a significantly increased overall incidence of fibrinolysis during the pandemic period [OR: 1.80 (1.18 to 2.75); $I^2 = 78\%$; $P = 0.00$; GRADE: Very low]. The incidence of fibrinolysis was not associated with the risk of all-cause mortality in any setting. The countries with a low-and middle-income status reported a higher incidence of fibrinolysis [OR: 5.16 (2.18 to 12.22); $I^2 = 81\%$; $P = 0.00$; GRADE: Very low] and an increased risk of all-cause mortality in STEMI patients [OR: 1.16 (1.03 to 1.30); $I^2 = 0\%$; $P = 0.01$; GRADE: Very low]. Meta-regression analysis showed a positive correlation of hyperlipidemia ($P = 0.001$) and hypertension ($P < 0.001$) with all-cause mortality.

CONCLUSION

There is an increased incidence of fibrinolysis during the pandemic period, but it has no effect on the risk of all-cause mortality. The low- and middle-income status has a significant impact on the all-cause mortality rate and the incidence of fibrinolysis.

Key Words: ST-elevation myocardial infarction; Myocardial infarction; Thrombolytic therapy; Fibrinolysis; COVID-19; Pandemics

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Core Tip: The guideline-recommended time goals for primary percutaneous coronary intervention (PPCI) could not be met during the coronavirus disease 2019 (COVID-19) pandemic for the treatment of ST-elevation myocardial infarction (STEMI) patients. Leading cardiology societies recommended considering a new fibrinolytic-based reperfusion strategy during the time of the COVID-19 pandemic; however, previous large-scale studies have indicated that fibrinolytic therapy may offer a reduced prognostic value and poor survival outcomes in patients with STEMI compared to PPCI. We investigated the differential prevalence of the use of fibrinolytic therapy by healthcare systems belonging to countries with distinct income status, and its effect on the risk of all-cause mortality in STEMI patients.

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INTRODUCTION

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease caused by transmural ischemia that affects the entire thickness of the myocardium. This condition is associated with high morbidity and mortality rates, making it a significant public health concern[1]. According to the Global Registry of Acute Coronary Syndrome Events (GRACE), STEMI accounts for approximately 30% of all acute coronary syndrome events[2].

The preferred treatment for STEMI is primary percutaneous coronary intervention (PPCI)[3]. However, the coronavirus disease 2019 (COVID-19) pandemic placed a significant strain on healthcare resources and providers, leading some experts to recommend changes in STEMI management. Fibrinolytic therapy was suggested as an alternative treatment for patients with severe resource limitations, a shortage of personal protective equipment, low-risk STEMI, systems of care delays, and the inability to provide PPCI in a timely fashion[4-8]. In a recent systematic review and meta-analysis conducted by Kamarullah and colleagues, it was found that the performance of STEMI care declined and clinical outcomes deteriorated in STEMI patients during the COVID-19 pandemic[9]. Despite this, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

Therefore, the aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era, and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

MATERIALS AND METHODS

Protocol and registration

To ensure transparent reporting, this systematic review and meta-analysis follow the PRISMA guidelines[10] and the MOOSE group's reporting guidelines[11] for observational studies in epidemiology. The research protocol has been registered with PROSPERO, the international prospective register of systematic reviews, under registration number CRD42022300242.

Literature search

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched systematically for articles in the English language between the time when severe acute respiratory syndrome coronavirus 2 was declared a Public Health emergency of international concern-PHIEC (January 2020) up until February 2022. We used the following keywords: STEMI, fibrinolysis, and COVID-19. We utilized minimum keywords to maximize the initial scope of research in order to ensure the largest number of articles recorded. Complete search strategies used for all electronic databases were developed by an experienced librarian and are reported in the [Supplementary material](#). Reference mining included scanning reference lists of relevant papers, included studies, and systematic reviews published during the analysis of literature.

Eligibility criteria and study selection

Our study population consisted of patients with confirmed STEMI. We included studies that reported the impact of the COVID-19 pandemic on STEMI care. We searched for clinical trials, cohort studies, case-control studies, and case series. Animal studies, expert opinions, literature reviews, news articles, letters, editorials, case reports, guidelines, and any studies that did not mention the timing, population, intervention, and outcomes of interest were excluded.

We imported articles retrieved from the systematic search and exported them to EndNote reference library software (Thomson Reuters), where duplicates were identified and removed. Initially, articles were screened based on titles and abstracts by two independent reviewers (H.A.H. and E.P), then filtered relevant articles underwent full-text screening by another two reviewers working independently (H.A.M. and A.B.J). Another reviewer (A.K.) was consulted for decisions regarding any discrepancies during screening.

Data extraction

Data were extracted in a standardized data extraction form. We extracted data related to the following: (1) Summary of the included studies: Authors, year, timing, country, study design, sample size, inclusion criteria, duration of symptoms to intervention, study arms, and duration of follow up; (2) baseline characteristics of the included patients for regression purpose: Age, gender, race, body mass index, comorbidities, smoking status, and type of STEMI; and (3) the study outcomes as stated below. Any disagreements during data extraction were discussed to reach a consensus.

Risk of bias and quality assessment

The Newcastle–Ottawa Scale for observational studies was used by two independent reviewers (M.E. and M.K.K.) to evaluate quality on three diverse characteristics: Selection of study groups, comparability of groups, and ascertainment of the outcome of interest[12]. Each article was given a score that indicated how biased it was. Studies with a total score of seven or above were regarded to have a minimal probability of bias. If a study had a total score of six or less, it was determined to have a significant risk of bias. Disagreements in quality ratings were solved by a third reviewer (A.K.).

Study outcomes

We included studies that reported the incidence of the use of fibrinolytic therapy for STEMI patients during the pandemic compared to the timeline before the pandemic. The primary outcomes were the incidence of fibrinolysis and all-cause mortality.

Data synthesis and analysis

The analysis was performed in a sequence of calculations; the odds ratio (OR) of the incidence of fibrinolysis was calculated, followed by the subgrouping of studies based on significant increase in the incidence of fibrinolysis, no change in the incidence of fibrinolysis, and economic status of the countries where the studies were carried out, respecting the World Bank's classification of developed and developing countries into high-income and low- and middle-income countries (HICs and LMICs), respectively[13]. The effect sizes and the corresponding 95% confidence intervals (CIs) were calculated from raw data and variability measures or extracted directly from the studies. The outcomes were calculated using the DerSimonian and Laird random-effects model. The Higgin I^2 test was used to evaluate the heterogeneity between studies, and higher percentages indicated higher heterogeneity. The summation effect measures were calculated as OR with 95% CIs. Statistical significance was set at < 0.05 for all calculations.

Publication bias was assessed using the Begg funnel plot test[14]. Sensitivity analysis was performed by adding and removing studies one after another. Meta-regression analysis was executed for all-cause mortality. Two covariates having significant correlation among all the tested ones were displayed in the results. MetaXL version 5.3 (Epigear) add-on for Microsoft Excel 365 and Review Manager 5.4 was used to perform all analyzes. The statistical methods of the study were reviewed by a biomedical statistician.

Evaluating certainty of evidence

A summary of estimated effects and the certainty of each piece of evidence was produced using the GRADE approach (Supplementary Table 1). The GRADE criteria categorize the certainty of evidence as High, Moderate, Low, and Very low. The rating process followed the GRADE manual. GRADEpro GDT was used to construct the certainty of evidence and the summary of findings table.

RESULTS

Search results

The process of study selection and the characteristics of the included studies are summarized in Figure 1 and Tables 1 and 2, respectively. A total of 2938 studies were initially identified through database

Table 1 Characteristics of included studies

Ref.	Country	Study design/Sa	Study group/time period of study / sample size
Daoulah <i>et al</i> [15]	Saudi Arabia	Retrospective Cohort/500	Pandemic period STEMI/01/01/2020–30/04/2020/500 Pre-pandemic period STEMI/2018–2019/1285
Leng <i>et al</i> [16]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–30/04/2020/164 Pre-pandemic period STEMI/Equivalent period in 2019/240
Song <i>et al</i> [17]	China	Retrospective Cohort	Pandemic period STEMI/24/01/2020–31/03/2020/73 Pre-pandemic period STEMI/24/01/2019–31/03/2019/95
Wang <i>et al</i> [18]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–20/03/2020/37 Pre-pandemic period STEMI/01/09/2019–02/12/2019/41
Wu <i>et al</i> [19]	England	Retrospective Cohort	Pandemic period STEMI/01/01/2019/1600 Pre-pandemic period STEMI/22/05/2020/15646
Xiang <i>et al</i> [20]	China	Retrospective Cohort	Pandemic period STEMI/20/02/2020/10516 Pre-pandemic period STEMI/27/12/2019/14634
Zhang <i>et al</i> [21]	China	Retrospective Cohort	Pandemic period STEMI/01/01/2020–31/03/2020/119 Pre-pandemic period STEMI/2018 and 2019/276
Huang <i>et al</i> [22]	China	Retrospective Cohort	Pandemic period STEMI/01/02/2020–15/04/2020/31 Pre-pandemic period STEMI/01/01/2019–31/12/2019/31
Erol <i>et al</i> [23]	Turkey	Retrospective Cohort	Pandemic period STEMI/2020/485 Pre-pandemic period STEMI/2018/711
Mesnier <i>et al</i> [24]	France	Retrospective Cohort	Pandemic period STEMI/16/03/2020–12/02/2020/252 Pre-pandemic period STEMI/17/02/2020–15/03/2020/331
Balghith[25]	Saudi Arabia	Retrospective Cohort	Pandemic period STEMI/01/2020–05/2020/81 Pre-pandemic period STEMI/08/2019–12/2019/92
Clifford <i>et al</i> [26]	Canada	Retrospective Cohort	Pandemic period STEMI/17/03/2020–16/07/2020/193 Pre-pandemic period STEMI/15/11/2019–16/03/2020/238
Rodríguez-Leor <i>et al</i> [27]	Spain	Retrospective Cohort	Pandemic period STEMI/16/03/2020–14/04/2020/1009 Pre-pandemic period STEMI/01/04/2019–30/04/2019/1305
Calvão <i>et al</i> [28]	Portugal	Retrospective Cohort	Pandemic period STEMI/03/2020–04/2020/71 Pre-pandemic period STEMI/03/2020–04/2020/80

STEMI: ST-elevation myocardial infarction.

searches, and after removing duplicates, 14 studies were found to be eligible for inclusion in this meta-analysis[15–28]. These studies involved 50136 adult STEMI patients, with 15142 patients receiving fibrinolytic therapy during the pandemic era and 34994 patients receiving standard of care before or during the pre-pandemic era. Our meta-analysis assessed the impact of fibrinolytic therapy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to standard-care before or during the pandemic.

Quality assessment

To assess the quality of the included studies, we used the Newcastle-Ottawa Scale for observational studies. Out of the 14 included studies, two were cohort studies, while the remaining 12 were case-control studies. Five studies had a low risk of bias (total score: 7–9), while the remaining studies were found to have a moderate risk of bias (total score: 4–6). None of the included studies had a high risk of bias (total score: 0–3). The detailed quality assessment of each study is provided in the (Supplementary Figure 1). The symmetrical funnel plot (Figure 2) indicated no small study or publication bias.

Table 2 Baseline characteristics of the included subjects

Ref.	Study group	Age, years (SD)	Male, n (%)	Hypertension, n (%)	Diabetes mellitus, n (%)	Hyperlipidemia, n (%)	Smoking, n (%)
Daoulah <i>et al</i> [15]	Pandemic period STEMI	55.4 (11.8)	454 (90.8)	229 (46.7)	257 (52.1)	190 (38.9)	213 (43)
	Pre-pandemic period STEMI	56.5 (12.8)	1123 (87.5)	599 (47.6)	632 (50.4)	450 (35.8)	318 (41.6)
Leng <i>et al</i> [16]	Pandemic period STEMI	63.13 (13.6)	131 (79.9)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.21 (13.14)	178 (73.9)	N/A	N/A	N/A	N/A
Song <i>et al</i> [17]	Pandemic period STEMI	61.6 (13.1)	59 (80.82)	43 (58.9)	16 (21.9)	39 (53.4)	36 (49.3)
	Pre-pandemic period STEMI	60.6 (13.9)	68 (71.57)	56 (59)	22 (23.2)	51 (53.7)	55 (57.9)
Wang <i>et al</i> [18]	Pandemic period STEMI	59.29 (11.46)	33 (89.18)	20 (54.05)	6 (16.21)	13 (35.13)	37 (100)
	Pre-pandemic period STEMI	55.49 (11.89)	35 (85.36)	18 (43.90)	5 (12.19)	15 (36.58)	31 (75.60)
Wu <i>et al</i> [19]	Pandemic period STEMI	65.1 (13.6)	1181 (73.81)	581 (36.31)	309 (19.31)	368 (23)	450 (28.12)
	Pre-pandemic period STEMI	65.76 (13.44)	11263 (71.98)	6060 (38.73)	3005 (19.20)	3645 (23.29)	4704 (30.06)
Xiang <i>et al</i> [20]	Pandemic period STEMI	61.59 (13.10)	7986 (75.94)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.86 (12.33)	11019 (75.29)	N/A	N/A	N/A	N/A
Zhang <i>et al</i> [21]	Pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
Huang <i>et al</i> [22]	Pandemic period STEMI	61	25 (80.6)	16 (51.6)	8 (25.8)	7 (22.6)	18 (58.1)
	Pre-pandemic period STEMI	60	25 (80.6)	18 (58.1)	6 (19.4)	8 (25.8)	20 (64.5)
Erol <i>et al</i> [23]	Pandemic period STEMI	59 (13)	552 (77.63)	221 (45.56)	151 (31.13)	108 (22.26)	248 (50.30)
	Pre-pandemic period STEMI	60 (14)	387 (79.79)	273 (38.39)	201 (28.27)	67 (9.4)	401 (56.39)
Mesnier <i>et al</i> [24]	Pandemic period STEMI	63.4 (12.5)	357 (74)	116 (24.11)	35 (7.27)	N/A	96 (19.95)
	Pre-pandemic period STEMI	64.4 (13.6)	509 (74)	139 (20.26)	55 (8.01)	N/A	131 (19.09)
Balghith[25]	Pandemic period STEMI	57.2 (12.6)	83 (90.21)	44 (54.32)	45 (48.91)	36 (39.13)	41 (44.56)
	Pre-pandemic period STEMI	51.3 (11.5)	81 (100)	38 (41.3)	41 (44.56)	31 (33.69)	35 (38.04)
Clifford <i>et al</i> [26]	Pandemic period STEMI	65 (12)	169 (71)	99 (51.29)	55 (28.49)	86 (44.55)	53 (27.46)
	Pre-pandemic period STEMI	64 (13)	135 (70)	123 (51.68)	54 (22.68)	99 (41.5)	93 (39.07)
Rodríguez-Leor <i>et al</i> [27]	Pandemic period STEMI	63.1 (12.5)	786 (78.4)	520 (51.9)	226 (22.6)	466 (46.7)	442 (44.6)
	Pre-pandemic period STEMI	63.7 (13.2)	1023 (78.4)	647 (50)	224 (25.2)	592 (45.8)	581 (45.7)

Calvão <i>et al</i> [28]	Pandemic period STEMI	63.3 (12.7)	56 (78.9)	49 (69.01)	23 (32.39)	38 (53.52)	40 (56.33)
	Pre-pandemic period STEMI	65.7 (12.8)	60 (75)	48 (60)	26 (32.5)	49 (57.5)	39 (48.75)

N/A: Not available; STEMI: ST-elevation myocardial infarction.

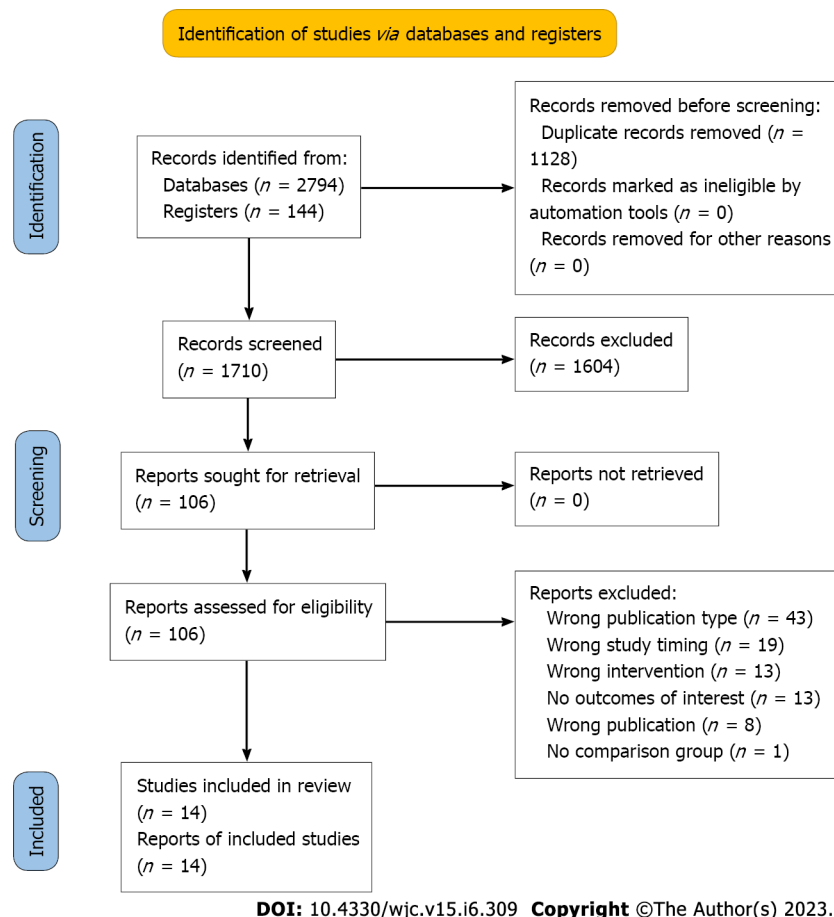


Figure 1 PRISMA chart displaying the process of search to study selection.

Frequency of fibrinolytic therapy

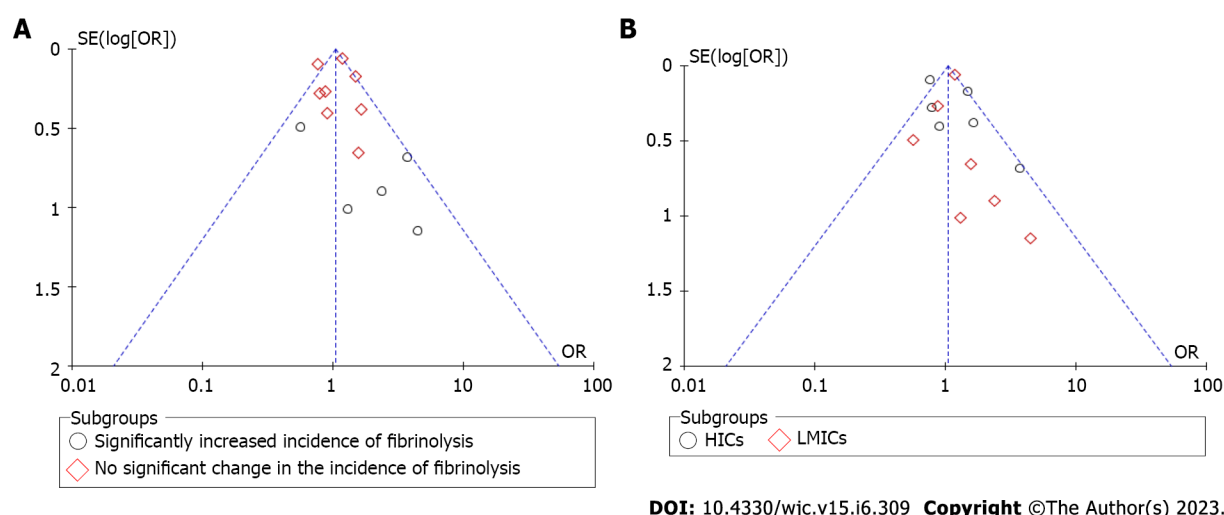
All 14 studies included in this meta-analysis investigated the frequency of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Our analysis revealed a significantly higher incidence of fibrinolytic therapy during the pandemic [OR: 1.80 (95%CI: 1.18-2.75); $I^2 = 78\%$; $P = 0.00$; GRADE: Very low] (Figure 3A). Moreover, we observed that patients treated in LMICs had a higher probability of receiving fibrinolytic therapy [OR: 5.16 (95%CI: 2.18-12.22); $I^2 = 81\%$; $P = 0.00$; GRADE: Very low] (Figure 3B).

All-cause mortality

We evaluated all-cause mortality in 13 of the included studies. The increased incidence of fibrinolytic therapy was not found to be associated with an increased risk of all-cause mortality [OR: 1.65 (95%CI: 0.67-4.06); $I^2 = 40\%$; $P = 0.27$; GRADE: Very low] (Figure 4). However, patients who received fibrinolytic therapy in LMICs were at a higher risk of all-cause mortality [OR: 1.16 (95%CI: 1.03-1.30); $I^2 = 0\%$; $P = 0.01$; GRADE: Very low]. Overall, we found no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy [OR: 1.09 (95%CI: 0.87-1.37); $I^2 = 58\%$; $P = 0.47$; GRADE: Very low] (Figure 5).

Meta-regression for exploring specific covariates

Meta-regression of heterogeneity was performed for the outcome of all-cause mortality, as it is one of our primary outcomes and more clinically relevant. Hyperlipidemia (reported in 9 studies[15,17-19,22,23,24-28]) and hypertension (reported in 10 studies[15,17-19,22-28]) were tested as covariates. The meta-



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Figure 2 No evidence of publication bias. A: When studies have been divided based on the incidence of fibrinolysis; B: When studies have been divided based on the income status of countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

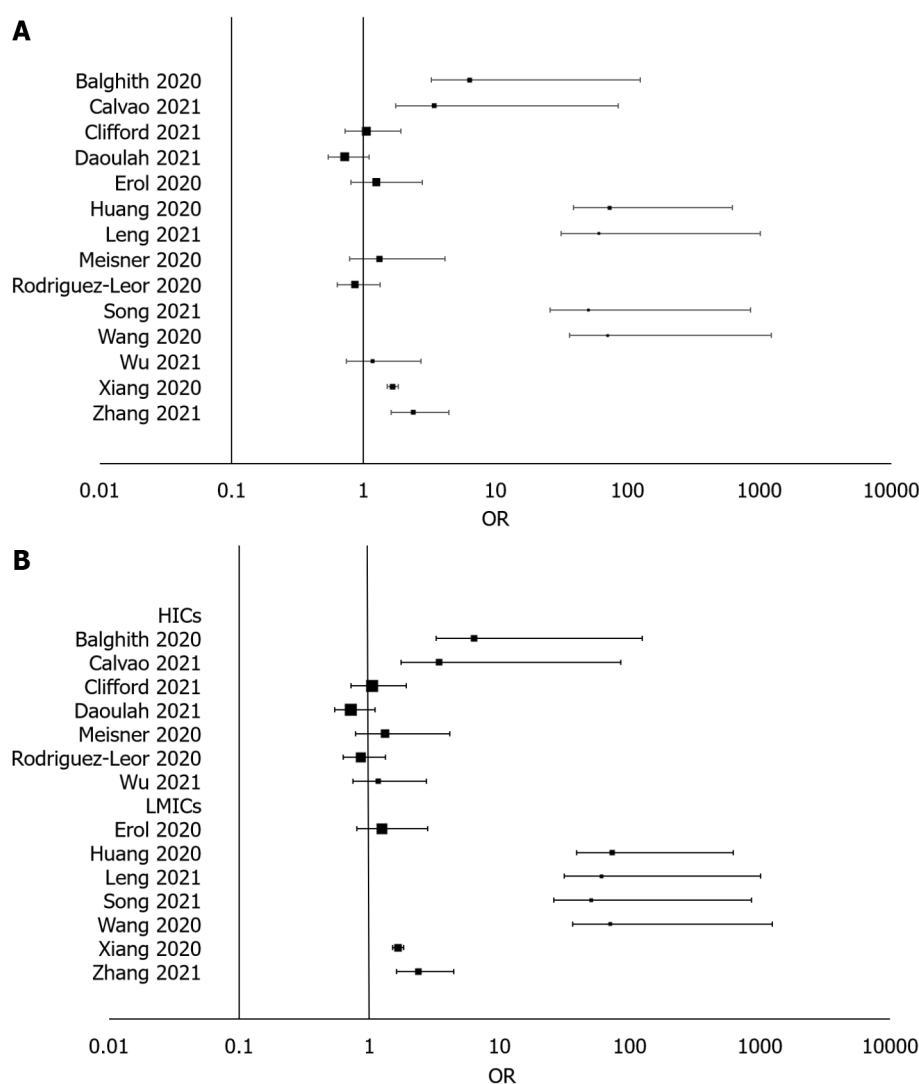
regression analysis provide evidence that hyperlipidemia is associated with an increased risk of all-cause mortality ($P = 0.001$) (Figure 6A). The meta-regression analysis further revealed that hypertension is also a significant predictor of all-cause mortality ($P < 0.001$) (Figure 6B). These findings suggest that managing hyperlipidemia and hypertension may be crucial for reducing the risk of all-cause mortality.

DISCUSSION

After conducting a thorough meta-analysis, we observed a significant increase in the use of fibrinolytic reperfusion in STEMI cases during the COVID-19 pandemic. Interestingly, we found no significant association between fibrinolysis and all-cause mortality rates. However, our analysis revealed that countries with lower-middle-income and low-income status reported a higher incidence of fibrinolysis, which in turn was associated with an elevated risk of all-cause mortality for STEMI patients.

In our meta-regression analysis, we found out that patients having hyperlipidemia and hypertension tend have an increased risk of all-cause mortality. Hyperlipidemia decreases the stability of plaques that are most likely to rupture and decreases endothelial function[29]. It also promotes the formation of platelet thromboses at the site of the injury[30]. LIPID trial also showed a decrease in the risk of mortality for those patients who were treated for hypercholesteremia with the help of Statins therapy [31]. hypertension is also a crucial prognostic factor for STEMI. Hypertension reduces the elastic ability of blood vessels and causes atherosclerosis[32].

The COVID-19 pandemic has added to the already existing challenges of chronically strained healthcare systems worldwide. Among the many areas of healthcare that have been impacted, primary cardiac interventions for STEMI patients have also faced significant obstacles[33]. In high-income countries, meeting the recommended time goals for such interventions was difficult even before the pandemic, with only 25%-50% of patients receiving PPCI within the recommended time frame of 120 minutes from first medical contact (FMC) to balloon[34]. Unfortunately, the pandemic has further exacerbated delays in symptoms-to-FMC and door-to-balloon time, creating an additional challenge for healthcare systems to provide timely and effective care to STEMI patients. A study reported that the mean time from symptoms to intervention was longer during the COVID-19 pandemic compared to the previous year[35]. The need to screen for COVID-19, which includes procedures such as chest radiographs, epidemiological screening, polymerase chain reaction swab tests, and other laboratory tests, has potentially contributed to delays in providing PPCI for STEMI patients. The goal of these screening measures is to prevent the spread of COVID-19 within healthcare settings. However, delays in PPCI have been linked to a significant increase in mortality rates for STEMI patients[36]. Moreover, the incidence of STEMI has been reported to decrease during the COVID-19 pandemic. A study by Furnica *et al*[37] found that the incidence of STEMI decreased by 48.8% during the COVID-19 pandemic compared to the same time in the previous year[37]. Another study by Oettinger *et al*[38] reported a similar increase in STEMI incidence of 22.9% during the COVID-19 pandemic[38]. These findings suggest that there may be an association between the declining incidence of STEMI and the COVID-19 pandemic. The use of fibrinolysis and PCI in the management of STEMI has been reported to differ before and during the COVID-19 pandemic. A study found that the use of fibrinolysis increased by 20.2% during the COVID-19 pandemic, while the use of PCI decreased by 74.6%[16]. While the use of



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Figure 3 Increased incidence. A: Fibrinolysis during the pandemic period; B: Fibrinolysis in low-and middle-income countries as compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

PCCI has become the standard of care for STEMI patients, fibrinolytic therapy may still be considered in situations where delays in PPCI are expected[39]. In light of major unexpected events like the COVID-19 pandemic, it is important to establish the effectiveness of fibrinolytic reperfusion therapy based on available evidence. Thus, the objective of this review is to critically evaluate the efficacy of fibrinolytic therapy in the context of such unprecedented and unpredictable events, like the COVID-19 pandemic.

The response to the COVID-19 pandemic has been rapidly evolving and may differ between countries based on their ability to adapt to the situation[40]. While previous studies have shown relatively consistent outcomes during the pandemic compared to the pre-pandemic period, our latest meta-analysis suggests a potential increase in the use of fibrinolytic therapy among countries with lower economic status, particularly in the eastern regions. Our subgroup analyses, which adjusted for income status, revealed that LMICs faced a higher incidence of fibrinolytic therapy and increased mortality rates for STEMI during the pandemic. Even before the pandemic, nearly three-quarters of myocardial infarction patients in such countries were treated with fibrinolytic therapy[41]. These findings raise concerns about the challenges faced by LMICs during the pandemic, as their lack of modern infrastructure may hinder their ability to provide timely reperfusion and cope with the pandemic's impact on STEMI care. Conversely, countries with high-income status and well-organized emergency systems have been able to continue using PPCI as the preferred treatment for patients requiring urgent intervention[42].

The fundamental principle of STEMI therapy is to achieve immediate, complete, and microvascular reperfusion to limit the extent of myocardial damage. Although PPCI remains the recommended reperfusion therapy by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, it must be performed by an experienced team within a specific time frame to achieve the best outcomes. Compared to fibrinolytic therapy, PPCI significantly improves

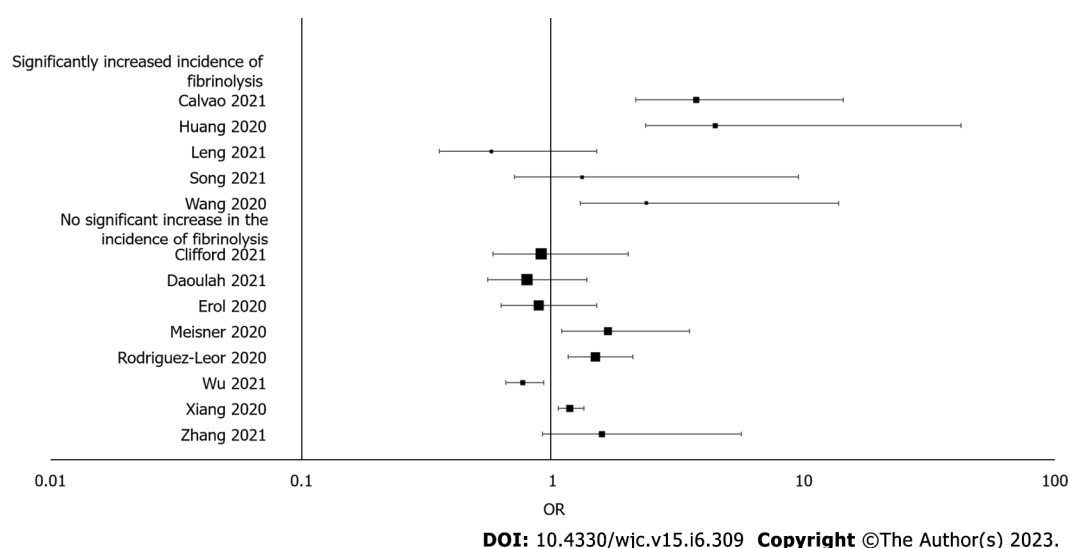


Figure 4 No association between all-cause mortality rate and the incidence of fibrinolysis.

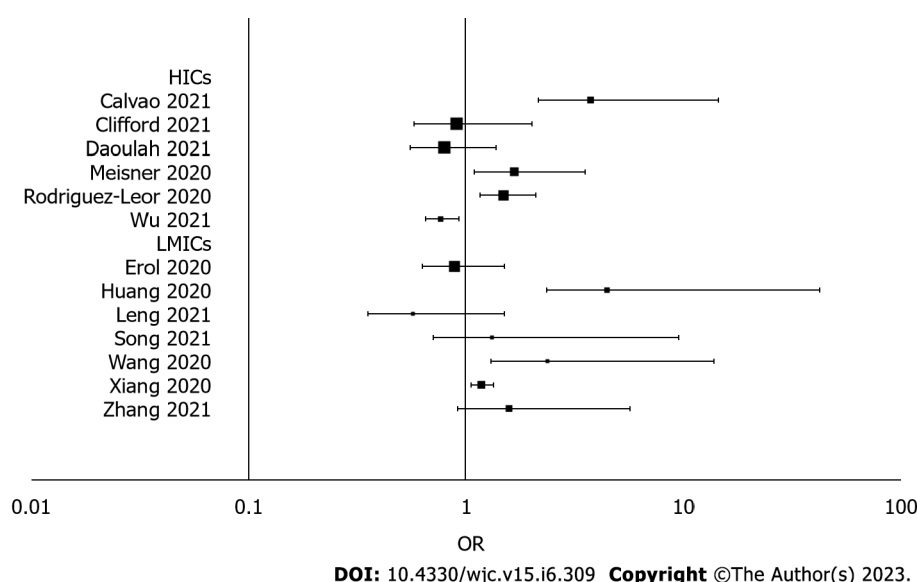


Figure 5 Increased all cause-mortality rate in low-and middle-income countries compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

survival and reduces the risk of major adverse cardiovascular events, reinfarction, and intracranial hemorrhage[43]. However, if PPCI cannot be delivered promptly, there is a sharp increase in mortality rates. In response to the pandemic, an interim guideline from China suggested the use of fibrinolytic therapy for STEMI patients presenting to healthcare facilities within 12 h of symptom onset[44]. As the saying goes, 'Time is muscle', emphasizing the importance of prompt treatment to preserve viable myocardium.

Regarding the clinical relevance of our findings, our results suggest that there may have been a decrease in the use of PCI during the COVID-19 pandemic, which could have important implications for patient outcomes. PCI is generally considered the preferred treatment for STEMI, as it has been shown to reduce mortality and the risk of complications compared to fibrinolysis. Therefore, any reduction in the use of PCI should be carefully evaluated to ensure that patient care is not compromised. Overall, the results of our study highlight the impact of the COVID-19 pandemic on the incidence, treatment, and outcomes of STEMI. These findings have important implications for clinical practice, as they underscore the need for continued efforts to promote timely recognition and treatment of STEMI, even in the midst of a pandemic. Strategies such as public education campaigns, telemedicine, and streamlined healthcare delivery systems may help to mitigate the impact of the pandemic on the management of STEMI and improve patient outcomes.

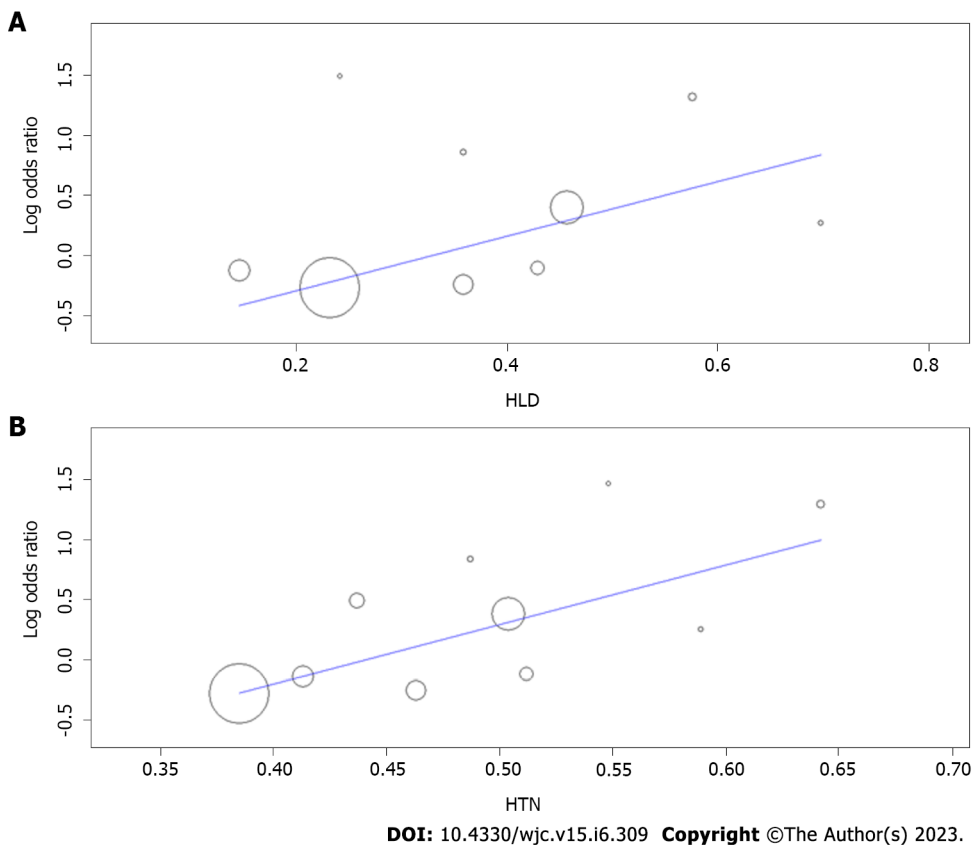


Figure 6 Meta-regression plot. A: The significant direct relationship between hyperlipidemia and the risk for all-cause of mortality; B: Meta-regression plot displaying the direct relationship between hypertension and the risk for all-cause of mortality. HLD: Hyperlipidemia; HTN: Hypertension.

Limitations

This meta-analysis has some limitations that warrant consideration. Firstly, it is possible that the use of diverse fibrinolytic agents might have had an impact on our findings, thus confounding the results. Secondly, some of the outcomes in our study displayed high heterogeneity and wide confidence intervals, indicating low certainty. This could be due to the fact that the results were based on small sample sizes with varied outcomes. Additionally, the restriction of the review to English-language studies might have resulted in the exclusion of data published in other languages, which could have affected the findings.

CONCLUSION

Fibrinolysis-based reperfusion was found to be a major reperfusion strategy during the pandemic period, but the hypothesis of an association between overall all-cause mortality and the incidence of fibrinolysis was nullified. The present analysis of non-randomized studies was suggestive of a high casual association in populations living in LMICs. These results should remain an important focus of public health initiatives. The non-randomized selection process in individual studies could have contributed bias to the current meta-analysis.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease with high morbidity and mortality rates. The preferred treatment is primary percutaneous coronary intervention, but the coronavirus disease 2019 (COVID-19) pandemic led to changes in STEMI management, including the use of fibrinolytic therapy as an alternative treatment.

Research motivation

The COVID-19 pandemic placed a significant strain on healthcare resources and providers, leading to changes in STEMI management. However, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

Research objectives

The aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

Research methods

This study analyzed the incidence of fibrinolytic therapy and all-cause mortality for STEMI patients during the COVID-19 pandemic compared to the pre-pandemic period. Data synthesis and analysis were performed using the DerSimonian and Laird random-effects model, subgrouping studies based on changes in fibrinolysis incidence and economic status of countries. The study used sensitivity analysis, meta-regression analysis, and Begg's funnel plot test to assess publication bias and heterogeneity. Statistical significance was set at < 0.05 .

Research results

This meta-analysis of 14 studies revealed a significantly higher incidence of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Patients in low- and middle-income countries (LMICs) were more likely to receive fibrinolytic therapy, and those who received it in LMICs had a higher risk of all-cause mortality. However, overall, there was no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy. Meta-regression analysis showed that hyperlipidemia and hypertension were significant predictors of all-cause mortality, indicating that managing these conditions may be crucial in reducing mortality risk.

Research conclusions

The incidence of fibrinolytic therapy for STEMI patients increased during the COVID-19 pandemic, particularly in LMICs. However, there was no significant association between fibrinolysis and all-cause mortality. The findings of this study have important implications for public health initiatives.

Research perspectives

Fibrinolytic therapy was more frequently used during the COVID-19 pandemic, particularly in LMICs, but no significant association was found between the incidence of fibrinolysis and overall all-cause mortality.

FOOTNOTES

Author contributions: Khedr A substantial contributions to conception and design of the study, drafting the article, final approval; Hennawi HA acquisition of data, or analysis and interpretation of data, drafting the article, final approval; Khan MK analysis of data, revising and drafting the article, final approval; Elbanna M performed the data analysis, drafting the article, final approval; Jama AB and Proskuriakova E interpretation of data, drafting the article, final approval; Mushtaq H and Jain N contributed to the acquisition of data, revising the article, final approval; Mir M, Boike S, Rauf I, Eissa A, Koritala T, and Khan SA contributed to the interpretation of data, revising the article, final approval; Urtecho M contributed to the interpretation of data, making critical revisions, final approval; Surani S contributed to the acquisition of data, making critical revisions, final approval.

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Virtual patient education for hypertension: The truth about behavioral change

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Abstract

Anti-hypertensive education is an important public health intervention to decrease the mortality and burden of the disease. Using digital technologies for education as a part of preventive measures for hypertension is a cost-effective approach and helps low-income communities and vulnerable populations overcome barriers to healthcare access. The coronavirus disease 19 pandemic further highlighted the need of new health interventions to address health inequalities. Virtual education is helpful to improve awareness, knowledge, and attitude toward hypertension. However, given the complexity of behavioral change, educational approaches do not always provide a change in behavior. Some of the obstacles in online hypertensive education could be time limitations, not being tailored to individual needs and not including the different elements of behavioral models to enhance behavior change. Studies regarding virtual education should be encouraged and involve lifestyle modifications emphasizing the importance of Dietary Approaches to Stop Hypertension diet, salt restriction, and exercise and should be used adjunct to in-person visits for the management of hypertension. Additionally, to stratify patients according to hypertension type (essential or secondary) would be useful to create specific educational materials. Virtual hypertension education is promising to increase awareness regarding risk factors and most importantly motivate patients to be more compliant with management helping to decrease hypertension related complications and hospitalizations.

Key Words: Hypertension; Virtual education; Health promotion; Public health; Patient education; Patient adherence; Dietary approaches to stop hypertension diet

Core Tip: Online anti-hypertensive education can play an important role in preventing and managing hypertension by providing individuals with the knowledge and resources they need to make lifestyle changes. Hypertensive management and education can be difficult in certain populations due to lack of access to healthcare, lack of information, and social determinants of health. Virtual education would promote health in those vulnerable populations.

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TO THE EDITOR

In a recent article titled "Impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and practice of hypertension management during the COVID-19 pandemic", Andrianto *et al*[1] emphasized the importance of online education in patients with hypertension[1]. Given the burden of hypertension, we found this article very interesting and promising for health promotion. Hypertension has been described as the "largest epidemic ever known to mankind"[2]. In the United States, nearly half of the adults have hypertension, and only 25% are under control[3]. Being an epidemic globally, it's not surprising that the economic burden of hypertension is enormous. In the United States itself, hypertension costs about \$131 billion each year[4]. From the public health intervention perspective, Andrianto *et al*'s study is brilliant as we believe that one of the ways to cut the cost of hypertension is community-based interventions, such as health education and support groups, which can help reduce the cost of hypertension by providing individuals with the information and resources they need to manage their condition effectively[1].

As highlighted by the authors, overall, the coronavirus disease 19 (COVID-19) pandemic has had a significant impact on health disparities and healthcare access[5]. Even in the non-COVID era, patients with low economic status have been disproportionately affected by hypertension. The Prospective Urban Rural Epidemiology study, including patients from 17 countries on five continents, showed that awareness, diagnosis, and control of hypertension were lower in low-income countries compared with other countries and in rural settings compared with urban areas[6]. Considering the disadvantages of the vulnerable population, the COVID-19 pandemic highlighted the importance of addressing health disparities to ensure that all individuals have access to the care they need. Some of the difficulties in the population-level management of hypertension for minorities are barriers to healthcare, awareness, and understanding of the importance of monitoring, which is often linked to social determinants of health such as poverty, cultural beliefs, illiteracy, discrimination, and language barriers[7].

In the current era, the increasing use of mobile applications and telemedicine for communication has the potential to bridge disparities and play a significant role in managing hypertension in outpatient settings. A study by Freund *et al*[8] suggests that even elderly patients can effectively use online interventions as an inexpensive way to find answers to their health-related questions and improve their medical knowledge[8]. To address the global burden of hypertension, the Lancet commission encourages governments, pharmaceutical companies, healthcare professionals, and professional societies to develop simple mobile apps and online education programs to provide equal basic health access to people in low-income and middle-income countries[9]. In sync with this concept, the study conducted by Andrianto *et al*[1] reveals the importance of anti-hypertensive education in lower-middle-income countries. They found that virtual anti-hypertensive educational campaign implementation led to a significant improvement in the knowledge and attitude of patients with hypertension; however, it did not reflect a change in patient practice in taking measures against hypertension[1].

We are curious as to why a prospective study such as this with robust methodology could detect an improvement in facets of hypertension management but could not alter patient behavior. The education provided by Andrianto *et al*[1] was mainly directed toward the Dietary Approaches to Stop Hypertension (DASH), which is known as one of the most effective dietary interventions to lower blood pressure (BP)[1,10]. While dietary changes constitute a part of the non-pharmacologic therapy of hypertension, trials have shown that DASH dietary pattern reduced BP by 6/4 mmHg compared to a typical American-style diet[11]. Interestingly, and contrary to popular belief, dietary salt restriction is not a constituent of the original DASH dietary approach. In a systematic review of well-controlled randomized control trials, sodium restriction was associated with a reduction of BP by 4.8/2.5 mmHg in hypertensive and 1.9/1.1 mmHg in normotensive patients, respectively[12]. The benefits of dietary

sodium restriction coupled with the DASH approach were only later studied[10]. Given the heterogeneity in the approach, we would like to know how much emphasis was placed on salt restriction education in the population. Further, the authors set the level of significance for practice-changing reduction of systolic BP at 10 mmHg. It is possible that since the primary education was directed at dietary changes amongst the non-pharmacologic measures, this reduction was not detected due to a higher set threshold. Upon reviewing Table 1 of the study, it appears that the intervention did not educate heavily on the importance of physical activity and weight loss. Multiple studies have shown that weight loss effectively reduces systolic blood pressure (SBP) and diastolic BP, and 10 kg of weight loss may lower SBP by 5 to 20 mmHg[13,14]. Integrating this could have potentially led to detecting a significant change in behavior. This is important, especially since a sedentary lifestyle is a well-known contributor to hypertension, accelerated due to the restrictions and lockdown measures during the COVID-19 pandemic.

The other reason could be a limited time of education and a lack of other intervention components. According to the behavior change wheel model, ten different intervention functions have been suggested, some of them being education, incentivization, persuasion, training, and enablement[15]. Given the complexity of behavior change required in hypertension; applying those intervention elements, such as providing patient-centered, tailored information and feedback by the healthcare professionals, would be required. Virtual education can also be tailored to an individual's specific needs and preferences. For example, some virtual programs may offer personalized meal and exercise plans, while others may provide resources and support for stress management or medication management. Although the study by Andrianto *et al*[1] did not show a major behavior change, it greatly impacted the patient's perception towards not stopping medications when the BP is under control. This is another achievement of this study, as patients obtained that awareness after education.

Lastly, we noticed that the inclusion criteria were all patients with a diagnosis of hypertension. Did the authors sub-stratify their findings for the etiology of hypertension (essential *vs* secondary)? It would be valuable to learn how many patients amongst the included 110 participants had secondary/renovascular etiology of hypertension, especially since Table 2 indicates that 30 participants were < 40 years, which is when secondary hypertension is more prevalent. Both pharmacologic and non-pharmacologic measures differ for secondary hypertension and could be a reason for not reflecting in the behavioral change of patients.

To conclude, this randomized clinical trial has nicely addressed the importance of virtual hypertension education in the current pandemic, showing an impact on knowledge and attitude specifically. Future studies could focus on the effect of behavior coaching and personalized interventions such as texting patients or following up *via* telemedicine by healthcare providers to change behavior on medication adherence, lifestyle, and BP monitoring. These interventions would make an impactful effect on health promotion when used as an adjunct to management of hypertension and reduce the risk of complications and hospitalizations.

FOOTNOTES

Author contributions: Yukselen Z and Singh Y conceived the idea for the study; Yukselen Z, Singh Y, Malempati S, Dasari M and Arun Kumar P undertook the literature review; Yukselen Z and Singh Y wrote the first draft of the manuscript; Yukselen Z, Malempati S, Singh Y, Dasari M, Arun Kumar P and Ramsaran E revised the subsequent drafts of the manuscript; All authors reviewed and agreed on the final draft of the manuscript.

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Therapies for patients with coexisting heart failure with reduced ejection fraction and non-alcoholic fatty liver disease

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Abstract

Heart failure with reduced ejection fraction (HFrEF) and nonalcoholic fatty liver disease (NAFLD) are two common comorbidities that share similar pathophysiological mechanisms. There is a growing interest in the potential of targeted therapies to improve outcomes in patients with coexisting HFrEF and NAFLD. This manuscript reviews current and potential therapies for patients with coexisting HFrEF and NAFLD. Pharmacological therapies, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoids receptor antagonist, and sodium-glucose cotransporter-2 inhibitors, have been shown to reduce fibrosis and fat deposits in the liver. However, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta blockers on NAFLD in patients with HFrEF. This study highlights the importance of considering HFrEF and NAFLD when developing treatment plans for patients with these comorbidities.

Further research is needed in patients with coexisting HFREF and NAFLD, with an emphasis on novel therapies and the importance of a multidisciplinary approach for managing these complex comorbidities.

Key Words: Non-alcoholic fatty liver disease; Heart Failure; Heart failure reduced ejection fraction; Novel therapies; Cardiovascular disease

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Core Tip: This manuscript provides an overview of potential therapies for patients with coexisting heart failure with reduced ejection fraction and nonalcoholic fatty liver disease (NAFLD). The authors discuss the current research of pathogenesis in heart failure and NAFLD, as well as pharmacological therapies that have been shown benefits. We also discuss the potential role of diet, physical activity and novel therapies in managing these conditions.

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INTRODUCTION

Heart failure (HF) is a major clinical, economic, and public health concern worldwide. The prevalence of HF in the United States and Europe is estimated to be 1.5% to 1.9% of the population, reaching a considerable number among people aged > 65 years[1]. The predominant etiologies of HF include coronary artery disease (CAD), hypertension, tachyarrhythmia, and valvular disease, and as an additional emerging risk factor, non-alcoholic fatty liver disease (NAFLD)[2].

NAFLD represents evidence of hepatic steatosis (*via* imaging or histology) with a lack of secondary causes of hepatic fat accumulation and can be categorized as non-alcoholic fatty liver (Without evidence of hepatocellular injury) or Non-alcoholic Steatohepatitis (NASH: Hepatocellular injury with or without fibrosis)[3]. Most patients with NAFLD have associated conditions, such as obesity, diabetes mellitus, hypertension, and dyslipidemia. Recently, NAFLD has been associated with other conditions such as chronic kidney disease, osteoporosis, obstructive sleep apnea, psoriasis, colorectal cancer, and HF.

Some authors have mentioned that the association between NAFLD and cardiovascular disease (CVD) is inconsistent. They hypothesized that this connection might disappear after controlling for modifiable CVD risk factors[4]. However, there are strong arguments connecting NAFLD to CVD. Chiang *et al*[5] demonstrated that non-obese and relatively healthy subjects with NAFLD have an increased risk of developing cardiovascular events[5]. In addition to Chiang *et al* [5], other studies have shown that NAFLD patients have an increased risk of CVD after adjusting for major demographic, clinical, and metabolic confounders[6].

Furthermore, emerging epidemiological studies support a strong and independent association between NAFLD and HF. These studies estimated that the prevalence of HF in patients diagnosed with NAFLD is 6.4%, with a higher risk for HF preserved ejection fraction (HFpEF) than HF reduced ejection fraction (HFREF)[7].

The association between HF and NAFLD involves similar processes in both HFpEF and HFREF, which are mediated by inflammatory and fibrotic processes. The pathophysiological relationship between NAFLD and HFpEF is attributable, at least in part, to the secretion of adipokines and proinflammatory cytokines, such as leptin, which, at the level of the liver tissue, has profibrotic activity, and in the heart, it produces cardiac hypertrophy and endothelial dysfunction. Other important factors are tumor necrosis factor- α (TNF- α) and interleukin (IL) -6, which contribute to hepatocyte injury and NAFLD, whereas damaged hepatocytes release IL-33, which promotes a profibrotic effect. In the heart, IL-33 is released in response to myocardial fiber stretching[8].

PATHOPHYSIOLOGY LINKING NAFLD WITH CARDIOVASCULAR DISEASE AND HFREF

Several pathophysiological mechanisms have been proposed to explain this relationship. One potential mechanism by which fatty liver may increase the risk of HF is an increased prothrombotic state and systemic inflammation[8]. The hypercoagulable state of NAFLD is multifactorial and complex. Some studies have suggested that oxidative injury to lipids and lipoproteins may underlie thrombophilia[9]. Plasminogen activator inhibitor type 1 (PAI-1), the most thrombophilic factor reported, significantly increases with exposure to non-oxidized low-density lipoprotein (LDL) and is directly related to hepatic steatosis[10]. Another important process in this proinflammatory stress is the apoptotic pathway, which is activated in NASH as a result of fatty acid-mediated changes in the permeability of lysosomes and mitochondria with the release of cathepsins and cytochrome C, respectively. This activates the proapoptotic caspase cascade (fatty acid

lipotoxicity), thereby resulting in a procoagulant state and contributing to atherosclerotic injury[11]. This process may explain why patients with NAFLD have a higher rate of major cardiovascular (CV) events (30% *vs* 8%)[12]. Additionally, NAFLD is associated with increased production of proinflammatory cytokines, such as IL-6 and high-sensitivity C-reactive protein (Hs-CRP), mitochondrial dysfunction eliciting reactive oxygen species (ROS) production, and stress biomarkers, such as fibroblast growth factors (FGFs), which increase the risk of CV and liver-related mortality[13,14] (Figure 1).

NAFLD is associated with high serum levels of total cholesterol, triglyceride, and LDL-cholesterol levels[15]. This dyslipidemia profile plays an important role in the pathogenesis of atherosclerosis. Nevertheless, existing data suggest that NAFLD *per se* might be an independent risk factor for CAD, even after adjusting for age, sex, traditional coronary risk factors, and visceral adipose tissue[16].

Cardiac structural and functional alterations are pivotal processes in HF in NAFLD patients. Most studies showed echocardiographic changes suggestive of left ventricular (LV) diastolic dysfunction, such as LV hypertrophy, increased left atrial volume, impaired LV relaxation, and higher left-sided filling pressures[17,18]. Furthermore, another study showed that hepatic steatosis and fibrosis are associated with diastolic dysfunction and are correlated with altered myocardial glucose uptake[19]. In addition, patients with NAFLD experience epicardial fat thickness, and both are at increased risk of coronary artery calcification[20].

Patients with NAFLD are also at an increased risk for cardiac arrhythmias, which can further increase the risk of LV dysfunction and HF. Cai *et al*[21] showed that NAFLD is associated with an increased risk of atrial fibrillation, and the strength of the association increases partially with the coexistence of cardiometabolic risk factors. In addition, Hung *et al* [22] found that mild, moderate, and severe NAFLD was associated with a high risk of heart rate-corrected QT (QTc) interval prolongation in both diabetic and nondiabetic subgroups. This mechanism is supported by the systemic inflammation and oxidative stress associated with NAFLD, which may trigger cardiac electrical and autonomic remodeling of the heart[23].

WHAT IS THE RELATIONSHIP BETWEEN NAFLD AND CARDIOVASCULAR DISEASE?

NAFLD and clinical CVD share similar risk factors (*i.e.*, sedentary lifestyle, smoking, physiological stress, and sleep deprivation/disorders). Accumulation of visceral and ectopic fat leads to the release of toxic metabolites and the activation of inflammatory pathways, ultimately leading to both entities[24]. With progressive NAFLD, factors such as insulin resistance, activated renin-angiotensin-aldosterone system (RAAS), and oxidative stress markers have the potential to increase the risk of cardiac disease and HF[25]. Specifically, the RAAS system is activated as a compensatory mechanism in early HF owing to hypoperfusion and sympathetic activation, leading to a cascade of angiotensin II and aldosterone, which are responsible for increased preload and afterload at the expense of salt and water retention, cardiac remodeling, and vasoconstriction[26,27].

It has been found that liver disease, renal failure, and diabetes contribute to greater mortality in patients with HFrEF compared to patients with HFpEF[28]. However, a recent cohort study and meta-analysis demonstrated that patients with NAFLD are at an increased risk of incident HFpEF rather than HFrEF[7,29].

Simon *et al*[30] showed that patients with biopsy-proven NAFLD had a significantly higher incidence of HF across all stages of NAFLD. Likewise, in a recent meta-analysis, NAFLD patients had a lower ejection fraction than non-NAFLD patients and increased left ventricular mass and epicardial adipose thickness[31].

These findings support the notion that NAFLD is a “multisystem” disease with multiple potential pathophysiological mechanisms that may increase the risk of HF. Herein, we discuss the possible mechanism of ventricular dysfunction and its impact on the patient's lifestyle. Therefore, our review provides an overview of novel therapies for patients with coexisting HFrEF and NAFLD with the aim of developing future interventions to prevent and treat both diseases.

NON-PHARMACOLOGICAL THERAPIES FOR PATIENTS WITH NAFLD AND HFrEF

Lifestyle modifications

Lifestyle modifications, such as dietary changes, physical activity, and weight loss, are first-line treatments for NAFLD. These modifications affect body fat adipose deposits, which also influences the development of CV comorbidities[18]. It has been studied that HF is associated with splanchnic circulation congestion, which leads to bowel wall edema and impaired intestinal barrier function, which concomitantly promotes bacterial translocation and inflammation[32]. For example, trimethylamine N-oxide, an organic compound from gut bacteria, is an independent predictor of poor prognosis in patients with HF and is strongly linked to the pathogenesis of CVD[33].

Dietary change is one of the most important factors for the treatment of NAFLD and HF. Montemayor *et al*[34] concluded that customized hypocaloric dietary and enhanced physical activity interventions may be useful in ameliorate NAFLD[34]. The Mediterranean Diet, rich in vegetables, fruits, legumes, potatoes, non-refined cereals, fish, white meat, and red wine, seems to have a favorable association with NAFLD in Iranian adults, especially in women and patients with or without abdominal obesity[35]. The DASH diet, which is rich in antioxidants, micronutrients, fiber, and nitrates and has low saturated and trans fats, has been shown to decrease proinflammatory cytokines and ROS, restore micronutrient status, and promote endothelial function[36]. Belanger *et al*[37] demonstrated that a DASH diet progressively reduced high-sensitivity cardiac troponin I and Hs-CRP over 12 wk[37].

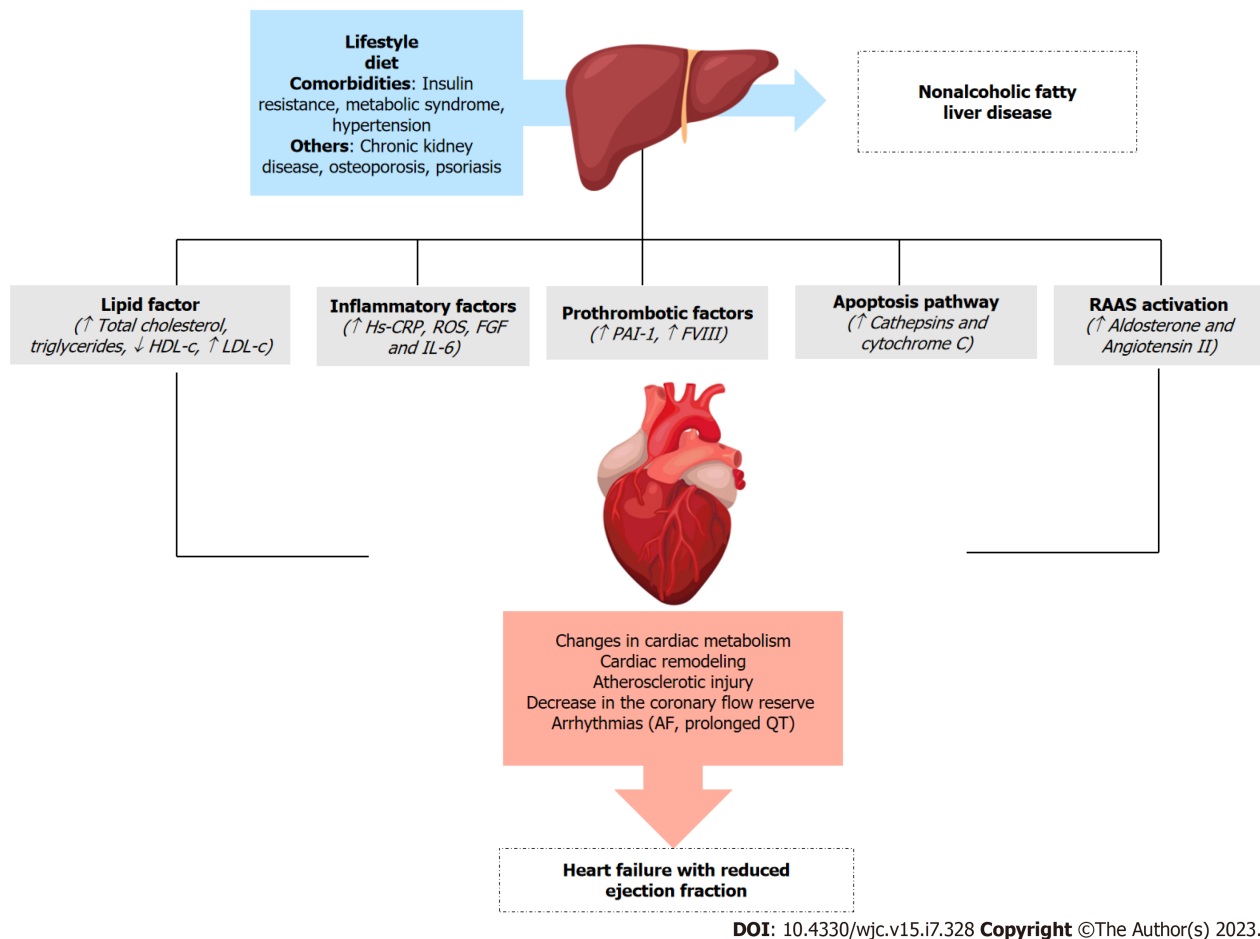


Figure 1 Pathophysiology of non-alcoholic fatty liver disease and heart failure with reduced ejection fraction. LDL-c: Low-density lipoprotein-cholesterol; HDL-c: High-density lipoprotein-cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ROS: Reactive oxygen species; FGF: Fibroblast growth factor; IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1; AF: Atrial fibrillation; RAAS: Renin angiotensin aldosterone system.

Bariatric Surgery

Bariatric surgery (BS) is one of the most effective treatments for obesity and its comorbidities[38]. The literature suggests that BS has also been associated with long-term improvements or even resolution of NAFLD in both clinical and histological features and has been shown to reduce CVD risk in patients with obesity by improving glucose tolerance and lipid panels[39-41]. Additionally, a recent meta-analysis showed that BS was associated with lower incidences of HF and myocardial infarction (MI)[42]. Another study showed that 96 months after BS, the cumulative incidence of HF was 4.2% and 11.5% in the surgical and non-surgical groups, respectively[43]. All these effects of BS seem to be related to changes triggered by gastrointestinal hormones such as Glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide, leptin, gut hormone peptide YY, and ghrelin after anatomical intervention.

Additionally, changes in the gut microbiota are crucial for NAFLD[38]. Studies have shown a relationship between the gut microbiome and HF development[44]. This interplay involves gut microbial metabolites (which serve as mediators in HF pathophysiology), immune responses, and a vicious cycle caused by gut hypoperfusion in HF and subsequent additional microbiome alterations[33,44].

PHARMACOLOGICAL THERAPIES IN HFREF WITH EFFECT ON NAFLD

Currently, several therapies with strong evidence of benefit for HFREF have also been reported to have an effect on NAFLD. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce fibrosis and fat deposition in the liver. Mineralocorticoids receptor antagonist (MRA), such as spironolactone, have been reported to have a clear effect on the combination of this diuretic with vitamin E. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have been reported to reduce liver stiffness and improve steatosis. Unfortunately, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta-blockers (BB) on NAFLD (Table 1).

ACEIs and ARBs

ACEIs and ARBs block the effects of angiotensin II. These drugs are commonly prescribed to treat high blood pressure

Table 1 Effects on non-alcoholic fatty liver disease of drugs that have strong evidence of benefit on heart failure

Drug	HF phenotype with evidence of benefit	Effect on NAFLD Population	Comparator	Study
ACEI	HFrEF	Reduced liver-related events, liver cancer, and cirrhosis complications[47]	Placebo	Cohort
ARB	HFrEF	Trial failed to evidence that losartan 50 mg has antifibrotic effects on NASH due to widespread use[102]	Placebo	Trial
		Patients with CKD-NAFLD taking ACEI or ARB had significantly lower liver stiffness degrees in comparison to those without those drugs[103]	Placebo	Cohort
		Losartan 100 mg in children reduced alkaline phosphatase, but not ALT at 24 wk[104]	Placebo	Trial
		Losartan 50 mg in children reduced ALT more frequently than those patients with placebo[105]	Placebo	Trial
		Telmisartan 40 mg reduced free fatty acid level and increased liver-to-spleen ratio in diabetic patients with NAFLD[106]	Losartan	Trial
		Telmisartan had similar effects to vitamin E in NAFLD histology[107]	Vitamin E	Trial
		Telmisartan 40/80 mg improved NAFLD activity score and fibrosis in NASH[108]	Lifestyle modification	Trial
		Telmisartan and olmesartan improved HOMA-IR and ALT levels[48]	Before-after comparison	Quasiexperimental
		Losartan significantly decreased steatosis degree and visceral adipose tissue, addition of simvastatin further decreased those parameters[109]	Amlodipine and simvastatin	Trial
Diuretics	HFrEF and congested HFpEF	Amlodipine, lisinopril and rosuvastatin decreased ALT and alkaline phosphatase[110]	Therapy without rosuvastatin	Trial
		In patients with NAFLD and diabetes lisinopril and hydrochlorothiazide were associated with less likelihood of advanced fibrosis, while furosemide and spironolactone had higher likelihood of it[111]	Other therapies	Cohort
		Spironolactone and vitamin E reduced NAFLD liver fat score, insulin, and HOMA-IR[55,112]	Vitamin E alone	Trial
SGLT2 inhibitors	HFrEF and HFpEF	Five subjects received eplerenone. The study stopped early due to an unexpected increase in hepatic fat at 24 wk[113]		Open-label proof-of-concept study
		Empagliflozin reduced liver stiffness measurement and steatosis (in patients with significant steatosis at baseline), liver fat level, AST, ALT and insulin in patients with NAFLD without diabetes[114]	Placebo	Trial
		Tofogliflozin significantly improved the fibrosis scores, steatosis, hepatocellular ballooning, and lobular inflammation[115]	Glimepiride	Trial
		Empagliflozin plus diabetes therapy better-improved liver fat in NAFLD patients with diabetes[116]	Diabetes therapy without empagliflozin	Trial
		Dapagliflozin and omega-3 carboxylic acids reduced liver fat[117]	Placebo	Trial
		Ipragliflozin as add-on diabetes therapy reduced liver steatosis in NAFLD patients with diabetes[118]	Metformin and pioglitazone	Trial
		Empagliflozin was associated with reduction of ALT, liver stiffness and controlled attenuation parameter in patients with NAFLD and diabetes[119]	Before-after comparison	Cohort
		Luseogliflozin improved liver-to-spleen ratio and liver fat in NAFLD patients with diabetes[120]	Metformin	Trial
		Dapagliflozin and pioglitazone significantly increased liver-to-spleen ratio. Only dapagliflozin decreased visceral fat area in patients with NAFLD and diabetes [121]	Pioglitazone and glimepiride	Trial

Ipragliflozin reduced visceral fat area, but not AST or ALT, in patients with NAFLD and diabetes[122]	Pioglitazone	Trial
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ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure preserved ejection fraction; NASH: Non-alcoholic Steatohepatitis; CKD: Chronic kidney disease; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferases; AST: Aspartate aminotransferases; SGLT2: Sodium-glucose cotransporter 2; HOMA-IR: Homeostatic model assessment for insulin resistance.

and HF. However, recent studies have suggested that ACEIs and ARBs may have beneficial effects on NAFLD[45]. Angiotensin II is a key contributor to abnormal lipid metabolism in NAFLD. Angiotensin II can worsen insulin sensitivity, generate ROS, and trigger the production of inflammatory cytokines such as TNF- α , IL-6, and PAI-1, all of which contribute to NAFLD progression[46]. For this reason, Zhang *et al*[47], in their retrospective cohort study of over 12000 patients with NAFLD, found that treatment with ACEIs for at least six months was associated with a lower risk of liver cancer and cirrhosis. Nevertheless, this effect was not seen with ARBs[42]. These data are surprising for Enjoji *et al* [48], who showed that ARBs can restore intracellular insulin signaling and facilitate the movement of excess fat from non-adipose tissues to adipocytes, which may improve markers of liver function such as transaminases, hepatic steatosis, and inflammation[48,49]. Furthermore, several clinical trials and meta-analyses have suggested that ACEIs and ARBs are effective in reducing mortality and hospitalization in patients with HFrEF and Advanced Kidney Disease[50]. Gilstrap *et al*[51] conducted a study to investigate the impact of BB and renin-angiotensin system inhibitors (RASi) on the outcomes of patients aged over 65 years with HFrEF. The study found that the use of BB and/or RASi at hospital discharge was associated with lower 30-d and 1-year mortality rates, even among patients aged > 85 years[51]. Similarly, the CHARM-Alternative trial investigated the use of candesartan *vs* placebo in patients with HF who were intolerant of ACE inhibitors. The study found that during a median follow-up of 3 years, hospitalization or cardiovascular-related death was reported in 33% of candesartan patients *vs* 40% of placebo patients[52].

Spironolactone

Patients with NAFLD and HFrEF may experience beneficial outcomes with the use of aldosterone antagonists such as spironolactone and eplerenone. Wada *et al*[53] investigated the effects of eplerenone on nonalcoholic steatohepatitis and metabolic syndrome in a mouse model. The results showed that Eplerenone effectively ameliorated insulin resistance, blood pressure, and hepatic steatosis with fibrotic changes by inhibiting the inflammatory response in Kupffer cells and macrophages[53]. Similarly, spironolactone effectively improves the accumulation of triglycerides in the liver, reduces inflammation, and downregulates gluconeogenic and lipogenic gene expression[54]. Furthermore, combination therapy with spironolactone and vitamin E appears to have a positive effect on serum insulin levels in individuals with NAFLD [55].

Patients with HF and reduced ejection fraction may benefit from the use of MRA such as spironolactone, as they have been shown to reduce mortality when administered at low doses of 25 mg to prevent hyperkalemia[56]. However, the ATHENA-HF Trial found that a high dose of spironolactone or eplerenone may be a safe and effective treatment option for patients with HFrEF because it is associated with a reduction in NT-pro brain natriuretic peptide (BNP) levels, reduction in body weight, and improved symptoms of HF, such as dyspnea and fatigue, by reducing myocardial fibrosis and improving ventricular function[57,58]. Thus, evidence suggests that RAAS inhibitors, regardless of dose, may be particularly beneficial in patients with HFrEF.

SGLT-2i

SGLT-2i suppress glucose reabsorption in the proximal tubule of the kidney, resulting in excretion of glucose in the urine and improvement of insulin resistance. Initially developed as a diabetes mellitus therapy strategy independent of insulin [59]. The improvement in hyperglycemia and insulin resistance may be related to the control of lipogenesis through transcriptional regulation of lipogenic genes, including acetyl-CoA carboxylase and fatty acid synthase, and the development of hepatic steatosis[60].

Several studies have reported that SGLT-2i can inhibit the development of NAFLD and improve histological hepatic steatosis or steatohepatitis in experimental animal models[61]. Another possible mechanism of action of SGLT-2i in NAFLD is the weight-and visceral fat-dependent effects and inhibition of de novo lipogenesis in the liver[62].

SGLT-2i have been shown to reduce the risk of cardiovascular death or hospitalization in patients with HFrEF with or without type 2 diabetes mellitus (T2DM). There are several randomized controlled trials such as DAPA-HF, EMPEROR-Reduced, EMPULSE[63], EMPIRE-HF, SOLOIST-WHF[64], and CANVAS trials[65]. In addition to the most updated American College of Cardiology (ACC) guidelines for the management of HF, SGLT-2i has become a mainstay in the treatment of HFrEF and HFpEF.

A recent meta-analysis, including 1950 patients, evaluated liver structure and function in patients taking SGLT-2i with placebo or other oral antidiabetic drugs. It revealed a decrease in liver function tests (LFT), such as serum alanine and aspartate aminotransferases and gamma-glutamyl transferase, and a decrease in liver steatosis[66]. Another meta-analysis showed that SGLT-2i also reduced liver fat content and improved LFT in patients with NAFLD, as estimated by cardiac magnetic resonance proton density fat fraction[67].

These findings imply that SGLT-2i may be an effective treatment for patients with both NAFLD and HFrEF.

POTENTIAL PHARMACOLOGICAL THERAPIES

GLP-1 receptor agonists

GLP-1 is an incretin hormone secreted in the gut in response to meal ingestion, which increases insulin secretion and inhibits glucagon production, targeting pancreatic β -cells. Consequently, GLP-1 receptor agonists improve hyperglycemia and delay gastric emptying, thereby promoting weight loss[68]. They can be an attractive therapeutic option for treating patients with NAFLD, particularly those with associated diabetes mellitus and obesity.

A multicenter, randomized, double-blind, placebo-controlled trial showed that liraglutide was associated with the resolution of NASH with no worsening of fibrosis score, improvement in steatosis, and hepatocyte ballooning score[69]. Liraglutide and exenatide have been attributed to decreases in trunk fat content, especially in the android region, which is associated with NAFLD and is closely associated with CVD risk[70,71].

In preclinical studies, some of the well-described effects of GLP-1 may reflect indirect mechanisms in the heart, such as augmentation of ventricular function in animals with HF or ischemia-induced ventricular dysfunction, attenuation of the development or progression of atherosclerosis or plaque formation, augmented myocardial or coronary artery blood flow rate control, reduced blood pressure, increased secretion of atrial natriuretic factor, and inhibition of platelet aggregation [72].

According to current guidelines, GLP-1 receptor agonists have no effect on the risk of HF hospitalization, which suggests that they are safe to use but are not beneficial in preventing HF in at-risk patients. Therefore, it should be used cautiously during acute decompensation[73].

Three small randomized controlled trials of GLP-1 receptor agonists were conducted in patients with HFrEF. The LIVE and FIGHT trials studied liraglutide *vs* placebo and showed no changes in left ventricular ejection fraction (LVEF), quality of life, or functional class at 24 wk. Albiglutide has also been studied and showed no significant differences in LVEF, BNP, 6-min walk test, myocardial glucose, or oxygen use[74]. GLP-1 RAs have a positive chronotropic effect, causing an increase in heart rate and induced increases in cAMP levels, which may worsen HF and increase the risk of death[75].

Although observations from treatment with GLP-1RAs and NAFLD suggest beneficial data, observations from randomized trials suggest no clear benefit in HF-related outcomes and even uncertainty regarding safety in patients with HFrEF. Larger studies of patients with HFrEF are recommended.

Tirzepatide

A novel medication for the treatment of T2DM, tirzepatide, a dual glucose-dependent insulinotropic polypeptide and a GLP-1 receptor agonist, has shown promising results in ongoing clinical trials, not only for T2DM but also for improving body weight and steatosis[76]. They compared its effects with those of dulaglutide on NAFLD biomarkers and fibrosis in patients with diabetes mellitus and found that a higher tirzepatide dose significantly decreased NAFLD biomarkers and increased adiponectin levels[77]. Additionally, SURPASS-3, using magnetic resonance imaging, demonstrated that tirzepatide significantly reduced liver fat content, visceral adipose tissue volume, and abdominal subcutaneous adipose tissue[78].

Currently, the efficacy and safety of tirzepatide in patients with HFpEF and obesity are being assessed[79]. No current data supports the use of tirzepatide in patients with HFrEF. Studies on patients with HFrEF are recommended.

Metformin

Metformin is a biguanide that can improve insulin sensitivity and regulate glucose utilization by the liver[80]. Metformin treatment has been shown to be effective in alleviating hepatic lipogenesis in animal models of NAFLD through various mechanisms. However, in clinical studies, metformin modestly reduced body mass index, liver fat content, and liver enzyme levels in patients with NAFLD and diabetes. Despite these reports on the benefits of metformin, some contradictory results still exist. Despite these reports on the benefits of metformin, conflicting results remain. Combination treatments with other antidiabetic drugs, especially thiazolidinedione, GLP-1 receptor agonists, and SGLT2 inhibitors, demonstrated greater efficacy. Further research with a larger sample size is required to confirm these findings[81].

Left ventricular hypertrophy is a common finding in patients with ischemic heart disease and is associated with mortality in those with CVD. Metformin has been shown to reduce oxidative stress and left ventricular mass index. These results suggest a favorable effect of metformin on the left ventricular mass index and LVEF in patients with or without preexisting CVD[82]. In a recent report of diabetic patients with advanced HFrEF, patients treated with metformin demonstrated better quality of life and improved outcomes than patients not receiving metformin. Metformin remains one of the frontline drugs for the treatment of patients with HFrEF and Diabetes Mellitus[83].

The long-term clinical impact of metformin on HFrEF requires additional research despite its potential therapeutic effects on NAFLD.

Thiazolidinediones

Thiazolidinediones act as peroxisome proliferator-activated receptor- γ activators in adipose, muscle, and liver tissues, resulting in a decrease in glucose production and subsequent increase in glucose utilization[84].

A recent meta-analysis compared placebo and pioglitazone, a thiazolidinedione, and found that it significantly improved steatosis grade, inflammation grade, and ballooning grade, whereas in the fibrosis stage, there was no significant improvement in pioglitazone compared with placebo. In addition, pioglitazone significantly reduced fasting blood glucose, glycosylated hemoglobin, serum alanine, and aspartate aminotransferase levels. Owing to the lack of relevant randomized controlled trials and short intervention times, long-term studies are needed to verify its efficacy and

safety[85]. Another systematic review showed that pioglitazone consistently improved histological parameters and normalized liver transaminases, although the evidence supporting the benefits of other drugs in this class is minimal. Thiazolidinediones, particularly pioglitazone, have proven efficacious in patients with NAFLD/NASH[86].

Rosiglitazone has been shown to increase the risk of MI and HF, whereas pioglitazone decreased the risk of major adverse cardiovascular events, such as MI and stroke, but increased the risk of HF[87]. Pioglitazone was associated with higher rates of HF hospitalization in a smaller randomized controlled trial of participants with more severe symptomatic HFrEF than placebo[88]. Patients with T2DM with New York Heart Association functional class I-II CHF and reduced LVEF were randomized to 52 wk of treatment with rosiglitazone, and there were significantly more confirmed events of new or worsening edema and increased HF medication in the rosiglitazone group[89]. According to current guidelines for the treatment of HF from the ACC, given the existing evidence, thiazolidinediones should be avoided in patients with reduced LVEF[90].

In conclusion, although thiazolidinediones have demonstrated efficacy in patients with NAFLD, they are not recommended for diabetic patients at a high risk of HF, as they have been proven to increase the risk of HF in this group of patients.

Statins

Statins are safe for patients with NAFLD across the disease spectrum, including those with advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality. The management of dyslipidemia in NAFLD should include the use of moderate- to high-intensity statins as first-line therapy, based on lipid risk levels and atherosclerotic ASCVD risk scores[91].

These medications can impair insulin sensitivity and secretion by pancreatic β -cells and increase insulin resistance in the peripheral tissues. Statins may also contribute to statin-induced T2DM[92]. Moreover, statin use is associated with a significant reduction in cardiovascular mortality and morbidity in both primary and secondary prevention strategies. A reduction in the risk of new-onset HF in patients with a high cardiovascular risk and hospitalization for HF has also been reported[25]. Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic HF, although it did reduce the number of cardiovascular hospitalizations[93].

Statins may have a beneficial effect on CV outcomes irrespective of HF etiology and LVEF. Lipophilic statins (*e.g.*, atorvastatin) and non-hydrophilic statins (*e.g.*, rosuvastatin or pravastatin) showed significant reductions in clinical outcomes; however, lipophilic statins seem to be much more favorable for patients with HF[94].

Statins appear to have beneficial effects in NAFLD. Although there is the possibility of triggering T2DM, statins have more benefits than inconveniences in the treatment of NAFLD and reduce the risk of HFrEF.

NOVEL THERAPIES OR *IN VITRO* STUDIES INVESTIGATING NEW DRUGS

Similarly, potential beneficial molecules for NAFLD are currently being investigated. Niacin, a vitamin derived from tryptophan metabolism, is known for its effect on dyslipidemia; however, recent studies have indicated that niacin reduces hepatic fat accumulation and steatosis, inflammation, and fibrosis by inhibiting diacylglycerol acyltransferase 2, an enzyme responsible for the synthesis of triglycerides, blocking the activation of hepatic stellate cells, and decreasing the activity of matrix metalloproteinases 2 and 9[95].

Sesquiterpene glycoside, an extract of the dried root *Codonopsis pilosula*, is a common drug used in traditional Chinese medicine because of its affordable cost and anti-inflammatory effects[96]. Therefore, a recent study provided evidence that the use of sesquiterpene glycosides in mice could protect against NAFLD in patients with T2DM. These findings were related to the repair of insulin signaling and inhibition of cytochrome P450 2E1 (CYP2E1) and NOD-like receptor family 3 *in vivo* and *in vitro*; thus, reducing oxidative stress, inflammation, and inflammatory cytokines and preventing insulin resistance[97].

Flavonoids (*i.e.* Baicalein, silymarin, rutin, and quercetin) has also shown hepatic protection by modulating the function of CYP2E1. These molecules are usually found in fruits, vegetables, and plant-derived beverages, and are used as nutritional supplements. They can improve insulin resistance, endoplasmic reticulum stress, lipid peroxidation, and fibrosis[98].

FGF21 is a hormone that plays an important role in regulating metabolic pathways[99]. This hormone is mainly produced by the liver and its signaling is associated with NAFLD pathogenesis[100]. In addition, FGF21 regulates lipid and glucose metabolism, which is correlated with CVD and HF. In summary, FGF21 may be a potential biomarker for prognosis prediction and as a treatment target in the future. However, further studies are required to determine their precise roles[101].

CONCLUSION

HFrEF is a major public health problem worldwide. Additionally, due to the rising incidence of obesity and associated comorbid conditions, such as diabetes mellitus and metabolic syndrome, NAFLD has also become a common condition. Multiple recent studies have shown a strong association between HF, especially the HFrEF subtype, and NAFLD. Although there are multiple proposed pathophysiological mechanisms, most are common factors in the development of systemic inflammation. To date, several non-pharmacological, pharmacological, and surgical interventions have been

studied in patients with concomitant HFrEF and NAFLD. Evidence shows the potential benefits of dietary changes; certain medications, such as ACEI, ARB, MRA, and SGLT-2i; and BS. However, there is still a lack of robust data and well-designed clinical trials investigating several other drugs or novel therapies that could benefit from these conditions and improve outcomes.

FOOTNOTES

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Observational Study

Risk factors in cardiovascular patients: Challenges and opportunities to improve secondary prevention

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Abstract

BACKGROUND

Effective management of major cardiovascular risk factors is of great importance to reduce mortality from cardiovascular disease (CVD). The Survey of Risk Factors in Coronary Heart Disease (SURF CHD) II study is a clinical audit of the recording and management of CHD risk factors. It was developed in collaboration with the European Association of Preventive Cardiology and the European

Society of Cardiology (ESC). Previous studies have shown that control of major cardiovascular risk factors in patients with established atherosclerotic CVD is generally inadequate. Azerbaijan is a country in the South Caucasus, a region at a very high risk for CVD.

AIM

To assess adherence to ESC recommendations for secondary prevention of CVD based on the measurement of both modifiable major risk factors and their therapeutic management in patients with confirmed CHD at different hospitals in Baku (Azerbaijan).

METHODS

Six tertiary health care centers participated in the SURF CHD II study between 2019 and 2021. Information on demographics, risk factors, physical and laboratory data, and medications was collected using a standard questionnaire in consecutive patients aged ≥ 18 years with established CHD during outpatient visits. Data from 687 patients (mean age 59.6 ± 9.58 years; 24.9% female) were included in the study.

RESULTS

Only 15.1% of participants were involved in cardiac rehabilitation programs. The rate of uncontrolled risk factors was high: Systolic blood pressure (BP) (SBP) (54.6%), low-density lipoprotein cholesterol (LDL-C) (86.8%), diabetes mellitus (DM) (60.6%), as well as overweight (66.6%) and obesity (25%). In addition, significant differences in the prevalence and control of some risk factors [smoking, body mass index (BMI), waist circumference, blood glucose (BG), and SBP] between female and male participants were found. The cardiovascular health index score (CHIS) was calculated from the six risk factors: Non- or ex-smoker, BMI < 25 kg/m², moderate/vigorous physical activity, controlled BP ($< 140/90$ mmHg; 140/80 mmHg for patients with DM), controlled LDL-C (< 70 mg/dL), and controlled BG (glycohemoglobin $< 7\%$ or BG < 126 mg/dL). Good, intermediate, and poor categories of CHIS were identified in 6%, 58.3%, and 35.7% of patients, respectively (without statistical differences between female and male patients).

CONCLUSION

Implementation of the current ESC recommendations for CHD secondary prevention and, in particular, the control rate of BP, are insufficient. Given the fact that patients with different comorbid pathologies are at a very high risk, this is of great importance in the management of such patients. This should be taken into account by healthcare organizers when planning secondary prevention activities and public health protection measures, especially in the regions at a high risk for CVD. A wide range of educational products based on the Clinical Practice Guidelines should be used to improve the adherence of healthcare professionals and patients to the management of CVD risk factors.

Key Words: Coronary heart disease; Cardiovascular risk factors; Secondary prevention; Clinical practice guidelines; Clinical audit; Survey of risk factors

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Core Tip: The article stresses the value of audit studies in clinical practice. It confirms that the control rate of major cardiovascular risk factors is insufficient and stresses the importance of an individual approach to the secondary prevention of atherosclerotic coronary heart disease, considering patients' gender, comorbidities, cultural peculiarities, and the region of their residence.

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INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) (ASCVD) remains the leading cause of morbidity and mortality worldwide. According to recent data, the incidence and mortality rates of CVDs have declined in high-income countries, and the majority of global deaths from CVD occur in low- and middle-income countries[1].

The World Health Organization's 'Global Plan of Action for Noncommunicable Diseases (NCDs) Prevention and Control 2013-2020' aims to reduce mortality from these causes by a quarter by 2025[2]. Two of the nine global targets

focus directly on CVD prevention and control. The recently published European Society of Cardiology (ESC) guidelines on CVD prevention are designed to help health professionals identify the best strategies for managing modifiable risk factors in patients with established ASCVD[3].

Effective control of CVD risk factors plays a critical role in reducing mortality from CVDs. International registry studies provide valuable information on the current status of the problem, identify deficits, and contribute to improving the quality of care and clinical outcomes in different countries.

The Survey of Risk Factors in Coronary Heart Disease (SURF CHD) II study is a clinical audit of the recording and management of CHD risk factors, developed in collaboration with the European Association of Preventive Cardiology and the ESC. It was conducted in countries representing Europe, Asia, and Middle East and more recently North Africa, and South America to assess the recording and monitoring of cardiovascular risk factors in patients with established CHD, and to evaluate the effectiveness of implementation of and adherence to clinical guidelines in daily practice[4,5]. Previous studies have shown that control of major cardiovascular risk factors in patients with established ASCVD varies from country to country, and is generally inadequate[4].

Azerbaijan is located in the South Caucasus region, at the crossroads of Asia and Europe, and is one of the regions at a very high risk for CVDs[6]. Our study aimed to assess adherence to ESC recommendations[7] for secondary prevention of a CVD based on the measurement of both modifiable risk factors and their therapeutic management in patients with confirmed CHD at different hospitals in Baku (Azerbaijan).

MATERIALS AND METHODS

Study design and data collection

Six tertiary public (3) and private (3) health care centres from Baku (Azerbaijan) participated in the cross-sectional SURF CHD II study between November 2019 and July 2021. A one-page standard questionnaire of the study was used to collect information electronically on demographics, diagnostic category, risk factors, physical and laboratory data, and prescribed medications from consecutive patients aged ≥ 18 years with established CHD during routine outpatient visits.

The study protocol was approved by the Ethics Committee of Azerbaijan Society of Cardiology (ASC). CHD was defined as any of the following events in the history: Coronary artery bypass grafting (CABG); elective or urgent percutaneous coronary intervention (PCI); acute coronary syndrome (ACS), defined as cardiac chest pain at rest with objective evidence of acute ischemia or infarction; or stable angina pectoris (SAP), defined as clinical angina with objective confirmation by a positive exercise electrocardiogram or positive myocardial perfusion imaging or presence of stenosis of 70% or more in at least one coronary artery on coronary angiogram.

The questionnaire included demographics, risk factor history, risk factor measurements, and most recent laboratory measurements taken during outpatient visits by cardiologists. Demographic information included age, sex, ethnic group, and educational level. For the risk factor history, information was collected on smoking history, physical activity, family history of CVD, and previous history of hypertension, dyslipidaemia, and diabetes mellitus (DM) type I or II. We also collected information on risk factor and laboratory measurements: Height, weight, calculated body mass index (BMI), waist circumference (WC), systolic blood pressure (BP) (SBP) and diastolic BP (DBP), fasting blood glucose (BG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and glycated haemoglobin (HbA1c) for patients with DM.

Participation in cardiac rehabilitation (CR) and use of cardiac medications such as antiplatelet agents, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Ca antagonists, other antihypertensive drugs, diuretics, statins, PCSK9 inhibitors, other lipid-lowering drugs, insulin, oral hypoglycaemic drugs, and nitrates were also reported in the questionnaire.

Variable definition

Smoking history was categorized into the current smoker (if participants were smokers at the time of the questionnaire or in the previous 6 mo), non-smoker, and ex-smoker (participants that had quit smoking more than 6 mo ago). The level of physical activity was divided into less, more, and equal to the recommended level: 30 min of moderately vigorous physical activity three to five times per week. It was considered that participants had a family history of premature CVD if they had a first-degree relative with a history of ASCVD before the age of 55 years for a male or 65 years for a female. The highest level of education, history of hypertension, dyslipidaemia, DM type 1 or type 2, and participation in CR were documented.

Depending on the BMI value, the following categories were identified[8]: Underweight < 18.5 kg/m², normal weight 18.5-24.9 kg/m², and overweight 25-29.9 kg/m²; obesity I degree: 30-34.9 kg/m², obesity II degree: 35-39.9 kg/m², and obesity III degree: ≥ 40 kg/m². WC ≥ 88 cm in women and ≥ 102 cm in men was defined as abdominal obesity[7,8]. Arterial hypertension (AH) was established with the use of antihypertensives or BP $> 140/90$ mmHg[9]. Dyslipidaemia was defined as the use of statins or TC level of ≥ 200 mg/dL, LDL-C level of ≥ 130 mg/dL, TG level of ≥ 150 mg/dL, and HDL-C level of ≤ 40 mg/dL in men and ≤ 50 mg/dL in women[10]. DM was defined as the use of an antidiabetic drug or HbA1c level of $\geq 6.5\%$ or fasting BG level of ≥ 126 mg/dL[11].

Therapeutic targets were in accordance with ESC Guidelines and were identified as follows: Uncontrolled AH-SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; uncontrolled DM-HbA1c $\geq 7\%$; uncontrolled LDL-C ≥ 70 mg/dL. Lifestyle targets were defined as reaching targets for smoking status (non-/ex-smoker), BMI < 25 , and moderate/vigorous physical activity[7].

A cardiovascular health index score (CHIS) was calculated to summarize the burden of risk factors. The CHIS was calculated as the number of risk factors that each participant presented, from the following six risk factors: Non-/ex-smoker, BMI < 25 kg/m², moderate/vigorous physical activity, controlled BP (< 140/90 mmHg; 140/80 mmHg for patients with DM), controlled LDL-C (< 70 mg/dL), and controlled BG (HbA1c < 7% or BG < 126 mg/dL). The following categories were defined: Poor, CHIS ≤ 2; intermediate, CHIS = 3-4; good, CHIS = 5-6[4].

Statistical analysis

Cases with missing data were excluded from the analysis. Statistical processing of the results was carried out using the Microsoft Excel and IBM SPSS Statistica v.21 software packages. The parameters were tested for normality of distribution using the Kolmogorov-Smirnov test. For normally distributed variables, descriptive statistics were used: mean ± SD, minimum, median, and maximum. To determine the statistical significance of differences between the two groups, Student's *t*-test (for continuous variables that showed a normal distribution), non-parametric Mann-Whitney *U* test (for continuous variables that did not show a normal distribution), and χ^2 test were used. *P* < 0.05 was accepted as being statistically significant.

RESULTS

Study population

Data from 687 consecutive CHD outpatients (mean age 59.6 ± 9.6 years) were included in the study, and 171 (24.9%) of the participants were women.

Demographic characteristics and CHD category, hospital admission, and participation in CR according to the sex of patients are summarized in Table 1. All patients were Caucasian. The mean age of the female patients was significantly higher than that of the men (*P* < 0.0001). Of all patients, 39.4% were admitted to the hospital during the last year for a CHD-related reason, and only 15.1% participated in CR programs. Male participants in this study were found to have a higher prevalence in ACS and PCI (*P* = 0.001 and *P* = 0.004, respectively). More women than men had systolic AH (SAH) (*P* = 0.0002). No significant differences in the number of patients who underwent CABG, hospital admission in the last year, and participation in CR were observed between male and female patients.

Prevalence of cardiovascular risk factors

Table 2 represents the cardiovascular risk factors stratified by sex. A higher rate of smoking was found among males (32% vs 1.8% in female patients). The number of female patients with no smoking history was significantly higher compared to the male participants (96.5% and 29%, respectively). The sex differences were statistically significant for all categories of smoking history (*P* < 0.00001).

Of all participants, 48.3% reported a family history of premature CVD. There were no sex differences on this indicator.

A history of hypertension was reported by most patients (78.2%), while dyslipidemia and diabetes were reported by 37.1% and 45.1% of patients, respectively. Statistically significant sex differences between the groups were found in the prevalence of diabetes (55.6% vs 41.7% in females and males, respectively; *P* = 0.002).

It should be mentioned that body weight and height were not measured in all subjects, and consequently, BMI was calculated only in 31.4% of all participants. The risk factor and laboratory measurement results are displayed in Table 3. The mean BMI value in these patients was found to be 28.4 kg/m², with the mean value of 29.6 kg/m² in females and 28 kg/m² in males (*P* = 0.002).

Waist circumference was measured only in 30 participants (4.4%, 13 females and 17 males), and it was high in 63.3% of those patients. Among them, 83.6% of females and 47.1% of males had abdominal obesity (*P* = 0.034).

In relation to laboratory data, there were no significant differences between male and female participants in TC, LDL, HDL, TG, or HbA1c values. However, BG levels were found to be higher in female patients (*P* = 0.04).

Risk factor targets and CHIS categories

Lifestyle targets and CHIS categories in patients are represented in Figure 1. Non/ex-smokers were predominant among female participants (*P* < 0.00001). Approximately 60% of patients showed adequate physical activity, without significant differences between groups. However, in terms of BMI values, female patients had significantly higher values than male participants (*P* = 0.0294).

CHIS categories were calculated in 84 (12.2%) patients who had all the necessary clinical and laboratory measurements done. Good, intermediate, and poor categories were identified in 6%, 58.3%, and 35.7% of patients, respectively (without statistical differences between female and male patients).

Risk factor control

When analyzing uncontrolled BP rates across different categories of AH, the prevalence of uncontrolled SBP was higher than that of other BP categories (Table 4). There were no statistical differences between females and males within each category. Differences between the two groups were only observed in the category of isolated systolic hypertension with a higher prevalence in women (*P* = 0.029).

The rates of uncontrolled risk factors in patients with a previous history of hypertension (*n* = 537), dyslipidaemia (*n* = 255), and DM (*n* = 310) are represented in Figure 2. As shown in the figure, uncontrolled SBP was detected in 292 (54.6%), and uncontrolled DBP was found in 204 (39%) participants. Systolic-diastolic AH (SDH) was found in 169 (31.5%),

Table 1 Demographic characteristics and disease category of the patients (n = 687)

	Total, n = 687	Female, n = 171	Male, n = 516	P value
Age (years)	59.6 ± 9.58	62.4 ± 8.9	58.6 ± 9.6	< 0.0001
CHD category, n (%)				
CABG	153 (22.3)	41 (24)	112 (22)	> 0.05
PCI	351 (51.1)	71 (42)	280 (54)	0.004
ACS	172 (25.0)	27 (16)	145 (28)	0.001
SAP	249 (36.2)	82 (48)	167 (32)	0.0002
HA	271 (39.4)	68 (40)	203 (39)	> 0.05
CR	104 (15.1)	19 (11.1)	85 (16.5)	> 0.05

CHD: Coronary heart disease; CABG: Coronary artery bypass surgery; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; SAP: Stable angina pectoris; HA: Hospital admission; CR: Cardiac rehabilitation. *P* value represents differences by sex.

Table 2 Cardiovascular risk factors stratified by sex, n (%)

	Total, n = 687	Female, n = 171	Male, n = 516	P value
Smoking history				
Current smoker	169 (24.6)	3 (1.8)	166 (32)	< 0.00001
Ex-smoker	169 (24.6)	2 (1.2)	167 (32)	< 0.00001
Never smoked	314 (45.7)	165 (96.5)	149 (29)	< 0.00001
Unknown	35 (5.1)	1 (0.6)	34 (7)	
Physical activity				
Less than below	223 (32.5)	66 (38.6)	157 (30.4)	> 0.05
Moderate	324 (47.2)	74 (43.3)	250 (48.4)	> 0.05
More than above	82 (11.9)	19 (11.1)	63 (12.2)	> 0.05
Unknown	58 (8.4)	12 (7.02)	46 (8.9)	
Family history of premature CVD				
Yes	265 (38.6)	58 (33.9)	207 (40.1)	> 0.05
No	355 (51.7)	96 (56.1)	259 (50.2)	> 0.05
Unknown	67 (9.8)	17 (9.9)	50 (9.7)	
Previous history of				
Hypertension	537 (78.2)	142 (83)	395 (76.6)	> 0.05
Dyslipidaemia	255 (37.1)	60 (35.1)	195 (37.8)	> 0.05
Diabetes	310 (45.1)	95 (55.6)	215 (41.7)	0.002

Less than below physical activity: < 30 min/week; Moderate physical activity: 30 min 3-5 times/week; More than above physical activity: > 30 min/week; *P* value represents differences by sex. CVD: Cardiovascular disease.

isolated SAH in 121 (22.5%), and isolated DAH in 34 (6.3%) patients with AH.

Medication use

The rate of medication use is shown in Table 5. Antiplatelet drugs were used in 84.6%, and beta-blockers in 53.3% of patients, both with an equal rate among female and male participants. Approximately 73.9% of patients were using statins, with a higher usage rate observed among male patients (*P* = 0.012). As for ACE inhibitors, 51.2% of patients were using them, with a higher usage rate observed among female patients (*P* = 0.044). Ca antagonists were used in 29.3%, oral hypoglycaemics in 23%, diuretics in 22.3%, and nitrates in 21.3% of patients. Other groups of medications were used in less than 6% of patients. Oral hypoglycemic drugs, insulin, and nitrate use was higher among female patients (*P* = 0.025, *P* = 0.043, and *P* < 0.00001, respectively).

Table 3 Clinical measurements and laboratory data of the patients (mean $\pm$ SD)

	Total	Female	Male	P value
Systolic BP (mmHg)	<i>n</i> = 663 138.4 (18.9)	<i>n</i> = 164 142.4 (1.4)	<i>n</i> = 499 137.1 (17.9)	0.004
Diastolic BP (mmHg)	<i>n</i> = 658 82.9 (10.7)	<i>n</i> = 162 82.7 (11.5)	<i>n</i> = 496 82.8 (10.4)	> 0.05
Heart rate (bpm)	<i>n</i> = 649 77.6 (12.7)	<i>n</i> = 156 78.5 (12.0)	<i>n</i> = 493 77.3 (12.9)	> 0.05
BMI (kg/m ²)	<i>n</i> = 216 28.4 (3.02)	<i>n</i> = 50 29.6 (3.4)	<i>n</i> = 166 28 (2.8)	0.002
WC (cm)	<i>n</i> = 30 101 (12.9)	<i>n</i> = 13 100.8 (15.2)	<i>n</i> = 17 101.0 (11.3)	> 0.05
TC (mg/dL)	<i>n</i> = 347 193.9 (52.4)	<i>n</i> = 86 200.4 (50.7)	<i>n</i> = 261 192.3 (53)	> 0.05
LDL-C (mg/dL)	<i>n</i> = 371 111.2 (49.6)	<i>n</i> = 101 118.3 (49.7)	<i>n</i> = 270 108.6 (49.3)	> 0.05
HDL-C (mg/dL)	<i>n</i> = 185 53.4 (13.8)	<i>n</i> = 50 54.4 (13.1)	<i>n</i> = 135 53 (14.1)	> 0.05
TG (mg/dL)	<i>n</i> = 367 161.0 (76.0)	<i>n</i> = 93 169.8 (77.8)	<i>n</i> = 274 158 (75.4)	> 0.05
BG (mg/dL)	<i>n</i> = 277 146.7 (71.5)	<i>n</i> = 73 162.7 (79.9)	<i>n</i> = 204 141 (67.5)	0.04
HbA1c (%)	<i>n</i> = 137 7.71 (1.72)	<i>n</i> = 44 8.1 (2.0)	<i>n</i> = 93 7.5 (1.5)	> 0.05

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WC: Waist circumference; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; BG: Blood glucose. *P* value represents differences by sex.

Table 4 Rates of uncontrolled blood pressure in different categories of arterial hypertension

BP category, <i>n</i> = 658	Total (%)	Female (%)	Male (%)	P value
SDH	27.5	27.8	27.4	0.929
ISH	20.9	26.8	18.8	0.029
IDH	6.8	6.8	6.9	0.977

BP: Blood pressure; ISH: Isolated systolic hypertension; IDH: Isolated diastolic hypertension; SDH: Systolic-diastolic hypertension. *P* value represents differences by sex.

DISCUSSION

Summary of main findings

A clinical audit is a 'quality improvement process that seeks to improve patient care and outcomes through a systematic review of care and the implementation of change' [12]. The SURF CHD II clinical audit conducted in Azerbaijan has shown that the prevalence of major cardiovascular risk factors in patients with ASCVD is high. The level of recordings of some risk factors was low, as there was a lack of information on BMI, WC, TC, LDL-C, HDL-C, TG, and HbA1c.

The number of patients involved in the CR program was inadequate (15.1%). The rate of uncontrolled RF was high: SBP (54.6%), DBP (39%), LDL-C (86.8%), DM (60.6%), as well as overweight (66.6%) and obesity (25%). In addition, significant differences in prevalence and control of some risk factors (smoking, BMI, WC, BG, and SBP) between female and male participants have been found.

Table 5 Medication use rate in patients with known coronary artery disease (%)

Medications	Total	Male	Female	P value
	n = 687	n = 516	n = 171	
Antiplatelets	84.6	85.3	82.5	0.377
Beta blockers	53.3	55.2	47.4	0.074
ACE inhibitors	51.2	49.0	57.9	0.044
Ca antagonists	29.3	28.7	31.0	0.565
ARB-s	6.0	5.8	6.4	0.767
Diuretics	22.3	20.5	27.5	0.059
Other antihypertensives	2.3	1.9	3.5	0.238
Nitrates	21.3	7.6	62.6	< 0.00001
Insulin	7.6	6.4	11.1	0.043
Oral hypoglycaemics	23	20.9	29.2	0.025
Statins	73.9	76.4	66.7	0.012
Other lipid lowering	1.3	1.2	1.8	0.555

Ca: Calcium; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker. P value represents differences by sex.

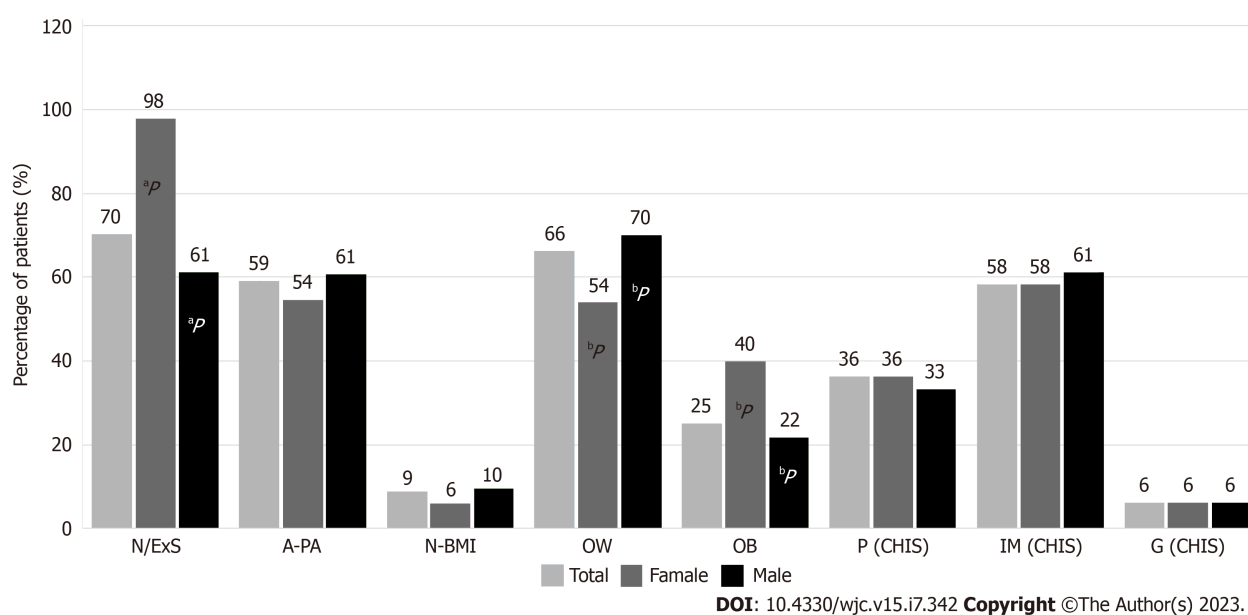


Figure 1 Lifestyle targets and cardiovascular health index score categories in patients with known coronary artery disease. N/ExS: Non/ex-smoker; A-PA: Adequate physical activity; N-BMI: Normal body mass index; OW: Overweight; OB: Obesity; P, IM, G (CHIS): Cardiovascular health index score categories: Poor, Intermediate, Good. ^aP < 0.00001; ^bP < 0.05.

Cardiovascular risk factors

To effectively manage CVDs, it is vital to recognize their multifactorial nature and implement preventive measures that target modifiable risk factors. These measures should include optimizing physical activity, encouraging smoking cessation, reducing BMI, and treating AH, diabetes, and hyperlipidemia. The positive effects of lifestyle modification and optimal pharmacological interventions on cardiovascular morbidity and mortality have been demonstrated in previous studies[13-15].

Smoking cessation is one of the most effective measures for reversing vascular injury and preventing the development of atherosclerosis and fatal cardiovascular outcomes[16,17].

The information collected in several national surveys conducted in Azerbaijan has shown that there is a high prevalence of risk factors such as smoking, overweight, unhealthy diet, and physical inactivity which are responsible for the great majority of NCD cases. One of the studies conducted to gather information on the health of the population is the WHO-recommended STEPS survey. This survey has been conducted nationwide in both 2011 and 2017[18]. Analysis of

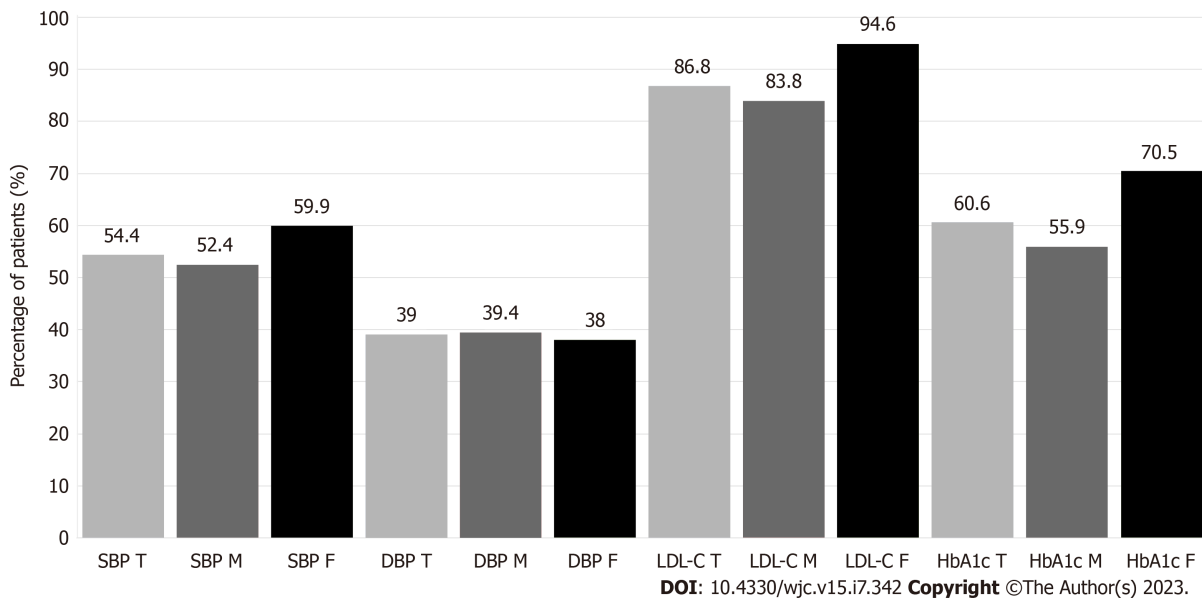


Figure 2 Rate of uncontrolled risk factors in patients with a previous history of hypertension, dyslipidaemia, and diabetes. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low density lipoprotein cholesterol; HbA1c: Glycated haemoglobin; T: Total, M: Males; F: Females. No statistically significant differences between the groups.

the study results, conducted among 3000 adult population aged 18 years and above, has shown that smoking is one of the major problems for Azerbaijani society. Overall, the prevalence of smoking was significantly higher among men (48.8%) than among women (0.2%) who were identified as current smokers. This difference in smoking prevalence can be largely attributed to the social stigma surrounding smoking among women, as it is often viewed negatively within the local culture.

The study also found that 24.9% of all respondents had been exposed to secondhand smoke at home, with men showing a higher incidence of exposure than women. The results of the SURF study are consistent with these data: The smoking rate was 24.6%, and it was significantly high among men than in women (32% *vs* 1.8%, accordingly).

Comorbidities such as hypertension, dyslipidaemia, and diabetes are known risk factors for CHD events and may indicate an increased susceptibility to atherosclerosis development. In the current study, uncontrolled SBP was found in 54.6% of patients with reported AH. According to the STEPS study, the prevalence of AH among the general population was about 30% [18]. Most of the respondents with high BP (65.4%) were not taking any medication. Salt intake was around 10 g per day, with a significant gender difference (11.4% of men *vs* 26.8% of women). The above-mentioned aspects of behaviour and dietary habits could also contribute to the poor management of BP in the participants of the SURF study.

The SURF study has demonstrated that BMI values were high in 91% of participants, which could indicate that BMI is one of the most common risk factors in the development of coronary artery disease (CAD). But it should also be taken into consideration that parameters such as BMI and WC were measured only in a small group of patients and mainly in persons with apparent high body weight and abdominal obesity. This circumstance may have an impact on the data obtained.

The study results have shown that approximately 50% of the patients did not reach even the first target level of lipids [7], despite the fact that the rate of statin usage among this category of patients was 86.4%. These reasons could include discontinuation of statin therapy due to poor adherence and compliance to treatment recommendations, as well as not achieving the target dosage of the medication [19]. A similar pattern was observed with respect to the patients with DM: Despite insulin and oral hypoglycemic drugs use, HbA1c level did not reach the targets in the majority (60.6%) of them.

The cross-sectional study European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV was undertaken at 78 centres in 24 European countries with the involvement of 7998 patients < 80 years of age with CAD [20]. While Azerbaijan did not participate in EUROASPIRE, the results acquired from the mentioned study can be compared with the results of the SURF study conducted in our country. It was observed that in Azerbaijani patients with ASCVD, the mean age was younger, the rate of smoking was higher, and the rate of controlled BP level was lower. Uncontrolled LDL-C levels (≥ 70 mg/dL) and BMI greater than 30 kg/m² were found to be lower in our study.

Gender-based differences in cardiovascular risk factors

According to the study results, despite that the smoking rate was significantly high among men than in women, higher values of BMI and WC, as well as BG level and history of DM type 2, were found in female participants. Furthermore, the STEPS study has demonstrated that in the general population, approximately 91% of women are not engaging in vigorous physical activity.

These findings comply with the literature data. A systematic review conducted on the distribution by gender of diabetes, risk factors, complications, and disease control in the Caribbean general population has shown that women were more likely than men to have diabetes and obesity. This review also found that women were less physically active than men, but they were less likely to smoke cigarettes[21]. The authors of this review discovered that there was a statistically significant association between gender and diabetes, with women being at a risk of more than one and a half times greater than men.

It could be concluded from the foregoing that the gender differences in the distribution of CV risk factors such as DM, obesity, lack of physical activity, and smoking should be taken into account in the pharmacological management of patients with and without CVD and when designing rehabilitation programmes.

Medication usage and CR

When comparing the rates of medication usage in our study and the results of the cross-sectional study EUROASPIRE IV [20], the rate of cardioprotective medication use was higher in the latter case (anti-platelets 93.8% *vs* 84.6%; statins 85.7% *vs* 73.9%, beta-blockers 82.6% *vs* 53.3%; ACE inhibitors/ARBs 75.1% *vs* 51.2%). According to the data of the SURF CHD II [5] study, the use of statins in the European region was 78.94%, which is broadly comparable to our data.

Adherence and compliance play a major role in all pharmacological therapies. The causes of non-compliance can be classified into the following categories: Patient, physician, and health system-related[22]. Similarly, with dyslipidemia, diabetes, and hypertension, the causes of poor control of risk factors should be carefully analyzed for the effective implementation of the guideline recommendations into clinical practice.

Only 15.1% of patients reported participation in CR in our study, despite this is a recommendation class I and the level of evidence A intervention[3]. The literature indicates that the number of patients who participate in CR programs, especially in low-income countries, is extremely low, and patients' adherence is often scarce[23]. There are several known barriers to the implementation of CR and adherence to such programs. Some of these barriers include limited availability of services, high program costs, long travel distances to access services, low referral rates from healthcare providers, and low levels of patient motivation to participate in rehabilitation programs[23-27], and these reasons may have contributed to the low participation in CR in Azerbaijan.

Another likely reason for the low participation rate in CR could be that these programs are only offered in a limited number of hospitals, and patients are required to cover almost all the costs out-of-pocket. It is expected that reforms in the health system and the financing of medical services, such as the introduction of compulsory health insurance, will help fill this missing gap in the secondary prevention of CVDs.

Context and direction of cardiovascular prevention and rehabilitation in Azerbaijan

In 2015, the 'Strategy for Non-Communicable Diseases' was adopted in order to achieve a significant reduction in premature deaths associated with NCDs in the country. The objectives of the Strategy are to establish an effective inter-sectoral cooperation mechanism to combat NCDs, to take measures to reduce the main risk factors (tobacco use, alcohol abuse, unhealthy diet, and physical inactivity), and to prevent and control these diseases. Their role does not merely focus on improving the healthcare system and healthcare services, but also on promoting a healthy lifestyle for the population [18].

As a result of the implementation of the project on improving the national legislative framework to combat the tobacco epidemic, the parliament of the country adopted a new law aimed at enhancing limitations on tobacco use in public spaces. This law supports the establishment of tobacco control programs, hotlines, and pharmacotherapy initiatives to assist individuals in smoking cessation[18,28].

Preventive campaigns are the mainstay of activities to combat NCDs in Azerbaijan. The Ministry of Health (MoH) developed a health awareness-raising web portal for the population, which includes articles about non-communicable diseases and their risk factors and prevention strategies. MoH and ASC provide information days and thematic conferences to increase awareness of CVD prevention among the population. Some non-governmental and public organisations also participate in the promotion and popularisation of healthy lifestyles and primary prevention.

Important steps have been taken to improve the rehabilitation services in the country: The new degree programs, which include cardiovascular rehabilitation modules, have been launched[28]. The cardiology curriculum for residents has been updated in line with the ESC standards, and now it contains a chapter on cardiovascular prevention and rehabilitation.

E-training courses for cardiologists from remote areas have been initiated by MoH and ASC. One of the successful programs included the establishment of a portal for specific e-training on cardiovascular risk factors, promotion of physical activity, and tobacco cessation skills for physicians, among others[28].

Despite these measures, the results of the SURF study and previous population-based studies have shown that the rate of risk factors is still high among both the general population and patients with documented CVD. This demonstrates once more the need of consistent training for healthcare professionals, notably primary care physicians, as well as patients, and the need for the healthcare system to pay more attention to this issue. Such measures will undoubtedly help to reduce the frequency of undesirable consequences and rehospitalisations in this category of patients, and hence reduce healthcare costs.

Strengths and limitations

The SURF CHD study uses a one-page, simple questionnaire that allows rapid data collection. It can be completed in a very short period during a routine outpatient visit, requires involving a larger population in the study with minimal effort.

Clinical audits such as SURF also enhance process improvement: In light of the results, changes can be implemented in the procedures to record and manage risk factors, and re-auditing can inform on the effectiveness of these changes to improve risk factor recording and management.

However, it should be mentioned that the current study has several limitations. First, it only included tertiary level hospitals in the capital city (however, it is planned to include primary and secondary health care facilities from the different regions of Azerbaijan at the further stages of the study). Second, for some risk factors such as waist circumference, data were not recorded in all participants. This suggests that some clinicians overlook certain risk factors, and one of the important roles of an audit such as SURF is to stimulate fuller recording of relevant data.

CONCLUSION

Our study has demonstrated that the control of cardiovascular risk factors and lifestyle changes recommended by clinical CVD prevention guidelines in patients with CHD is unsatisfactory. The number of patients involved in CR program is low, and the high level of uncontrolled risk factors among patients who participated in CR indicates the poor adherence and compliance among patients. Monitoring and control of the modifiable risk factors are not at a desired level, and require more organized work and collaboration of healthcare providers from different healthcare facilities.

The above-mentioned trends and individual and gender characteristics of patients should be considered by healthcare organizers when planning secondary prevention activities and public health protection measures.

The strategic needs for prevention and rehabilitation in Azerbaijan are to increase the number of rehabilitation centres and ensure their adequate geographical distribution, with a particular focus on the regions of the country, and to expand indications of CR services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk. More efforts are needed to improve and strengthen the mechanism for education of primary healthcare providers in the field of cardiac prevention and rehabilitation.

It is also suggested that Standard Operating Procedures should be developed for cardiac clinics in regions to facilitate process improvement.

ARTICLE HIGHLIGHTS

Research background

Low level of monitoring and control of modifiable risk factors necessitates better structured effort and coordination of health care specialists from various healthcare facilities. The strategic needs for prevention and rehabilitation in Azerbaijan are to increase the number of rehabilitation centers and ensure their adequate geographical distribution, with a particular focus on the country's regions, and to expand indications of cardiac rehabilitation (CR) services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk, and to expand indications of CR services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk. It is also proposed that cardiac clinics adopt Standard Operating Procedures. More effort is required to improve and reinforce the process for primary health care provider education in the field of cardiac prevention and rehabilitation.

Research motivation

Previous studies have shown that control of major cardiovascular risk factors is generally inadequate in patients with established atherosclerotic cardiovascular disease (CVD) (ASCVD). Azerbaijan is a country in the South Caucasus, a region at very high risk for CVD. The aim of this study was to evaluate compliance with the recommendations of the European Society of Cardiology (ESC) for secondary prevention of CVD based on the measurement of both modifiable major risk factors and their therapeutic management in patients with confirmed coronary heart disease (CHD) in Azerbaijan. We believe that these results will contribute to the improvement of the situation in secondary prevention of CHD in the country.

Research objectives

This study focused on the national results of the Survey of Risk Factors in CHD (SURF CHD) II study in Azerbaijan.

Research methods

SURF CHD II study uses a one-page, standard questionnaire that allows rapid data collection. Information on demographics, risk factors, physical and laboratory data, and medications was collected in consecutive outpatients aged ≥ 18 years with established atherosclerotic CHD. Data from 687 patients (mean age 59.6 ± 9.58 years; 24.9% female) were included in the study.

Research results

The study results show that the control of cardiovascular risk factors and lifestyle modification measures indicated by clinical CVD prevention recommendations in patients with CHD are inadequate. The number of patients with CHD enrolled in a CR program is small as well.

Research conclusions

The findings of the SURF study can be used to improve processes by changing the techniques for documenting and monitoring CVD risk variables, and re-auditing can provide insight into the effectiveness of these modifications in improving the management of patients with ASCVD.

Research perspectives

It is critical to efficiently manage the main cardiovascular risk factors in order to prevent CVD mortality. The international SURF CHD II clinical audit measures modifiable risk factors to assess adherence to ESC recommendations for secondary prevention of CVD in patients with established CHD.

FOOTNOTES

Author contributions: Gabulova R analyzed the data and wrote the manuscript; Marzà-Florensa A was involved in all stages of developing the final version of the manuscript; Rahimov U, Isayeva M, Alasgarli S, Musayeva A, Gahramanova S, Ibrahimov F, Aliyev F, and Imanov G collected the clinical data and contributed equally to this work; Rasulova R analyzed the data; Vaartjes I and Klipstein-Grobusch K critically reviewed the manuscript; Graham I and Grobbee DE designed the research study and critically reviewed the work; all authors have read and approved the final manuscript.

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Effects of time-restricted eating with different eating duration on anthropometrics and cardiometabolic health: A systematic review and meta-analysis

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Abstract

BACKGROUND

Time-restricted eating (TRE) is a dietary approach that limits eating to a set number of hours per day. Human studies on the effects of TRE intervention on cardiometabolic health have been contradictory. Heterogeneity in subjects and TRE interventions have led to inconsistency in results. Furthermore, the impact of the duration of eating/fasting in the TRE approach has yet to be fully explored.

AIM

To analyze the existing literature on the effects of TRE with different eating durations on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases.

METHODS

We reviewed a series of prominent scientific databases, including Medline, Scopus, Web of Science, Academic Search Complete, and Cochrane Library arti-

cles to identify published clinical trials on daily TRE in adults with excessive weight and obesity-related metabolic diseases. Randomized controlled trials were assessed for methodological rigor and risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2). Outcomes of interest include body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, homeostasis model assessment for insulin resistance (HOMA-IR), lipid profiles, C-reactive protein, blood pressure, and heart rate.

RESULTS

Fifteen studies were included in our systematic review. TRE significantly reduces body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, and triglyceride. However, no significant changes were observed in HbA1c, HOMA-IR, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, heart rate, systolic and diastolic blood pressure. Furthermore, subgroup analyses based on the duration of the eating window revealed significant variation in the effects of TRE intervention depending on the length of the eating window.

CONCLUSION

TRE is a promising chrononutrition-based dietary approach for improving anthropometric and cardiometabolic health. However, further clinical trials are needed to determine the optimal eating duration in TRE intervention for cardiovascular disease prevention.

Key Words: Cardiovascular disease; Cardiometabolic health; Time-restricted eating; Chrononutrition; Intermittent fasting; Obesity

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Core Tip: Beneficial effects of time-restricted eating (TRE) on adults with excessive weight and obesity-related metabolic diseases remain under investigation, and results are conflicting. We explored the effectiveness of TRE on anthropometric and cardiometabolic health in adults with excessive weight and obesity-related metabolic diseases. We found that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, and triglyceride in individuals with excessive weight or weight-related metabolic disorders. Moreover, the meta-analysis demonstrates the varying effects of fasting duration on the outcomes of interest.

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INTRODUCTION

The global prevalence of overweight and obesity has become a major public health problem. High body mass was responsible for over five million deaths and 160 million disability-adjusted life years worldwide[1]. According to the World Health Organization reports, the number of overweight and obese individuals has doubled globally since 1980, affecting both developed and developing countries. As a result, weight-related diseases, including obesity and related conditions such as type 2 diabetes, cardiovascular disease (CVD), and certain cancers, have become a major public health challenge worldwide and a burden on healthcare systems[2,3]. Researchers and healthcare professionals have explored multiple dietary strategies to improve weight and cardiometabolic health and prevent cardiovascular disease through caloric and macronutrient restriction, specific foods or nutrients, adherence to selected dietary patterns, and fasting. Continuous energy restriction (CER) has been frequently used to manage the body weight of individuals with excessive weight[4]. However, adherence to this diet pattern is challenging due to the daunting task of reducing daily caloric intake [5]. Additionally, CER may promote adaptive responses such as decreased physical activity, increased hunger, and deactivation of the hypothalamic-pituitary-thyroid axis, hindering weight and fat loss[6]. Moreover, CER increases the risk of adverse effects such as hypoglycemia, nutrient deficiencies, and extreme fatigue.

In recent years, intermittent fasting (IF) has emerged as an alternative weight loss and CVD prevention strategy. It refers to a cyclic eating pattern that rotates between periods of abstinence from consuming any caloric-containing food or drinks and periods of eating[7]. Current human research indicates that chrononutrition-based dietary interventions, such as time-restricted eating (TRE), have gained substantial interest from the public as one of the sustainable strategies for CVD prevention[8]. TRE is a lifestyle approach that limits eating duration to a set number of hours per day (typically within 4–12 h) during waking hours, allowing for adequate fasting[9,10]. TRE aims to align dietary intake with daily circadian rhythms. It is considered a more sustainable approach than caloric restriction, as it involves lower-intensity

adaptation for long-term lifestyle modifications to reduce weight[8]. Animal studies have linked TRE to lower body weight, total cholesterol (TC), triglycerides, glucose, insulin, interleukin-6, tumor necrosis factor, and improved insulin sensitivity[11-13].

The effects of TRE with different eating durations, ranging from four to 12 h, have been studied on humans[14]. These studies have reported varying results, with some showing improvements in weight loss, insulin sensitivity, and cardiovascular markers, while others exhibiting no significant changes. Several recent systematic reviews have been conducted to review the effects of TRE interventions on anthropometric and cardiometabolic health[15-23]. The most consistent findings from these reviews were significant weight reduction with TRE intervention, with mixed results for the TRE effects on cardiometabolic health. This inconsistency is mainly due to heterogeneity in subjects and the implemented TRE interventions.

Additionally, combining results from individuals with normal body mass index (BMI) and those with metabolic dysregulation may obscure differences in the effectiveness of the intervention. To our knowledge, no systematic review has evaluated the effects of variation in TRE's eating duration on anthropometric and cardiometabolic health. Therefore, this systematic review and meta-analysis aimed to examine the effects of varying eating durations in TRE interventions on body weight and composition, waist circumference, biomarkers of glucose metabolism, lipid metabolism, inflammatory marker, blood pressure, and heart rate in adults with excessive weight and obesity-related metabolic diseases. The findings of this review will shed light on the overall effectiveness of TRE and its optimal eating duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

MATERIALS AND METHODS

Protocol and registration

This systematic review was reported according to the updated version of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement[24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (<http://www.crd.york.ac.uk/PROSPERO>), with a record number of CRD42022341232. Before conducting the review, PROSPERO and the Cochrane Library were searched to identify existing or ongoing similar work by other researchers.

Search strategy

Multiple electronic databases were queried using selected search terms until May 2022. MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection were used for the systematic search (Supplementary Table 1). The search strategy was tailored to each database's keywords to identify literature for the intervention of interest, TRE. The search terms included "time-restricted diet" OR "time-restricted eating" OR "time-restricted feeding" OR "time-restricted fasting" OR "time-restricted meal", which have been identified in previous systematic reviews[19,21,22]. The search was not limited to specific years of publication or languages, and no additional terms were used to avoid filtering out relevant literature. All search outputs were exported to reference manager software (Endnote 20; endnote.com). After removing duplicates, two independent reviewers screened the articles for eligibility based on title, abstract, and full text (Zaman MK and Teng NIMF). A consensus was reached for included articles through discussions after each screening round, and a third reviewer resolved any disagreements (Juliana N).

Study selection

The eligibility criteria for this systematic review were based on the predetermined inclusion and exclusion criteria. We included studies with the following characteristics: (1) Population: Adults with excess weight and obesity-related metabolic diseases; (2) Intervention: TRE, which involves daily (seven days per week) eating window restriction; (3) Comparator: The comparator accepted for this study were dietary intake with ad libitum eating window or eating window of 12 h or more; (4) Outcomes: Changes in body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, homeostasis model assessment for insulin resistance (HOMA-IR), lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides], C-reactive protein, blood pressure (systolic and diastolic), and heart rate were identified as outcomes of interest—studies with any reported outcomes of interest were included; and (5) Study design: Only controlled/clinical trials with at least one outcome measurement performed within two weeks to 6 mo of intervention commencement were included in this review.

We excluded studies based on the following characteristics: (1) Population: Studies involving subjects younger than 18 years of age, animal models, or studies including adult subjects with normal BMI were excluded; (2) Intervention: Studies with intermittent TRE (*e.g.*, ad libitum dietary intake during selected days) were excluded; and (3) Study design: Abstracts, and non-original articles such as expert opinions and reviews were excluded from this systematic review.

Risk of bias assessment

Risk of bias (RoB) assessments of the included studies were conducted and graded using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2)[25]. This tool evaluates the RoB across five key domains: Randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported

results. Trials were classified as having either low risk, unclear risk, or high RoB for each domain and overall. Two reviewers were involved independently in the RoB assessments of the included studies (Zaman MK and Teng NIMF). Disagreements were resolved through consensus or discussion with a third reviewer (Kasim SS).

Data extraction

Data collection forms were used to extract data from each study. The extraction form was piloted in at least one study included in this review. Two reviewers were involved in the data extraction from included studies (Zaman MK and Teng NIMF). Data extracted include: (1) Information about the trial: Authors, publication year, study design, sample size, and study duration; (2) Study participants: Population characteristics, location, age, gender, and BMI; (3) Intervention characteristics: Description of intervention and control arm, eating window, and timing of intervention; and (4) Outcome measures: Body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, HOMA-IR, lipid profile (TC, HDL-C, LDL-C, and triglycerides), C-reactive protein, blood pressure (systolic and diastolic), and heart rate.

Data synthesis and analysis

Standardized mean differences (SMDs), or mean differences (MDs) with 95%CI, were used to report intervention effects for each study based on pre-and post-TRE intervention. Meta-analyses were conducted, if feasible, using a minimum of two included studies with similar outcomes for each outcome of interest. Forest plots were constructed for all studies included in the meta-analysis. A two-sided *P* value of < 0.05 was considered statistically significant. The heterogeneity was evaluated statistically using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity. The random-effects model was employed when substantial heterogeneity was present. Publication bias was examined using a funnel plot visualization for outcomes with ten or more studies. Considering the heterogeneity protocol and duration of the eating window in TRE intervention, subgroup analyses were performed by applying a different range of TRE duration. All analyses were conducted using RevMan software, version 5.4.

RESULTS

Search results

The systematic search process identified 2067 articles (Figure 1) from multiple resources, including Medline ($n = 425$), Scopus ($n = 567$), Web of Science ($n = 483$), Academic Search Complete ($n = 224$), Cochrane Library ($n = 216$), Food Science Source ($n = 126$), OpenDissertations ($n = 10$), Education Research Complete ($n = 9$), and Psychology and Behavioural Science collection ($n = 7$). After removing duplicates, 829 records were screened, and 51 were assessed for eligibility after excluding articles not meeting the inclusion criteria. Further screening and quality assessment resulted in 15 studies being selected for the systematic review and meta-analysis, involving 927 subjects[26-40]. The largest study recruited 139 subjects, while the smallest enrolled eight subjects[32,39]. Most studies were conducted in the United States of America ($n = 7$), followed by Brazil ($n = 3$), China ($n = 3$), Switzerland ($n = 1$), and Germany ($n = 1$).

Study characteristics

Table 1 displays the characteristics of the participants in the included studies. The participants were adults with overweight/obesity, prediabetes, or Type 2 Diabetes Mellitus. The participants ranged from 27 to 74 years old[26,30], with a BMI above the normal cut-off, ranging from 26.4 to 38.9 kg/m². The majority of the included studies were parallel arms randomized controlled trials (RCT) ($n = 13$), randomized crossover trial (RXT) ($n = 1$), and non-RCT ($n = 1$). All studies involved at least one intervention group with a TRE regimen and a comparator group with an unrestricted time of food intake. The interventions were conducted over three weeks to twelve months, with the fasting period lasting between 12 and 20 h per day and the eating period lasting from four to 12 h daily. The timing of the start of the fasting period was either self-selected by participants or predetermined by the study (Table 1). Most TRE interventions in the included studies restricted food intake during the day, with the last meal completed by 20:00[27,29-34,37-39].

Risk of bias assessment

The RoB assessments for the RCTs are summarized in Figure 2. Overall, seven studies posed a high RoB[30-33,35,38,40], and eight studies posed concerns regarding the overall RoB[26-29,34,36,37,39]. In the domain of the randomization process, all included studies were identified as randomized studies except for one. Ten studies had limited or no information on randomization and concealment, leading to concerns in the domain of the randomization process[28-34, 37,38,40]. Due to the nature of the intervention of interest, blinding participants may not be feasible. Information on blinding of the participants, carers, and personnel assessing in the laboratory or statistical analyses was often unknown or limited, introducing possible risk of bias due to deviations from the intended intervention. Most studies showed a low RoB due to missing outcome data[26-29,31-34,36,37,40] and outcomes measurement[26-37,39,40]. In the domain of selection of the reported result, most studies were classified as posing concern[26-30,36-39] or high risk[31-33,35,40] due to the limited availability of a prespecified analysis plan (*i.e.*, protocol) or/and missing outcomes measurement.

Effects of TRE on weight and body composition

Body weight: A total of 15 studies were included in the analysis to assess the effect of TRE on body weight (kg) (Figure 3). Individuals assigned to the TRE intervention showed a significant reduction in body weight levels compared to the comparator group [MD -2.26; 95%CI: -3.10 to -1.43, $P < 0.00001$; $I^2 = 93\%$]. Random-effects subgroup analysis was

Table 1 Characteristics of the participants in the included studies

Ref.	Study design	Sample size	Study duration	Characteristics	Location	Sex	Baseline BMI (kg/m ²)	Age (yr)	Fasting: Eating period (hours)	Timing of intervention
Chair <i>et al</i> [26], 2022	Three arm RCT	101	3 wk	Prediabetes	Weight management clinic, Hunan Provincial People's Hospital, Changsha, China	M: 3, F: 64	35.23 ± 6.19	74.30 ± 8.39	16:08	Free to arrange the 8-h eating window based on personal preferences
Che <i>et al</i> [27], 2021	RCT	120	14 wk	Overweight adults with type 2 diabetes	Diabetes Clinic, Zhu Xianyi Hospital of Tianjin Medical University, China	M: 65, F: 55	TRE: 26.42 ± 1.96; Comparator: 26.08 ± 2.14	TRE: 48.21 ± 9.32; Comparator: 48.78 ± 9.56	14:10	08:00 to 18:00 and fasted from 18:00 to 08:00 daily
Chow <i>et al</i> [28], 2020	RCT	20	12 wk	Adults with BMI ≥ 25 kg/m ²	Minnesota, United States	M: 3, F: 17	TRE: 33.8 ± 7.6; Comparator: 34.4 ± 7.8	TRE: 46.5 ± 9.32; Comparator: 44.2 ± 12.3	16:08	Self-select
Cienfuegos <i>et al</i> [29], 2020	RCT (3-arms)	58	10 wk	Adults with BMI of 30-49.9 kg/m ²	Chicago, United States	F: 53 M: 5	4-h TRE: 37 ± 1; 6-h TRE: 37.0 ± 1.0; Comparator: 36.0 ± 1.0	4-h: 47 ± 2; 6-h: 47 ± 3; Comparator: 45 ± 2	4-h: 20:04; 6-h: 18:06	4-h TRE: 15:00-19:00; 6-h TRE: 13:00-19:00
Isenmann <i>et al</i> [30], 2021	RCT	35	16 wk	Adults with BMI ≥ 25, physically active	Gymnasium, (Windhagen, Germany)	F: 21 M: 21	TRE: 26.3 ± 3.0; Comparator: 25.7 ± 3.3	TRE: 27.9 ± 5.3; Comparator: 27.4 ± 5.8	16:08	12:00-20:00
Kotarsky <i>et al</i> [31], 2021	RCT	21	8 wk	Adults with BMI 25.0 and 34.9 kg/m ²	North Dakota State university, United States	F: 18 M: 3	29.6 ± 2.6 kg/m ²	44 ± 7	16:08	12:00-20:00
Liu <i>et al</i> [32], 2022	RCT	139	6/12 mo	Adults with BMI of 28-45 kg/m ²	Guangzhou, China	F: 68 M: 71	TRE: 31.8 ± 2.9; Comparator: 31.3 ± 2.6	TRE: 31.6 ± 9.3; Comparator: 32.2 ± 8.8	16:08	08:00-16:00
Lowe <i>et al</i> [33], 2020	RCT	116	12 wk	Adults with BMI 27-43 kg/m ²	United States, primarily San Francisco	F: 70 M: 46	32.7 ± 4.2	46.5 ± 10.5	16:08	TRE, 8 h, 12:00-20:00
Peeke <i>et al</i> [34], 2021	RCT (Virtual)	60	8 wk	Adults with BMI ≥ 30 kg/m ²	United States	F: 69 M: 9	38.9 ± 7.7	44.0 ± 11.0	12:12 (14:10, with fasting snack 12 h post fasting)	Fasting began after dinner (between 17:00-20:00)
Phillips <i>et al</i> [35], 2021	RCT	54	6 mo	Adults with at least one component of metabolic syndrome	Switzerland	Not reported	TRE: 28.0 ± 4.1; Comparator: 27.0 ± 4.0	43.4 ± 13.3	12:12	-
de Oliveira Maranhão Pureza <i>et al</i> [36], 2021	RCT	58	21/81 d	Adults with BMI 30-45 kg/m ²	Outpatient clinic of the Centro de Recuperação e Educação Nutricional, Brazil	F: 58	TRE: 31.80 (CI: 29.25-34.36); Comparator: 31.03 (CI: 28.20-33.87)	TRE: 33.53 (CI: 32.00-35.50); Comparator: 33.12 (CI: 31.68-34.56)	12:12	Self-select
Ribeiro <i>et al</i> [37], 2021	RCT	24	8 wk	Physically active adults with BMI 25 kg/m ²	Brazil	F: 20 M: 4	TRE :30.5 ± 3.5; Comparator: 31.7 ± 5.6	TRE: 32.4 ± 5.5; Comparator: 33.0 ± 8.7	16:08	12:00-20:00

Schroder <i>et al</i> [38], 2021	NRCT	40	3 mo	Women with BMI ≥ 30 kg/m ²	Brazil	F: 40	TRE: 32.53 $\pm$ 1.13; Comparator: 4.55 $\pm$ 1.20	TRE: 36.6 $\pm$ 1.6; Comparator: 42.3 $\pm$ 3.5	16:08	12:00-20:00
Sutton <i>et al</i> [39], 2018	RXT	8	5 wk	Pre-diabetic men with BMI ≥ 25 kg/m ²	Greater Baton Rouge, United States	M: 12	32.2 $\pm$ 4.4	56.0 $\pm$ 9.0	18:06	Self-select eating window between 06:30-08:30; For early TRE to end eating window by 15:00
Thomas <i>et al</i> [40], 2022	RCT	81	12/39 wk	Adults with BMI 27-45 kg/m ²	Colorado, United States	F: 20 M: 4	34.1 $\pm$ 5.7	38.0 $\pm$ 7.8	14:10	Start eating window 3 h post waking up

RCT: Randomized control trial; NRCT: Non-randomized control trial; RXT: Randomized crossover trial; BMI: Body mass index; M: Male; F: Female; TRE: Time-restricted eating.

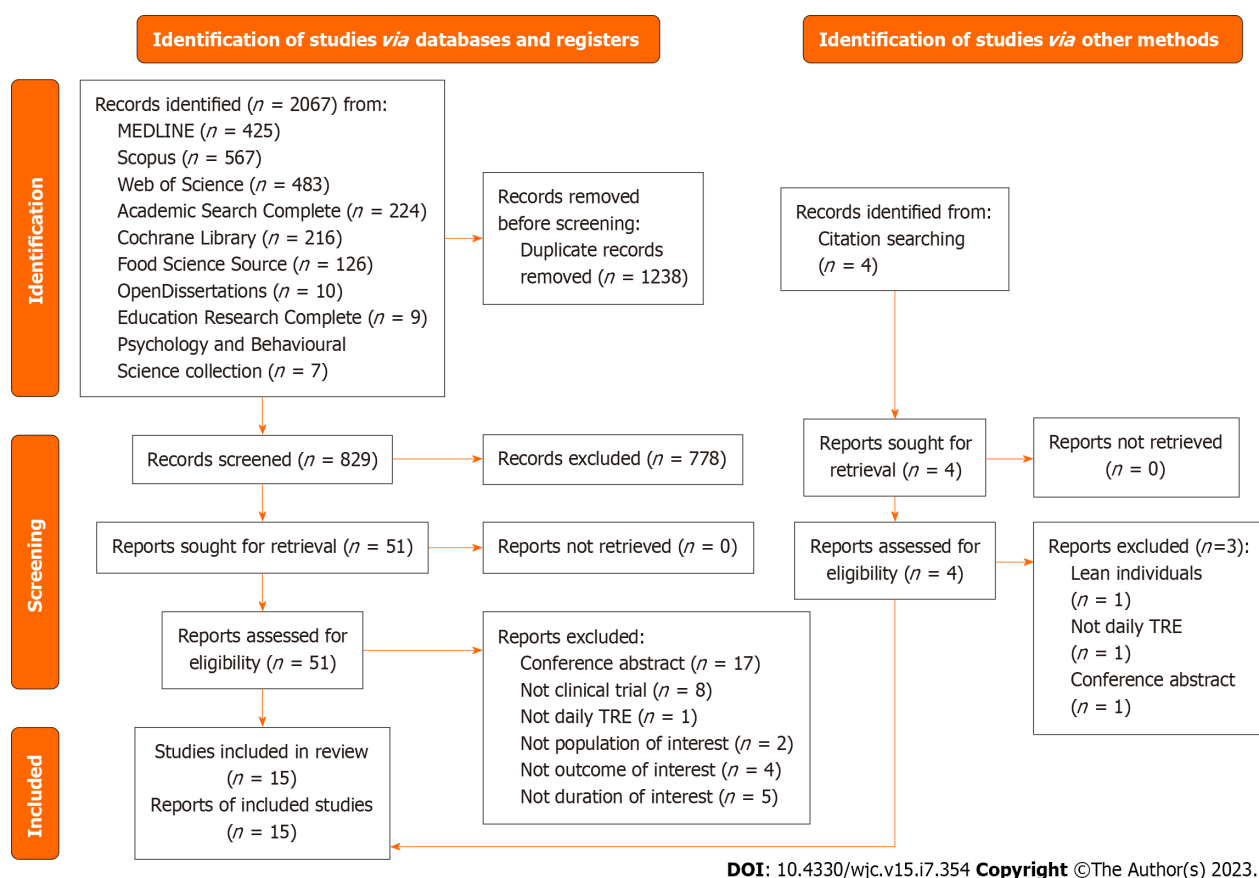


Figure 1 The preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram for systematic review, which included searches of databases, registers, and other sources. TRE: Time-restricted eating.

conducted based on the duration of TRE intervention revealed no significant changes in body weight in TRE interventions ranging from ten to 12 h [MD -1.11; 95%CI: -2.31 to 0.10, $P = 0.07$; $I^2 = 84\%$]. Meanwhile, a significant reduction was observed in TRE interventions ranging from seven to nine hours [MD -2.36; 95%CI: -4.37 to -0.35, $P = 0.02$; $I^2 = 79\%$] and TRE interventions ranging from four to six hours [MD -3.85; 95%CI: -4.29 to -3.41, $P < 0.00001$; $I^2 = 58\%$].

Waist circumference: A meta-analysis of nine studies demonstrated a significant overall effect of TRE on waist circumference reduction compared to 261 subjects in the comparator group [MD -2.35; 95%CI: -4.43 to -0.27, $P = 0.03$; $I^2 = 81\%$] (Figure 4). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in waist circumference following TRE interventions ranging from ten to 12 h [MD -1.11; 95%CI: -2.83 to 0.60, $P = 0.20$; $I^2 = 0\%$]. However, a significant reduction in waist circumference was observed in TRE interventions ranging from seven to nine hours [MD -2.70; 95%CI: -5.24 to -0.17, $P = 0.04$; $I^2 = 84\%$]. The effect of TRE ranging from four to six hours on the measured outcome was not reported in any of the included studies.

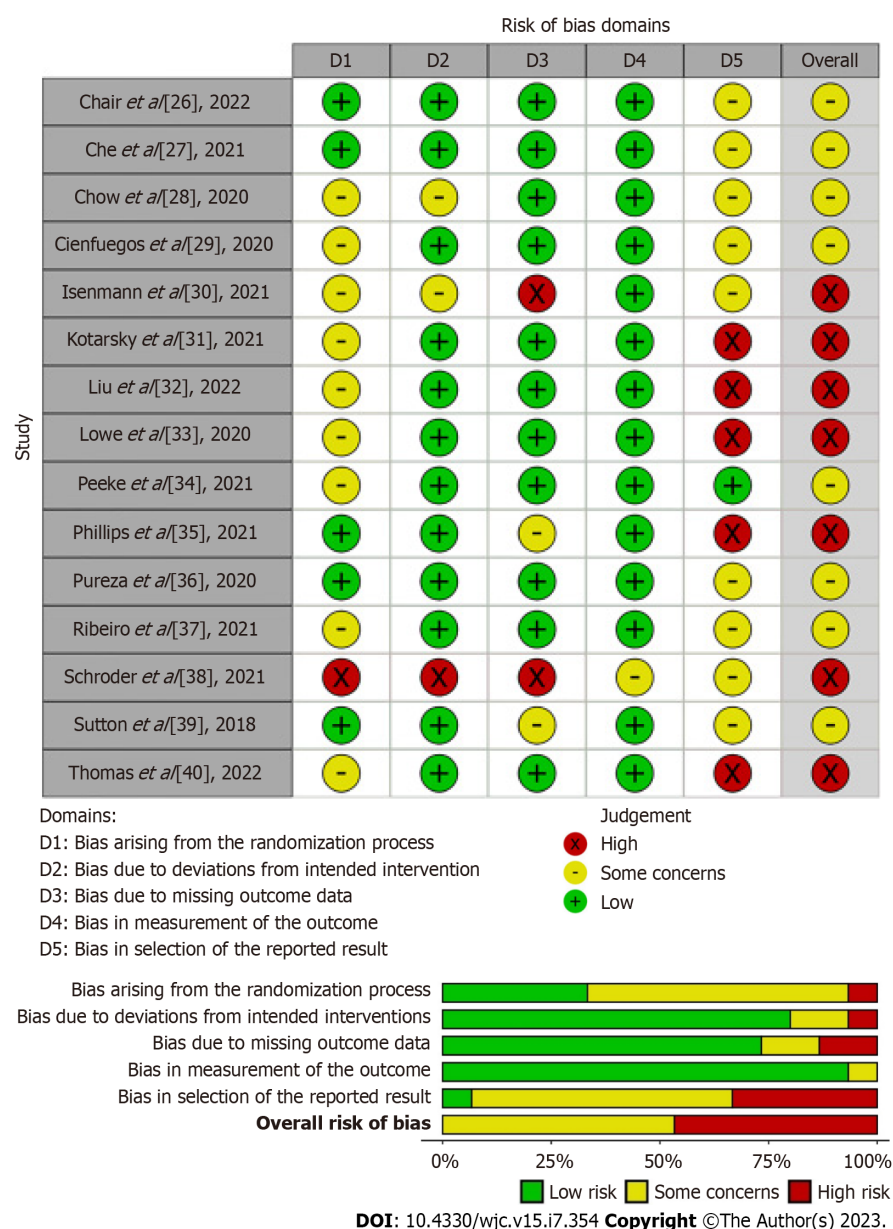


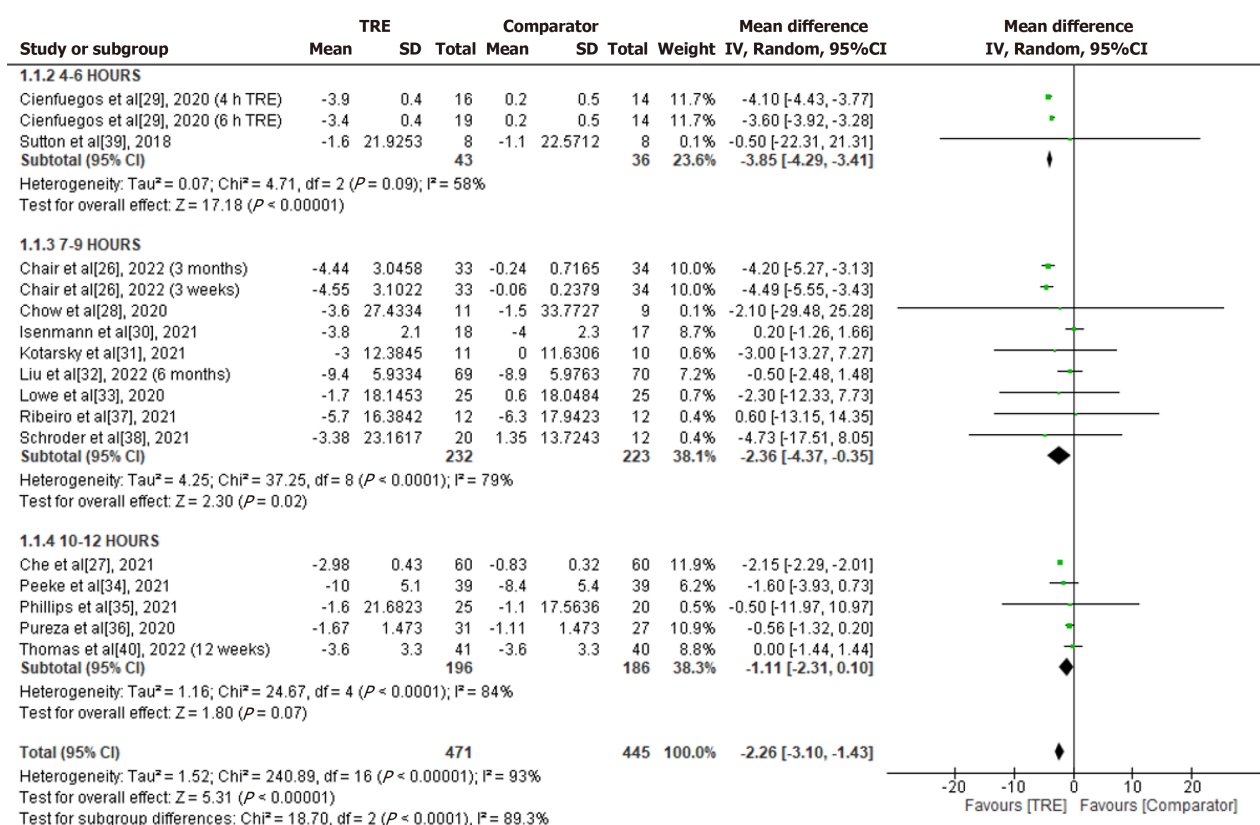
Figure 2 Risk of bias assessment of the studies included in the meta-analyses.

Total fat mass: A meta-analysis of ten studies evaluated the effect of TRE on total fat mass. Individuals assigned to TRE intervention showed a significant reduction in total fat mass levels compared to the comparator group [SMD -0.63; 95%CI: -1.10 to -0.17, $P = 0.008$; $I^2 = 83\%$] (Figure 5). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which revealed a significant reduction in total fat mass following TRE interventions ranging from ten to 12 h [SMD -0.41; 95%CI: -0.75 to -0.08, $P = 0.02$; $I^2 = 0\%$], and TRE interventions ranging from four to six hours [SMD -3.73; 95%CI: -6.76 to -0.70, $P = 0.02$; $I^2 = 91\%$]. However, no significant changes were observed in TRE interventions ranging from seven to nine hours [SMD -0.13; 95%CI: -0.35 to 0.09, $P = 0.25$; $I^2 = 0\%$].

Lean body mass: A meta-analysis of nine studies was evaluated the effect of TRE on lean body mass. Individuals assigned to TRE intervention showed a significant overall reduction in lean body mass compared to the comparator group [MD -0.64; 95%CI: -1.11 to -0.16, $P = 0.009$; $I^2 = 75\%$] (Figure 6). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in lean body mass following TRE interventions ranging from seven to nine hours [MD -0.23; 95%CI: -0.90 to 0.43, $P = 0.49$; $I^2 = 0\%$]. A significant reduction in lean body mass was observed in the TRE intervention group compared to the comparator following TRE interventions ranging from four to six hours [MD -0.86; 95%CI: -1.54 to -0.17, $P = 0.01$; $I^2 = 96\%$]. Subgroup analysis for TRE interventions ranging from ten to 12 h was not calculated since only one study reported this outcome.

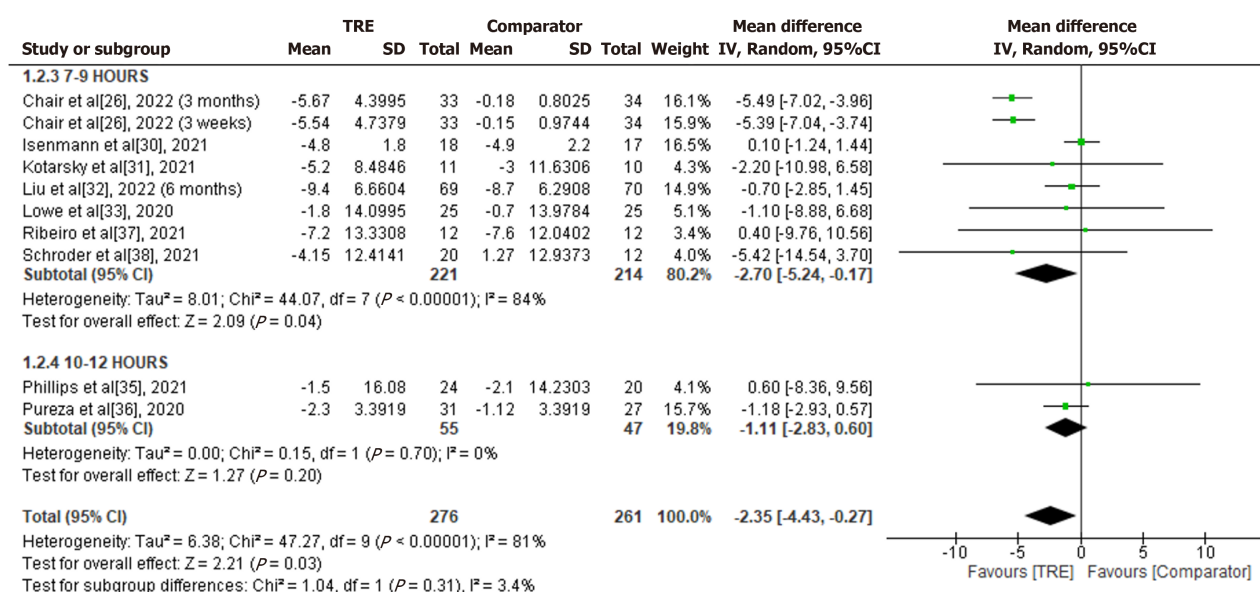
Effects of TRE on biomarkers of glucose metabolism.

Glucose: A meta-analysis of eleven studies reported a significant overall effect of TRE on glucose levels reduction compared to the comparator group [MD -4.13; 95%CI: -6.98 to -1.28, $P = 0.005$; $I^2 = 89\%$] (Figure 7). Random-effects



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Figure 3 Meta-analysis of the effects of time-restricted eating vs comparator on body weight, kg. TRE: Time-restricted eating.



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Figure 4 Meta-analysis of the effects of time-restricted eating vs comparator on waist circumference. TRE: Time-restricted eating.

subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in glucose levels following TRE interventions ranging from ten to 12 h [MD -5.91; 95%CI: -13.29 to 1.48, $P = 0.12$; $I^2 = 82\%$]. However, a significant reduction was reported in TRE interventions ranging from seven to nine hours [MD -2.20; 95%CI: -3.64 to -0.77, $P = 0.003$; $I^2 = 0\%$] and TRE interventions ranging from four to six hours [MD -5.79; 95%CI: -8.18 to -3.41, $P = 0.00001$; $I^2 = 54\%$].

HbA1c: A meta-analysis of six studies revealed the effect of TRE on HbA1c. There was no significant difference in HbA1c levels between the test and comparator groups [MD -0.12; 95%CI: -0.46 to 0.21, $P = 0.47$; $I^2 = 99\%$] (Figure 8). Random-

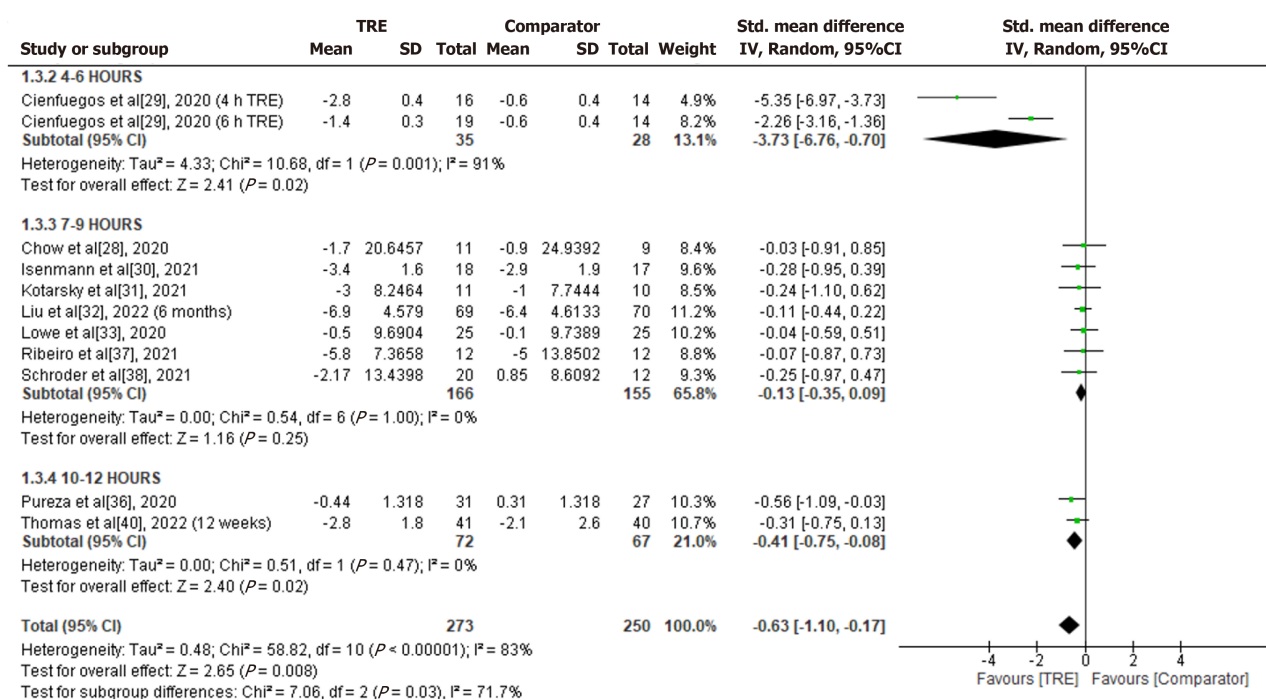


Figure 5 Meta-analysis of the effects of time-restricted eating vs comparator on total fat mass. TRE: Time-restricted eating.

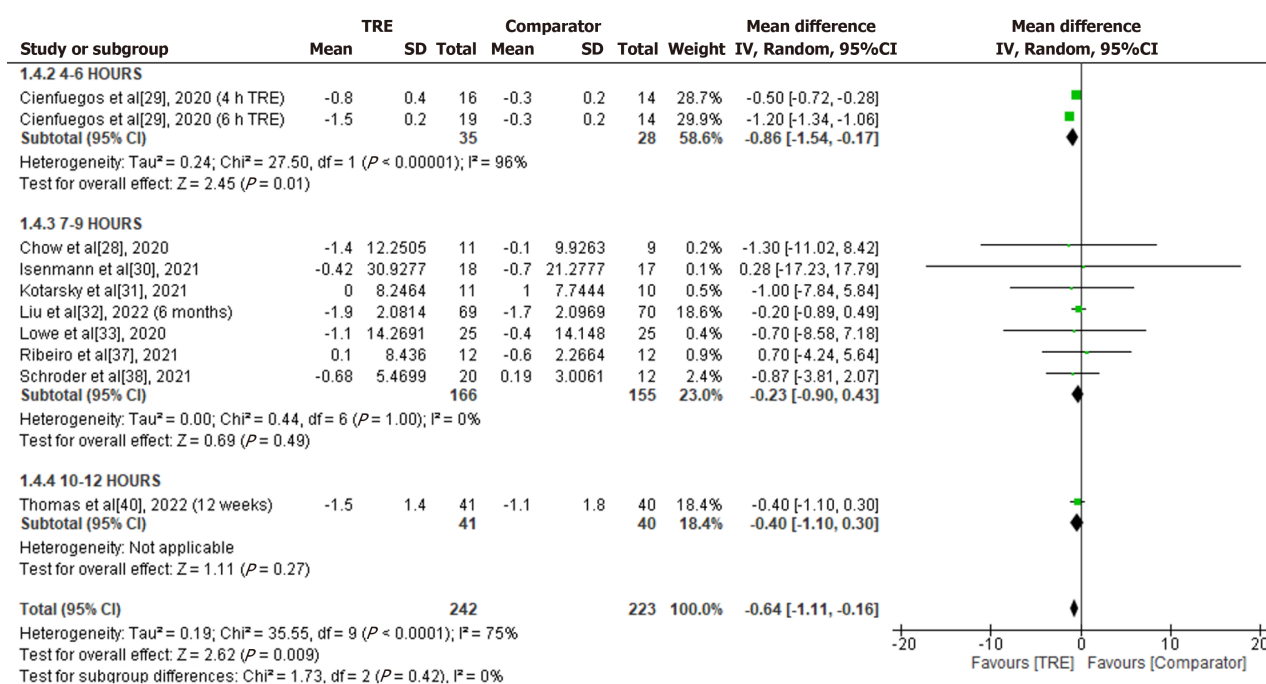
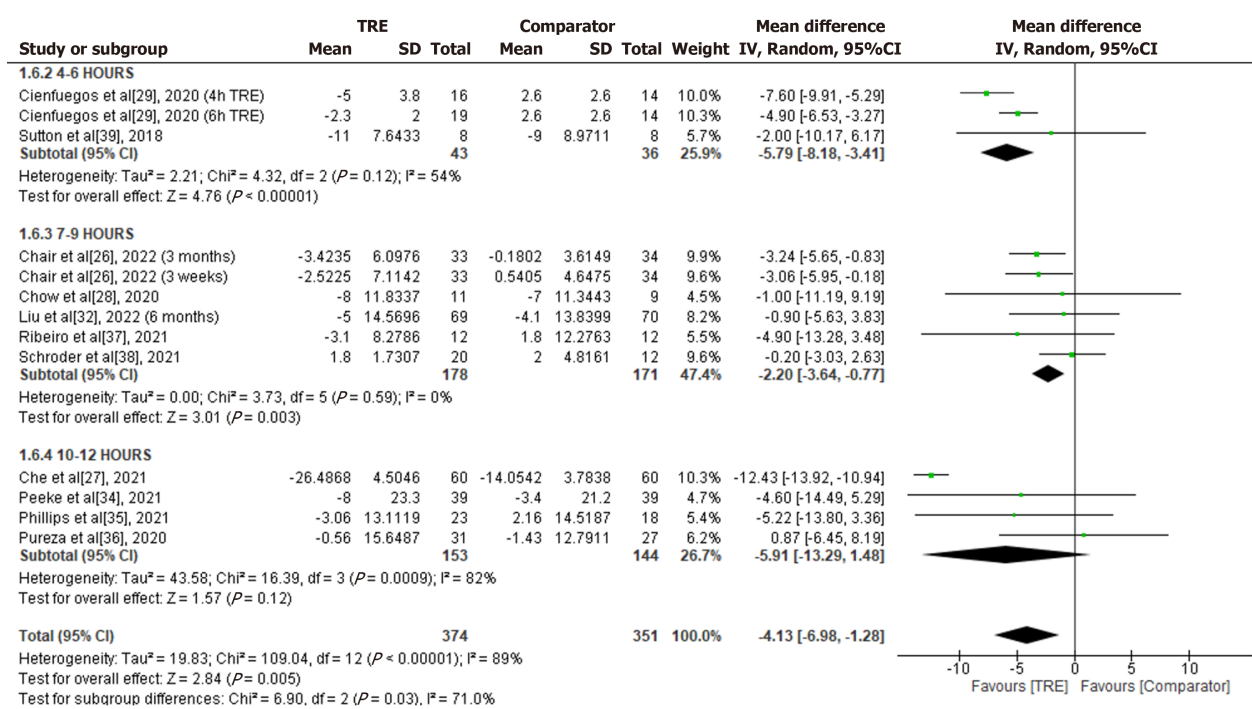


Figure 6 Meta-analysis of the effects of time-restricted eating vs comparator on lean body mass.

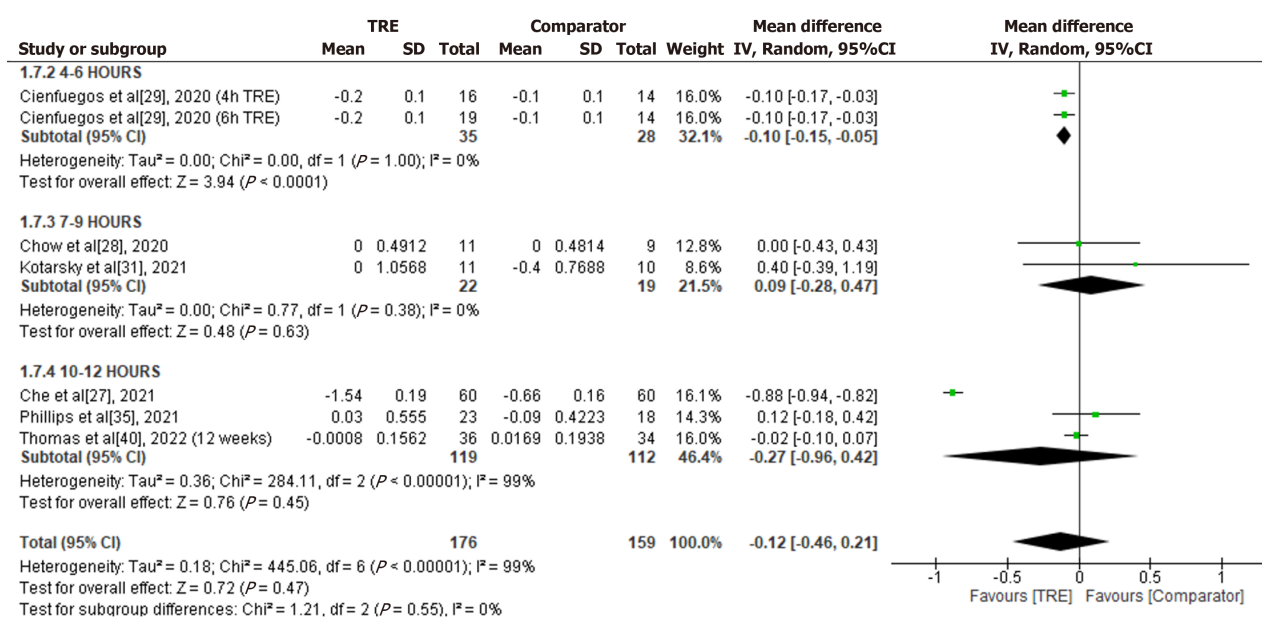
effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in HbA1c following TRE interventions ranging from ten to 12 h [MD -0.27; 95%CI: -0.96 to 0.42, $P = 0.45$; $I^2 = 99\%$] and TRE interventions ranging from seven to nine hours [MD 0.09; 95%CI: -0.28 to 0.47, $P = 0.63$; $I^2 = 0\%$]. However, a significant reduction was reported in TRE interventions ranging from four to six hours [MD -0.10; 95%CI: -0.15 to -0.05, $P < 0.0001$; $I^2 = 0\%$].

HOMA-IR: A meta-analysis of seven studies reported the effect of TRE on HOMA-IR. There was no significant difference in HOMA-IR levels compared to the comparator group [MD -0.24; 95%CI: -0.52 to 0.05, $P = 0.10$; $I^2 = 76\%$] (Figure 9). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant



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Figure 7 Meta-analysis of the effects of time-restricted eating vs comparator on blood glucose. TRE: Time-restricted eating.



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Figure 8 Meta-analysis of the effects of time-restricted eating vs comparator on HbA1c. TRE: Time-restricted eating.

changes in HOMA-IR following TRE interventions ranging from ten to 12 h [MD -0.21; 95%CI: -0.58 to 0.16, $P = 0.27$; $I^2 = 96\%$] and TRE interventions ranging from seven to nine hours [MD -0.32; 95%CI: -0.84 to 0.20, $P = 0.23$; $I^2 = 0\%$]. Subgroup analysis for TRE interventions ranging from four to six hours was not calculated since it was reported in only one study.

Insulin: A meta-analysis of eight studies revealed a significant overall reduction of insulin levels with TRE compared to the comparator group (SMD -1.39; 95%CI: -2.54 to -0.25, $P = 0.02$; $I^2 = 95\%$) (Figure 10). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in insulin in TRE interventions ranging from ten to 12 h (SMD -1.60; 95%CI: -4.85 to 1.65, $P = 0.34$; $I^2 = 99\%$) and TRE interventions ranging from seven to nine hours (SMD -0.35; 95%CI: -1.17 to 0.47, $P = 0.41$; $I^2 = 74\%$). A significant reduction in insulin level was observed in TRE interventions ranging from four to six hours (SMD -2.75; 95%CI: -5.49 to -0.01, $P = 0.05$; $I^2 = 94\%$).

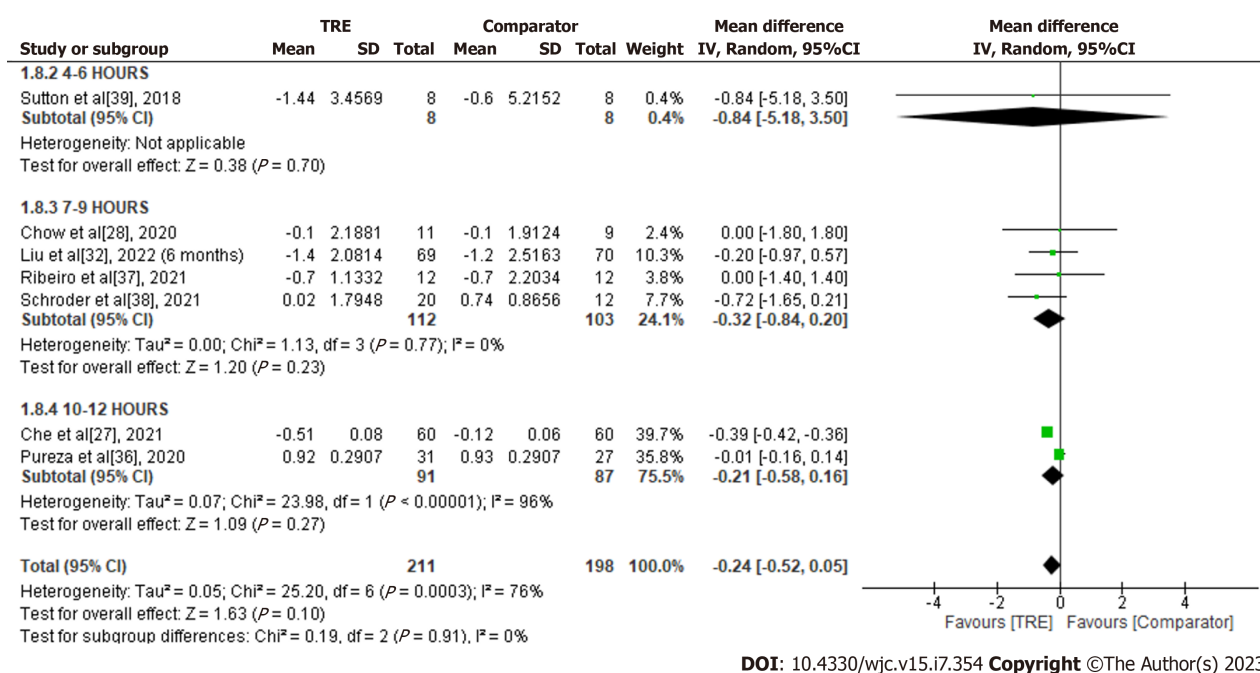


Figure 9 Meta-analysis of the effects of time-restricted eating vs comparator on HOMA-IR. TRE: Time-restricted eating.

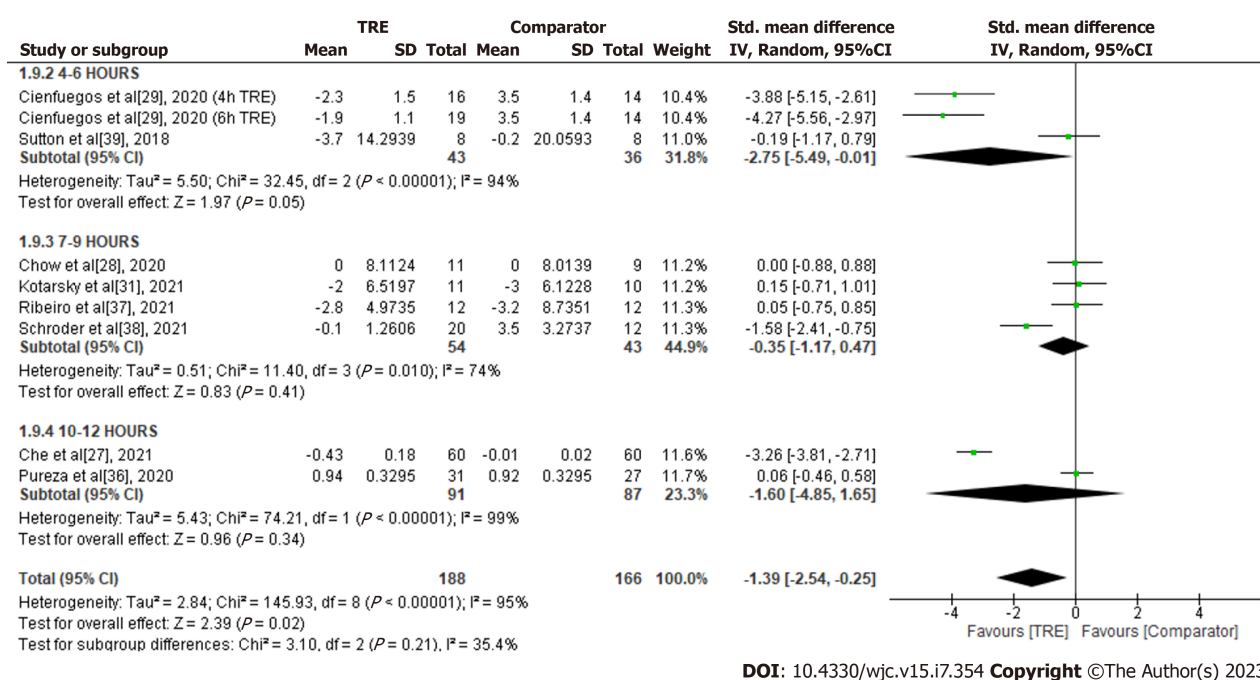
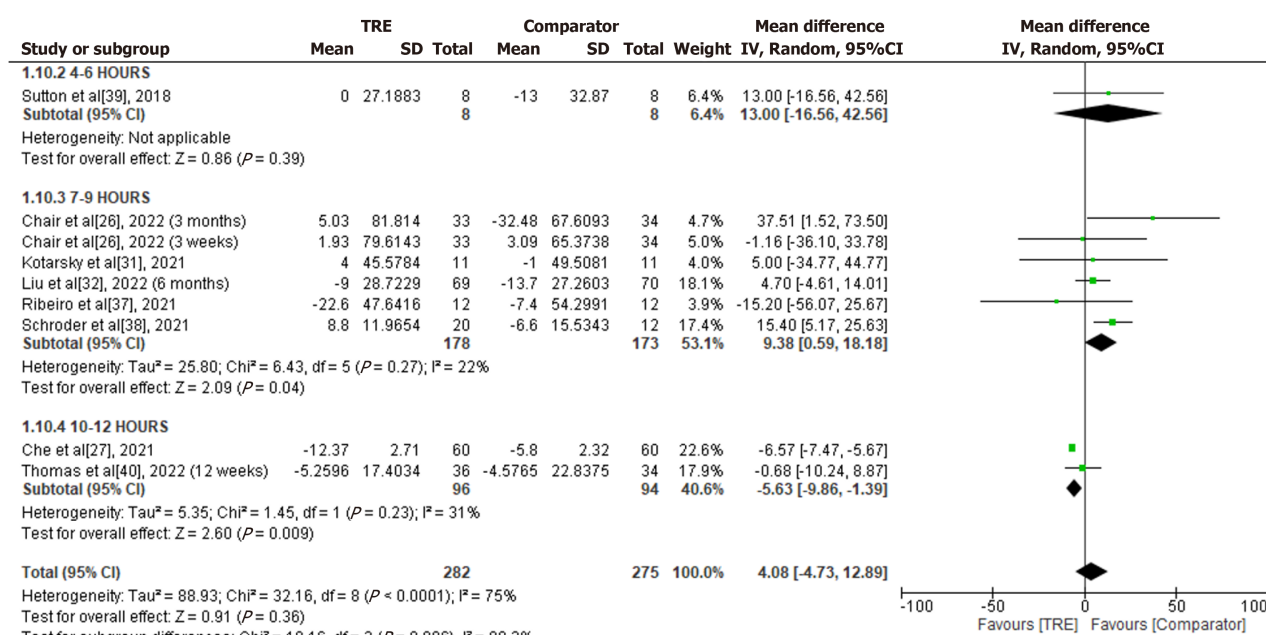


Figure 10 Meta-analysis of the effects of time-restricted eating vs comparator on insulin level. TRE: Time-restricted eating.

Effects of TRE on biomarkers of lipid metabolism

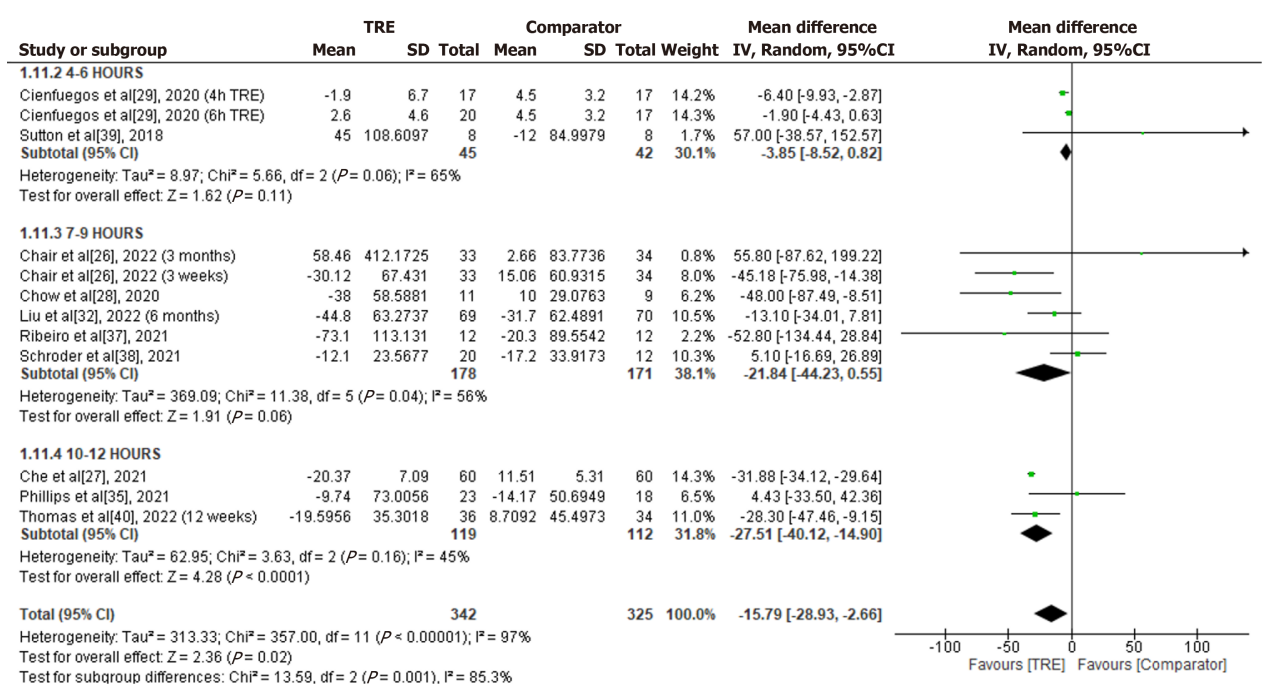
Total cholesterol: A meta-analysis of eight studies evaluated the effect of TRE on TC. There was no significant difference in TC levels between the test and comparator groups [MD 4.08; 95%CI: -4.73 to 12.89, $P = 0.36$; $I^2 = 75\%$] (Figure 11). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed a significant reduction in TC following TRE interventions ranging from ten to 12 h [MD -5.63; 95%CI: -9.86 to -1.39, $P = 0.009$; $I^2 = 31\%$]. Meanwhile, a significant increase in TC was observed in the TRE groups following TRE interventions ranging from seven to nine hours [MD 9.38; 95%CI: 0.59 to 18.18, $P = 0.04$; $I^2 = 22\%$]. Subgroup analysis for TRE interventions ranging from four to six hours was not calculated since it was reported only in one study.

Triglycerides: A meta-analysis of ten studies evaluated the effect of TRE on triglycerides (Figure 12). Individuals assigned to TRE intervention exhibited significantly reduced triglyceride levels compared to the comparator group [MD -15.79; 95%CI: -28.93 to -2.66, $P = 0.02$; $I^2 = 97\%$]. Random-effects subgroup analyses were conducted based on the duration



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Figure 11 Meta-analysis of the effects of time-restricted eating vs comparator on total cholesterol. TRE: Time-restricted eating.



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Figure 12 Meta-analysis of the effects of time-restricted eating vs comparator on triglycerides. TRE: Time-restricted eating.

of TRE intervention revealed a significant reduction in triglycerides following TRE interventions ranging from ten to 12 h [MD -27.51; 95%CI: -40.12 to -14.90, $P < 0.0001$; $I^2 = 45\%$]. However, there were no significant changes in triglyceride levels observed following TRE interventions ranging from seven to nine hours [MD -21.84; 95%CI: -44.23 to 0.55, $P = 0.06$; $I^2 = 56\%$] and TRE interventions ranging from four to six hours [MD -3.85; 95%CI: -8.52 to 0.82], $P = 0.11$; $I^2 = 65\%$].

LDL-C: A meta-analysis of nine studies showed no significant overall effect of TRE on LDL-C levels compared to the comparator group [MD 1.26; 95%CI: -3.94 to 6.46, $P = 0.63$; $I^2 = 86\%$] (Figure 13). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which showed no significant changes in LDL-C following TRE interventions ranging from ten to 12 h [MD -1.56; 95%CI: -15.99 to 12.88, $P = 0.83$; $I^2 = 88\%$] and TRE interventions ranging from four to six hours [MD 0.94; 95%CI: -5.64 to 7.52, $P = 0.78$; $I^2 = 82\%$]. In contrast, a significant increase of LDL-C was observed in TRE interventions ranging from seven to nine hours [MD 5.98; 95%CI: 1.02 to 10.94, $P = 0.02$; $I^2 = 82\%$].

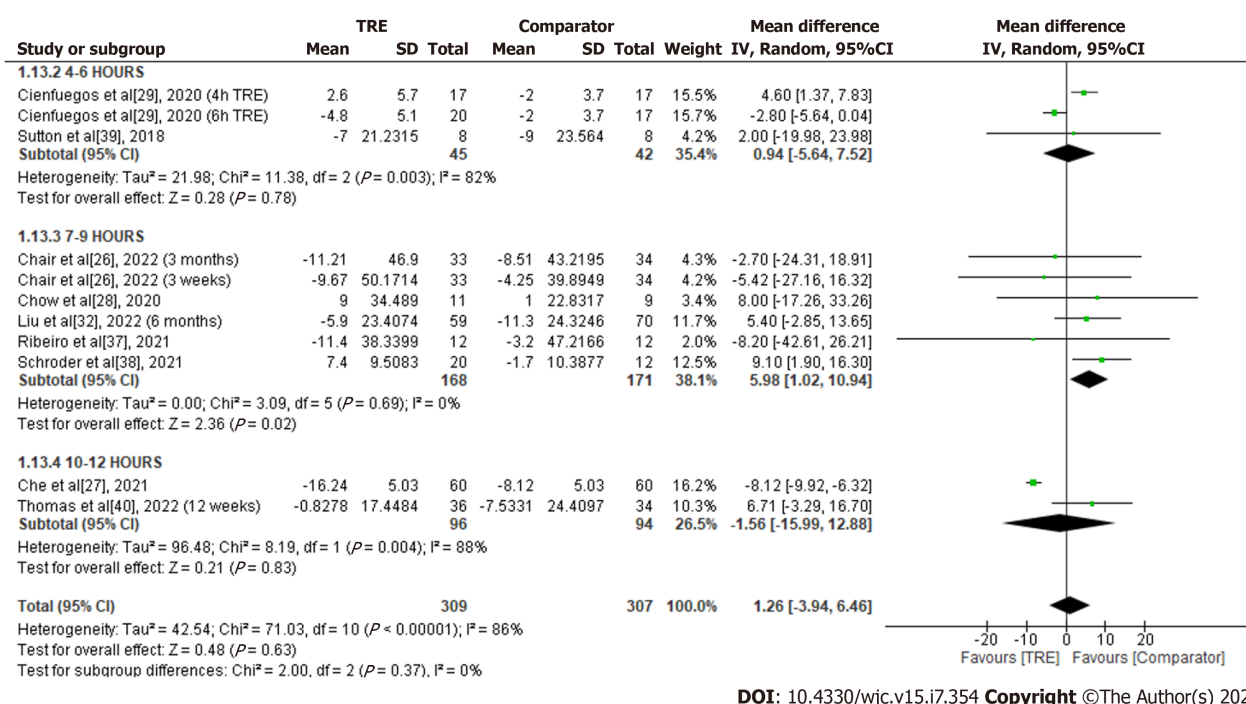


Figure 13 Meta-analysis of the effects of time-restricted eating vs comparator on low-density lipoprotein cholesterol. TRE: Time-restricted eating.

HDL-C: A meta-analysis of ten studies showed no significant overall effect of TRE on HDL-C levels compared to the comparator group [MD -0.17; 95%CI: -1.19 to 0.85, $P = 0.74$; $I^2 = 58\%$] (Figure 14). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in HDL-C following TRE interventions ranging from ten to 12 h [MD -0.38; 95%CI: -1.00 to 0.24, $P = 0.23$; $I^2 = 0\%$], TRE interventions ranging from seven to nine hours [MD 1.62; 95%CI: -2.48 to 5.71, $P = 0.44$; $I^2 = 53\%$], and TRE interventions ranging from four to six hours [MD -0.88; 95%CI: -2.28 to 0.52, $P = 0.22$; $I^2 = 75\%$].

Effects of TRE on biomarkers of inflammation

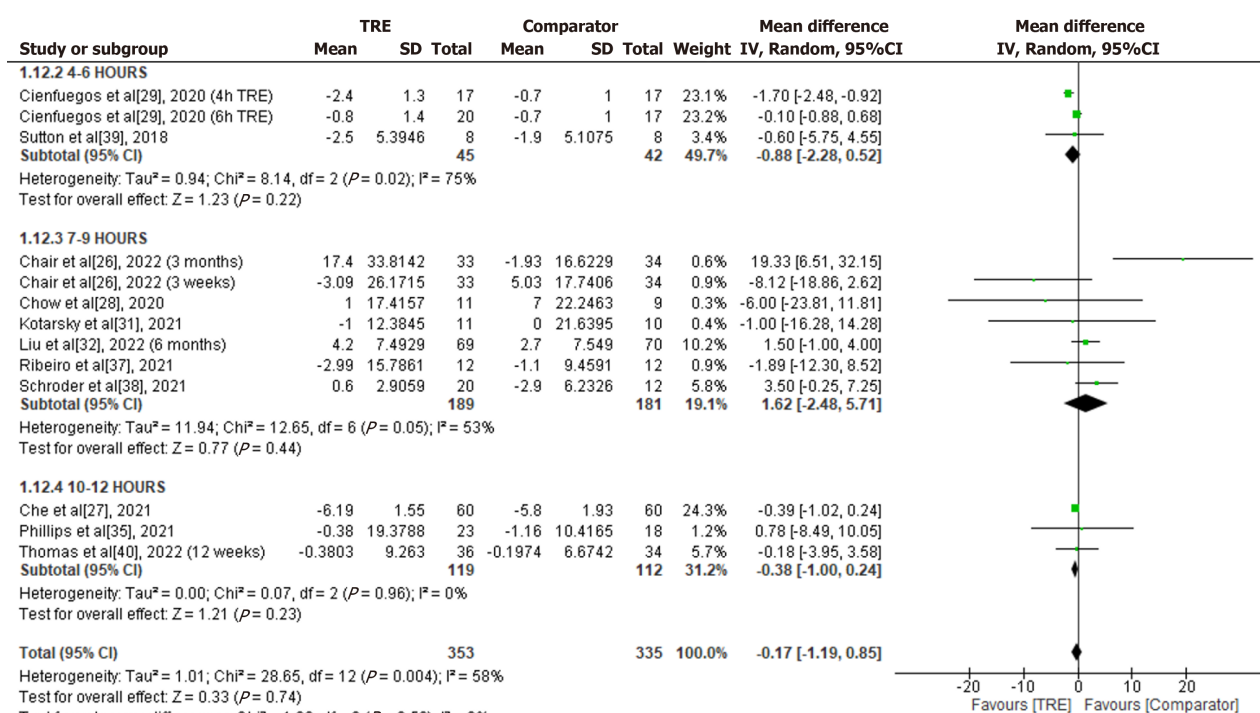
C-reactive protein: A meta-analysis of three studies evaluated the effect of TRE on C-reactive protein (Figure 15). There was no significant difference in C-reactive protein levels between the test and comparator groups [MD -0.35; 95%CI: -1.79 to 1.08, $P = 0.63$; $I^2 = 0\%$]. No subgroup analysis was conducted due to the limited included studies reporting this outcome.

Effects of TRE on blood pressure and heart rate

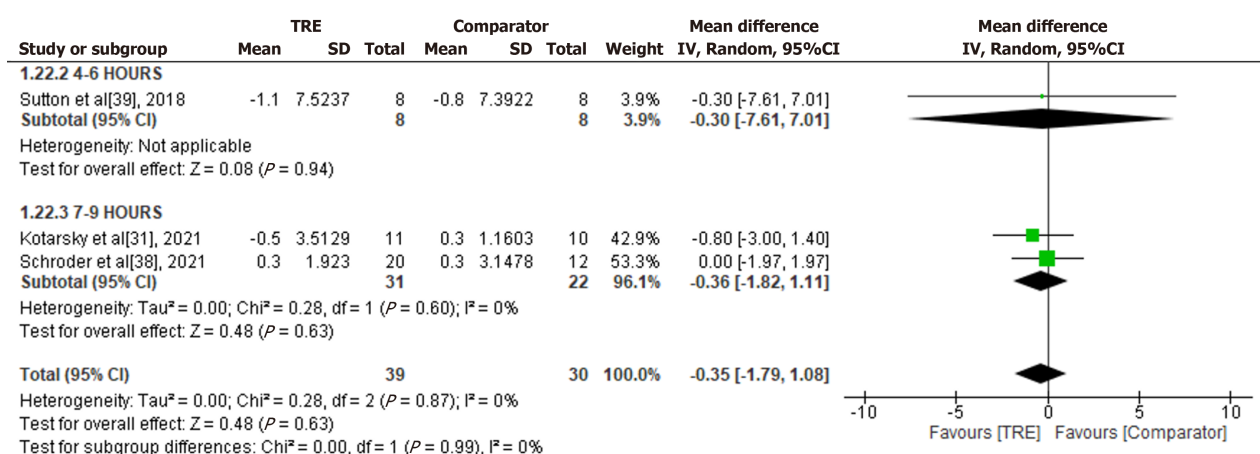
Systolic blood pressure: A meta-analysis of eight studies evaluated the effect of TRE on systolic blood pressure (Figure 16). There was no significant difference in systolic blood pressure levels between groups [MD -0.87; 95%CI: -1.90 to 0.16, $P = 0.10$; $I^2 = 0\%$]. Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no changes in systolic blood pressure following TRE interventions ranging from ten to 12 h [MD 2.08; 95%CI: -1.83 to 5.99, $P = 0.30$; $I^2 = 0\%$], TRE interventions ranging from seven to nine hours [MD -1.28; 95%CI: -3.74 to 1.18, $P = 0.31$; $I^2 = 0\%$], and TRE interventions ranging from four to six hours [MD -1.04; 95%CI: -2.23 to 0.14, $P = 0.08$; $I^2 = 0\%$].

Diastolic blood pressure: A meta-analysis of eight studies evaluated the effect of TRE on diastolic blood pressure (Figure 17). There was no significant difference in diastolic blood pressure levels between the test and comparator groups [MD -1.36; 95%CI: -3.83 to 1.11, $P = 0.28$; $I^2 = 83\%$]. Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in diastolic blood pressure following TRE interventions ranging from ten to 12 h [MD 2.87; 95%CI: -0.79 to 6.52, $P = 0.12$; $I^2 = 0\%$] and TRE interventions ranging from seven to nine hours [MD 0.25; 95%CI: -1.56 to 2.06, $P = 0.79$; $I^2 = 0\%$]. In contrast, there was a significant reduction observed in TRE interventions ranging from four to six hours [MD -5.41; 95%CI: -6.25 to -4.57, $P = < 0.00001$; $I^2 = 0\%$].

Heart rate: A meta-analysis of five studies reported no significant overall effect of TRE on heart rate levels in comparison to the comparator group [MD 0.15; 95%CI: -1.86 to 2.15, $P = 0.89$; $I^2 = 67\%$] (Figure 18). Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in heart rate following TRE interventions ranging from seven to nine hours [MD -1.00; 95%CI: -3.85 to 1.84, $P = 0.49$; $I^2 = 0\%$] and TRE interventions ranging from four to six hours [MD 1.04; 95%CI: -2.06 to 4.14, $P = 0.51$; $I^2 = 85\%$]. Subgroup analysis for TRE interventions ranging from ten to 12 h was not calculated since only one study reported the outcome for this particular duration.



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Figure 14 Meta-analysis of the effects of time-restricted eating vs comparator on high-density lipoprotein cholesterol. TRE: Time-restricted eating.

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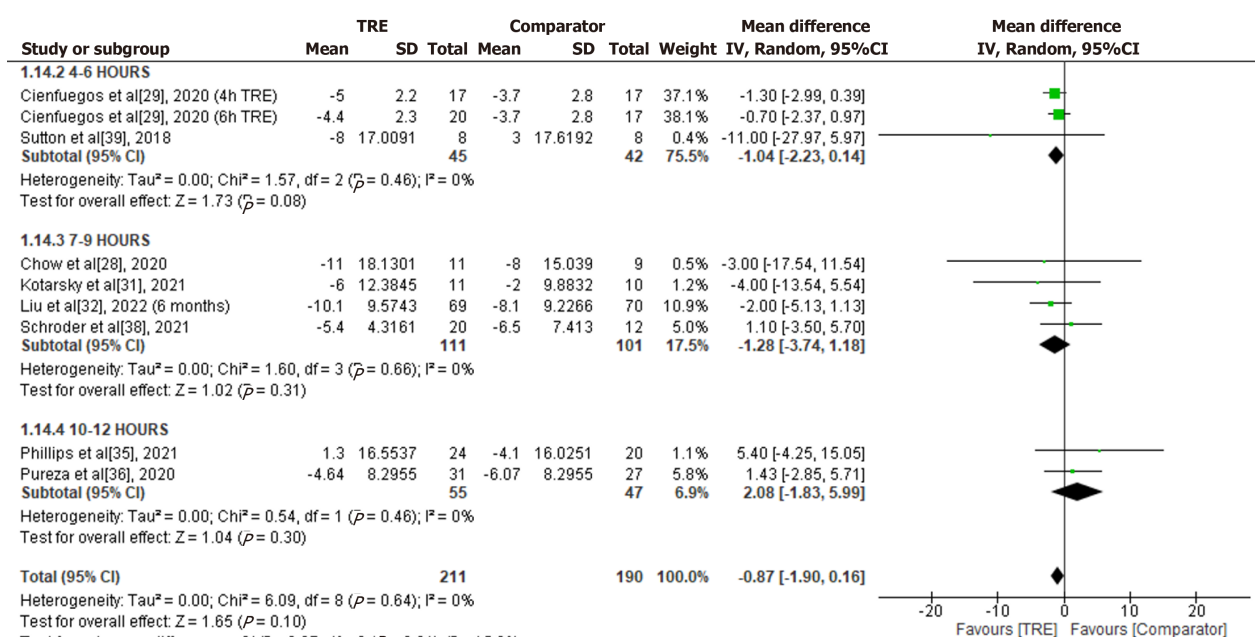
Figure 15 Meta-analysis of the effects of time-restricted eating vs comparator on C-reactive protein. TRE: Time-restricted eating.

Funnel plots

The potential publication biases were assessed using funnel plots based on the outcomes of interest (Supplementary Figure 1). The funnel plots were generally symmetric, indicating a low probability of publication bias in most outcomes. However, the glucose outcome showed an asymmetric funnel plot, suggesting a possible publication bias.

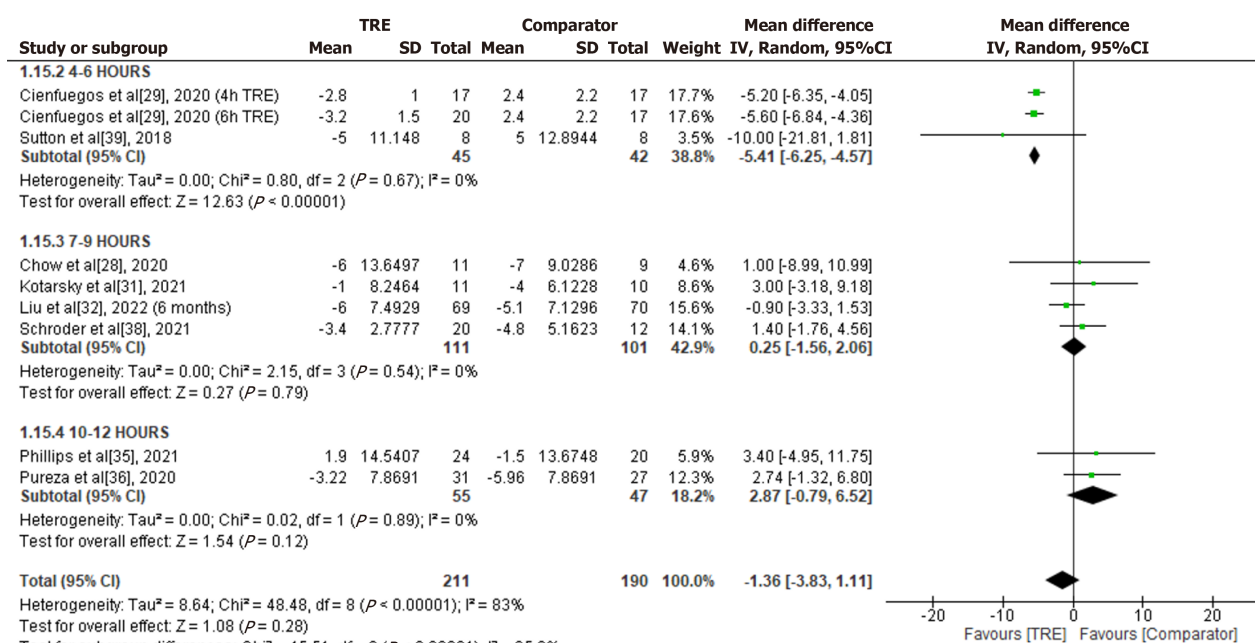
DISCUSSION

Adopting IF, including time-restricted eating interventions, to potentially optimize metabolic health by altering the duration of food consumption is a topic of increasing interest in research and others[41]. The present review analyzed the effects of TRE intervention on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases. The meta-analysis showed that TRE significantly reduced body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, and triglyceride. However, no changes were observed in HbA1c, HOMA-IR, TC, LDL-C, HDL-C, heart rate, systolic and diastolic blood pressure. Interestingly, subgroup analyses



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Figure 16 Meta-analysis of the effects of time-restricted eating vs comparator on systolic blood pressure. TRE: Time-restricted eating.



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Figure 17 Meta-analysis of the effects of time-restricted eating vs comparator on diastolic blood pressure. TRE: Time-restricted eating.

based on the duration of the eating window revealed that TRE interventions with shorter eating windows (4-6 h) resulted in a more pronounced effect size than longer eating windows as measured for all outcomes. The meta-analysis results suggest that TRE is an effective treatment strategy for adults with excessive weight and obesity-related metabolic diseases as it improves specific metabolic parameters and potentially decreases the risk of atherosclerotic cardiovascular disease.

Limiting food intake to a shorter duration, without explicitly attempting to reduce energy intake, induces fasting physiology. This adaptive mechanism in the human body has evolved to cope with periods of food scarcity and prolonged fasting and is critical for survival[42]. A fasting regime, including TRE, activates metabolic switching from energy production through liver-derived glucose to adipose cell-derived ketones[43,44]. At the molecular level, TRE triggers circadian coordination with nutrient-sensing pathways to regulate metabolic health and protects against metabolic disorders induced by poor dietary intake[45]. Findings from this review are consistent with previous meta-analyses where TRE was shown effective in weight reduction despite mixed findings on body composition[16,18,21,22]. Compared to CER, weight loss achieved through IF is comparable to[46], if not superior to CER[47]. TRE may spontan-

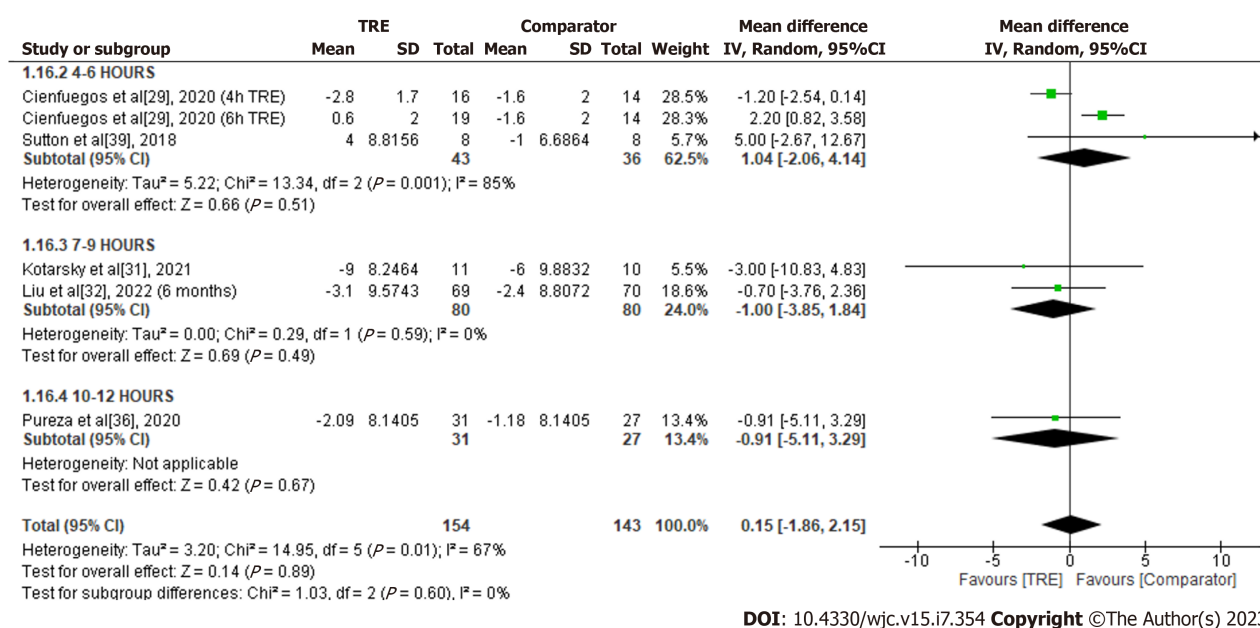


Figure 18 Meta-analysis of the effects of time-restricted eating vs comparator on heart rate. TRE: Time-restricted eating.

ously decrease energy intake by 20%-30% under ad libitum conditions, resulting in weight loss of 1%-4% [48]. During periods of fasting and CER, macro- and micronutrients are less accessible to cells and tissues. Hence, several pathways play comparable roles in mediating CER and IF effects. Decreased glucose levels or decreased protein and amino acid availability, as generated by caloric restriction or fasting, activate AMP-activated protein kinase (AMPK) and inhibit mTOR, resulting in reduced protein synthesis and ribosome biogenesis, as well as the activation of autophagy [49].

Nutrient timing has been proposed as a potential approach to restoring metabolic health by synchronizing dietary intake with the circadian clock [50]. TRE interventions consistently improved glucose metabolism by reducing glucose levels in human studies, as confirmed in the current meta-analysis [16,18,19,21,22]. The glucoregulatory mechanisms of TRE demonstrate that eating within a limited eating window during the day restores cAMP Response Element-Binding Protein phosphorylation, decreases gluconeogenesis, and increases glucogenesis during the fed state *via* enhanced autophagic flux, mild production in ketone bodies, reduced oxidative stress, and promotion of β -cell responsiveness [51]. However, the effects of TRE on lipid profiles, blood pressure, and heart rate have been inconsistent [16,18,19,21,22]. Nonetheless, the meta-analyses revealed that TRE did not worsen any outcomes studied. While it is widely accepted that TRE improves circadian rhythms, it remains unknown whether the metabolic improvements are the result of calorie limitation or time restriction [52].

The duration of the eating window in TRE interventions on humans varies, which has led to heterogeneous results between studies. This systematic review suggests that TRE's beneficial effects may be time-dependent, with a shorter eating window resulting in better weight management and cardiometabolic health than a longer eating duration. The mechanisms by which this occurs have yet to be fully understood. An animal study revealed that a 4-h time-restricted feeding could reprogram the circadian clock by restoring the expression phase of clock genes, despite the high-fat diet [11]. At the cellular level, prolonged fasting leads to increased AMP levels, gene expression, and activation of AMPK, a critical intracellular energy sensor that regulates processes associated with energy metabolism [11,53]. This results in reduced fatty acid synthesis and enhanced fatty acid oxidation in the liver [54]. Similar to AMPK, Sirtuin 1 (SIRT1) activity increases in response to prolonged fasting [55]. SIRT1 regulates numerous biological processes, such as insulin response, glycolysis, apoptosis, antioxidant defense, DNA repair, inflammatory response, metabolism, cancer, and stress, improving cardiometabolic health and CVD prevention [56-58].

Jamshed *et al* [59] conducted a 4-d randomized crossover study to elucidate the possible mechanisms of actions of TRE with short eating duration in humans. This study revealed that TRE with a short eating window improved multiple health aspects *via* circadian and fasting-related mechanisms [59]. The authors postulated that eating earlier in the day and having shorter inter-meal intervals could help minimize glycemic excursions, suggesting that TRE interventions with longer inter-meal intervals may be less effective in lowering glucose levels. Additionally, the study found that TRE may alter diurnal patterns in fasting cholesterol, ketones, cortisol, and circadian clock genes, particularly by increasing ketone levels in the morning and improving the amplitude of the cortisol rhythm. The study also demonstrated that six hours of TRE may produce a favorable effect on hormones and genes related to lifespan and autophagy, such as brain-derived neurotrophic factor, SIRT1, and LC3A, the autophagosome protein.

The findings of this meta-analysis provide evidence to support the hypothesis that longer fasting duration is associated with better weight control [60,61]. Contrary to animal studies, restricting eating duration does not affect 24-h energy expenditure in humans [62,63]. Animal studies have suggested that time-restricted feeding may increase energy expenditure by enhancing oxidative metabolism and expression of the mitochondrial uncoupling protein, which is responsible for non-shivering thermogenesis in brown and white adipose tissue [13,64,65]. Nevertheless, a human study detected an increased thermic effect of food during the early postprandial period [63]. The study demonstrated that short

TRE interventions primarily promote weight loss by decreasing appetite, as evidenced by reduced ghrelin levels and normalized hunger, which tend to promote fullness and reduced appetite. Furthermore, TRE with a short eating window leads to alterations in substrate oxidation, with an increase in 24-h protein oxidation and a decrease in 24-h non-protein Respiratory Quotient (npRQ), indicative of increased fat oxidation. This metabolic alteration is likely attributed to the prolonged daily fasting phase rather than circadian effects[43]. Furthermore, the short TRE group showed higher metabolic flexibility, defined as the difference between the maximum and minimum values of the npRQ, indicating a better ability to switch between different oxidizing substrates than the *ad libitum* group.

It is important to note that the associations between fasting duration and weight and cardiometabolic health may vary depending on the time of fasting and eating[15]. The early fasting window, characterized by breakfast consumption and early evening meals, may have different metabolic consequences than the late fasting window, characterized by breakfast omission and night-time snacking[60]. Since humans are diurnal organisms, eating closer to daylight is consistent with the 24-h circadian rhythms of metabolism, leading to better metabolic health. The alignment of meals with typical circadian oscillations of hormonal profiles is necessary for TRE to be considered a nutritional strategy utilizing chrononutrition concepts. For example, plasma glucose concentration exhibits diurnal fluctuation, with peak values occurring at the start of the activity phase[66]. Since food intake promotes insulin production, plasma insulin levels reflect the daily rhythm of food intake. Thus, night eating results in a misalignment of central and peripheral endogenous glucose circadian rhythms and impaired glucose tolerance, while restricting meals to the daytime prevents such dysregulation [67]. Accordingly, the current pool of evidence suggests that later or self-selected TRE periods are less effective in improving metabolic health markers[68].

Although the findings of this meta-analysis suggest that short TRE may improve cardiometabolic outcomes, it is crucial to consider the sustainability of a restrictive eating pattern. The primary concern with a short eating window is that it may be too limiting for many individuals, making it challenging to adhere to over the long term. Adherence is a crucial factor in the success of any dietary intervention, as a lack of adherence can lead to the failure of the intervention. Additionally, limiting eating periods may lead to disordered eating patterns or restrictive dieting behaviors. A recent study found that individuals who engaged in TRE were at a higher risk for disordered eating behaviors, such as overeating, losing control, binge eating, vomiting, laxative use, and compulsive exercise[69]. The application of short TRE may not be suitable for all individuals, particularly those with certain medical conditions or who are pregnant or breast-feeding. Alteration in the metabolism and nutrient needs of these individuals may necessitate a more frequent or longer eating duration than the general population.

We have identified several strengths in our meta-analysis. We utilized multiple databases to search existing literature and identify eligible studies related to TRE conducted on individuals with excessive weight or weight-related metabolic diseases while excluding individuals with a normal BMI. This approach ensured the homogeneity of the population of interest, as this group of individuals may have a higher tendency to experience metabolic disturbances than individuals with a normal BMI. Additionally, we performed subgroup analyses based on arbitrary clustering of the eating window duration of TRE intervention to explore methodological heterogeneity. Furthermore, we only included studies involving clinical trials that lasted two weeks up to six months to reduce heterogeneity from short-term interventions (*i.e.*, less than seven days) and studies reporting long-term effects of TRE. However, this meta-analysis has some limitations. Most included studies had small sample sizes, with several posing a high RoB in some domains. Blinding participants was impossible due to the nature of behavioral interventions. Nonetheless, this factor is unlikely to affect the results as outcomes were objectively measured, with some studies executed blinding of assessors. Additionally, there was high heterogeneity in some of the outcomes, which could be due to differences in population, fasting/eating duration, duration of the intervention, meal timing, meal frequency, co-interventions, and level of adherence. Data on such factors, including dietary intake, physical activity, and adherence level, were unavailable in some reports, which might have resulted in biased conclusions. Future large-randomized-controlled trials with rigorous methodology are necessary to elucidate the role of different TRE duration on cardiometabolic health and determine the optimal TRE duration to translate into clinical practice.

CONCLUSION

In conclusion, findings from this meta-analysis demonstrate that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, and triglyceride in individuals with excessive weight or weight-related metabolic disorders. Moreover, this study demonstrated that the favorable benefits of TRE on health are dependent on eating duration, with shorter durations resulting in more significant changes in anthropometric and cardiometabolic health markers. However, due to the challenges of adhering to a strict regimen, the TRE interventions with short eating windows may only suit specific individuals and must be monitored vigilantly. Therefore, extensive studies with larger sample sizes and higher quality are required to confirm the findings of this meta-analysis and determine the optimal duration of the eating window for primary and secondary CVD prevention.

ARTICLE HIGHLIGHTS

Research background

There is growing interest in time-based dietary intervention as an alternative to caloric restriction or nutrient-based

dietary intervention for cardiovascular disease prevention.

Research motivation

Time-restricted eating (TRE) is considered a mild form of intermittent fasting and has shown conflicting cardiometabolic health outcomes in humans.

Research objectives

Our study aimed to explore the overall effectiveness of TRE and its optimal duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

Research methods

Systematic searches were conducted *via* multiple databases (MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection) to identify the relevant articles. The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB-2). Meta-analyses were conducted depending on feasibility. Analysis was performed using RevMan software.

Research results

TRE significantly decreased body weight, waist circumference, adipose mass, lean body mass, blood glucose, insulin, and triglyceride. HbA1c, homeostasis model assessment for insulin resistance, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, systolic and diastolic blood pressure showed no significant changes with the treatment. In addition, subgroup analyses based on the eating duration revealed significant variation in the effects of the TRE intervention on the measured outcomes.

Research conclusions

TRE is an effective and sustainable dietary strategy to improve the anthropometric and cardiometabolic health of individuals with excessive weight or weight-related metabolic disorders.

Research perspectives

A larger sample size and higher quality studies are necessary to corroborate the findings of this meta-analysis and define the optimal duration of the eating window for cardiovascular disease prevention.

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FOOTNOTES

Author contributions: Zaman MK, Teng NIMF, Juliana N, and Kasim SS contributed to the conceptualization of the study, systematic search, and studies selection; Zaman MK and Teng NIMF performed data extraction and risk of bias assessments; data analysis, synthesis, and interpretation were conducted by Zaman MK, and Alshawsh MA; Zaman MK drafted the manuscript; All authors contributed to the manuscript revision and approved the final manuscript.

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Proton pump inhibitors and gastroprotection in patients treated with antithrombotic drugs: A cardiologic point of view

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

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Abstract

Aspirin, other antiplatelet agents, and anticoagulant drugs are used across a wide spectrum of cardiovascular and cerebrovascular diseases. A concomitant proton pump inhibitor (PPI) treatment is often prescribed in these patients, as gastrointestinal complications are relatively frequent. On the other hand, a potential increased risk of cardiovascular events has been suggested in patients treated with PPIs; in particular, it has been discussed whether these drugs may reduce the cardiovascular protection of clopidogrel, due to pharmacodynamic and pharmacokinetic interactions through hepatic metabolism. Previously, the concomitant use of clopidogrel and omeprazole or esomeprazole has been discouraged. In contrast, it remains less known whether PPI use may affect the clinical efficacy of ticagrelor and prasugrel, new P2Y₁₂ receptor antagonists. Current guidelines recommend PPI use in combination with antiplatelet treatment in patients with risk factors for gastrointestinal bleeding, including advanced age, concurrent use of anticoagulants, steroids, or non-steroidal anti-inflammatory drugs, and *Helicobacter pylori* (*H. pylori*) infection. In patients taking oral anticoagulant with risk factors for gastrointestinal bleeding, PPIs could be recommended, even if their usefulness deserves further data. *H. pylori* infection should always be investigated and treated in patients with a history of peptic ulcer disease (with or without complication) treated with antithrombotic drugs. The present review summarizes

the current knowledge regarding the widespread combined use of platelet inhibitors, anticoagulants, and PPIs, discussing consequent clinical implications.

Key Words: Antithrombotic drugs; Anticoagulants; Aspirin; Clopidogrel; Gastrointestinal bleeding; Proton pump inhibitors

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Core Tip: Antiplatelet and anticoagulant drugs are used across a wide spectrum of cardio-cerebrovascular diseases, but they are related to relatively frequent gastrointestinal bleeding complications, thus requiring a concomitant proton pump inhibitor (PPI) treatment. On the other hand, a potential increased cardiovascular risk has been suggested in patients treated with PPIs. Current guidelines recommend PPI use in combination with antiplatelet treatment in patients with risk factors for gastrointestinal bleeding. In patients taking oral anticoagulant with risk factors for gastrointestinal bleeding, PPIs could also be recommended, even if their usefulness deserves further data. The present review summarizes the current knowledge on this topic.

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INTRODUCTION

The use of proton pump inhibitors (PPIs), potent gastric acid secretion antagonists, for treating acid-related disorders, such as gastroesophageal reflux disease and peptic ulcer, as well as for prophylaxis of gastroduodenal lesions in patients treated with acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs), has increased rapidly during the last decades; they are now among the most prescribed medications in the world[1-3].

The risk of upper gastrointestinal bleeding (GIB) is noticeable in patients suffering from cardiovascular diseases (CVD) treated with antithrombotic therapy, particularly when different agents are administered together, *i.e.*, in double antiplatelet therapy (DAPT), or even in triple therapy with DAPT plus oral anticoagulant drugs [vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs)]. It is still controversial what the risk/benefit ratio is in terms of ischemic/bleeding events in primary prevention with ASA. PPIs are commonly used in patients taking antiplatelet agents and/or anticoagulants and with risk factors to reduce bleeding risk[1-3]. In 2009, several reassessments of pharmacokinetic and pharmacodynamic data, using platelet aggregation tests as a surrogate endpoint, suggested that PPI treatment might alter the therapeutic efficacy of clopidogrel. The clinical consequence of this interaction, which does not seem a class effect, is controversial. However, after this alert a reduced use of PPIs in patients treated with clopidogrel has been observed, leading to an increase in upper GIB episodes. Possible interactions between aspirin and PPIs have been recently suggested, too.

Finally, the evidence of cardiovascular risk associated with PPIs, the recent introduction of new antiplatelet agents (such as prasugrel and ticagrelor), the need for long-term DAPT in selected cases, the increasingly frequent indication for anticoagulant therapy, often concomitant with antiplatelet agents, and the introduction of DOACs, stressed the importance of an appropriate preventive PPI prescription.

This review aims to discuss and summarize the current pharmacological and clinical evidence about the widespread combined use of PPIs, platelet inhibitors, and anticoagulants.

CARDIOVASCULAR RISK ASSOCIATED WITH PPIs USE

The overall safety of PPIs is considered good, and they are well tolerated. They are, however, highly lipophilic drugs; thus, they may have potential interactions with different pathophysiological pathways involved in immune response, absorption of selected nutrients, infections, cognitive function, bone metabolism, and cardiovascular and kidney morbidity[3]. Several studies, in fact, showed concerns about potential risks associated with PPI use, including impaired kidney function, tubular-interstitial nephritis and chronic kidney disease, hypomagnesemia, fractures, infections, nutritional disorders, cognitive impairment and dementia, and even CVD[3]. Sehested *et al*[4] conducted a study among all registry-Danish population with no prior history of myocardial infarction (MI) or stroke who had an elective upper gastrointestinal endoscopy demonstrating that PPI users, compared with non-users, had a 29% greater adjusted absolute risk of ischemic stroke and a 36% greater risk of MI. In a retrospective nationwide study using a database from Taiwan National Health Insurance[5], patients treated with PPIs had a greater risk of hospitalization for ischemic stroke [hazard ratio (HR): 1.36]. People aged < 60 years were more susceptible; in contrast, gender, history of MI, diabetes mellitus, arterial hypertension, use of antiplatelet agents or NSAIDs, or type of PPIs had no effect on the risk of stroke[5]. PPI

treatment was significantly associated with an increased cerebrovascular risk (adjusted odds ratios [ORs] for PPI use: 1.77 within 1e mo, 1.65 between 1 and 3 mo, and 1.28 between 3 and 6 mo)[5]. Patients treated with PPIs, regardless of the administration of antithrombotic drugs, had a significantly increased cardiovascular risk in a case-control study based on a regional prescriptive database[6]. A meta-analysis of 17 randomized controlled trials (RCTs) showed that PPI monotherapy was associated with a 70% increase of CVD[7]; furthermore, significantly higher risks of adverse cardiovascular events in the omeprazole subgroup and the long-term treatment subgroup were found[7]. Likewise, another recent meta-analysis of 37 observational studies found that the rates of CVD and all-cause mortality were significantly higher among PPI users compared with non-users[8].

In contrast, other studies did not show a significant association between PPI use and CVD. Large American and German administrative claims data failed in demonstrating evidence that risk of MI or stroke was increased after prescription of PPIs compared with H₂ receptor antagonists (H₂RAs)[9,10]. Nguyen and colleagues and Lo and colleagues studied sex-different cohorts of women enrolled in the Nurses' Health Study and men in the Health Professionals Follow-up Study, observing non-significant association with new cerebrovascular events[11] and all-cause mortality[12] after adjusting for potential confounders.

A meta-analysis of observational studies showed pooled HRs for association between PPIs and MI, PPIs and acute cardiovascular events, and PPIs and cardiovascular mortality of 1.05, 0.99, and 1.06, respectively, after adjusting for bias [13]. Finally, another meta-analysis of ten articles did not demonstrate significant differences in risk of all-cause death, major adverse cardiovascular events (MACEs), or target vessel revascularization (TVR) between patients treated with PPIs and controls[14]. Thus, regarding the association of PPIs with CVD, the results remain inconsistent due to medium to high-risk biases among the pooled studies[15]. It is obvious that results may differ greatly among selected population used in each study. Clinical epidemiology evidence from observational data suggests, in fact, that among patients treated with thienopyridines, cardiovascular risk may be increased by long-term use of PPIs[1]. In contrast, in patients not treated with thienopyridines, the impact of PPIs on cardiovascular risk is limited by confounding[1].

POTENTIAL MECHANISMS OF CARDIOVASCULAR DAMAGE FROM PPIs

According to *in vitro* studies, a potential mechanism explaining the association between PPIs and CVD might be the inhibition of nitrate-nitrite-nitric oxide (NO) pathway that results in cardiovascular protective effect. Omeprazole prevents the effects of nitrite and nitrate, which require low pH in the stomach to generate NO and other NO-related species[16-18].

PPIs, besides, may inhibit NO production by inhibiting the enzyme dimethylarginine dimethylaminohydrolase, thus increasing levels of asymmetric dimethylarginine, an endogenous inhibitor of endothelial function, implied in vascular cell proliferation, platelet adhesion and aggregation, and inflammation[17-19].

Omeprazole may also reduce endothelium-dependent aortic responses to acetylcholine and increase vascular oxidative stress, which might be associated with endothelial dysfunction by reducing NO bioavailability[20]. It is unknown, however, whether impaired vascular redox biology mediated by PPIs may induce endothelial dysfunction, impairment in flow mediated vasodilation, or arterial hypertension[17].

RISK OF GIB AFTER USE OF ANTIPLATELET OR ANTICOAGULATION THERAPY AND CONTRIBUTING FACTORS

In primary or secondary cardiovascular prevention, mainly in the elderly, low-dose aspirin (LDA) is commonly prescribed. Prescribers and consumers, however, do not often appreciate the potential risk of upper GIB associated with LDA use[21]. Antiplatelet therapy is, in fact, burdened by a significant risk of GIB, which is increased 1.8-fold during LDA therapy, and up to 7.4-fold with DAPT[22]. Treatment with antiplatelet medications, in fact, may cause mucosal lesions (erosions and ulcers), and reduce the formation of the platelet plug on the lesions, thus inducing GIB[23]. Therapy with anticoagulants is associated with a higher risk of bleeding, too, although it should be underlined that patients with upper GIB while on long-term anticoagulant therapy had a clinical outcome which is not different from that of patients not taking anticoagulants[24]. On the other hand, patients with a major GIB on oral anticoagulants (OACs) had a high rate of discontinuation and significantly higher risk of stroke/systemic embolism, major bleeding, and mortality after hospital discharge than those without[25]. Anyway, the combined intake of anticoagulants and antiplatelet agents rises the risk of upper GIB by 60%[1,26,27]. Thus, the appropriate management of patients treated with these drugs requires an adequate knowledge of risk factors for upper GIB.

The main risk factors predisposing to upper GIB while taking ASA are age > 70 years, aspirin dose, concomitant therapy with another antiplatelet agent or NSAIDs, previous peptic ulcer disease, and *Helicobacter pylori* (*H. pylori*) infection[1,22,28,29]. In the recent ASPirin in Reducing Events in the Elderly (ASPREE) trial, age, smoking, hypertension, chronic kidney disease, and obesity increased bleeding risk in aspirin users[30]. In patients with *H. pylori* infection, during therapy with other antiplatelet agents, when compared to ASA, the risk of upper GIB is doubled[31]. It is still controversial over the risk associated with alcohol use, smoking, obesity, and systemic comorbidities[1]. Finally, the risk of bleeding is often proportional to cardiovascular risk.

The risk factors associated with GIB in VKA users are age > 65 years, previous GIB, previous stroke, cardiovascular or chronic kidney disease, and liver cirrhosis[1,26,31-33]. The risk of upper GIB is also increased by the concomitant use of

lipid-lowering agents, NSAIDs, ASA, and cyclooxygenase 2 inhibitors[2].

The main risk factors associated with GIB in DOAC users are age > 75 years, systemic comorbidities, kidney failure, history of peptic ulcer complicated by bleeding, concomitant use of ASA or NSAIDs, and drug interactions with medications sharing cytochrome P450 metabolism, such as amiodarone, rifampicin, barbiturates, and fluconazole[34-37]. In a multicentre retrospective study, concomitant treatment with PPIs was a protective factor; in contrast concomitant treatment with antiplatelet agent or NSAIDs, age ≥ 65 years, alcohol use, abnormal liver function or renal function, cancer, history of peptic ulcer or major bleeding, anaemia, and thrombocytopenia were independent GIB risk factors[38]. Using these factors, Lv *et al*[38] constructed a new model to predict the risk of major GIB in patients on DOACs, the Alfalfa-DOAC-GIB score.

RISK OF GIB WITH ANTIPLATELET AGENTS IN CLINICAL TRIALS

In the meta-analysis of the Antithrombotic Trialists' Collaboration, aspirin increased major GIB (usually defined as a bleed requiring transfusion or resulting in death)[39]. In the ASPREE trial, aspirin use increased the risk of GIB in elderly patients by 87% *vs* placebo[30].

When LDA is used in association with clopidogrel, or in prolonged antiplatelet treatment, in patients with previous GIB, the incidence of major GIB is even higher[40]. The risk of GIB was clearly greater (1.3% *vs* 0.7%) in patients undergoing DAPT (aspirin plus clopidogrel) than in those treated with aspirin alone in the CURE trial[41]. Clopidogrel does not act on cyclooxygenase, thus its risk of inducing GIB should be lower than that of aspirin, as demonstrated in the CAPRIE study[42]. Therefore, clopidogrel use, particularly in association with PPI, seems a safer monotherapy in patients with recent aspirin-related gastric damage. However, also clopidogrel use seems associated with impaired spontaneous healing of gastric ulcers. In two RCTs enrolling patients in primary prevention with healed ulcer bleeding, comparing clopidogrel with LDA plus 20 mg esomeprazole, the cumulative incidence of recurrent bleeding was significantly higher in the first group[43,44]. Therefore, in patients with a previous history of peptic ulcer disease, clopidogrel monotherapy appears questionable[42,43].

Clopidogrel, *vice versa*, seems safer than ticagrelor, as regards GI-related risks, including fewer overall and spontaneous GIB events[40,45,46]. Fewer data are available for prasugrel, compared to ticagrelor and clopidogrel; this drug, however, seems also associated with a significant increase in GIB[40,47]. A recent meta-analysis of RCTs showed that third generation P2Y₁₂ inhibitors were associated with a higher risk of upper GIB (32.95%) and unspecified GIB (25.95%) compared to clopidogrel[48].

RISK OF GIB WITH ANTIPLATELET AGENTS IN THE REAL WORD

In RCTs, patients are often different from real world as regards risk factors, clinical characteristics, and comorbidities. Therefore, clinical practice evidence has a fundamental role[26,49-52]. Table 1 shows some real world observational studies on this topic[53-57].

RISK OF GIB WITH OAC AGENTS IN CLINICAL TRIALS

OAC therapy (VKAs and DOAC) favours, also, the bleeding of pre-existing lesions (erosions, angiodysplasias, polyps, and diverticula)[58-60]. In the RE-LY trial, a higher risk (+ 50%) of GIB was shown with dabigatran 150 mg bid treatment in comparison to warfarin, while there was no significant difference between dabigatran 110 mg bid and warfarin[53]. This increased risk, however, could be attributed to the blind administration of higher dose of dabigatran also in very fragile patients[58]. A *post-hoc* simulation using the RE-LY dataset, in fact, compared dabigatran, used according to the European label (dose of 150 mg bid only in patients aged < 80 years without an increased risk for bleeding, *e.g.*, HAS-BLED score < 3, and not on concomitant verapamil), compared to well-controlled warfarin treatment [international normalized ratios (INR): 2-3]; there was no significant difference between the two medications in terms of major GIB[61]. Rivaroxaban was associated with a significantly higher incidence of GIB (3.15% *vs* 2.16%) than warfarin in the ROCKET-AF trial, although the frequency of fatal bleeding was comparable[62]. In the ENGAGE AF-TIMI 48 study, the higher dose of edoxaban (60 mg daily) increased (+ 23%), although barely significantly, the risk of major GIB in comparison to warfarin[63]. However, in patients who received the lower dose (30 mg daily), the rate of GI bleeding was significantly lower compared to warfarin[63]. Apixaban seems the only DOAC not associated with a GIB increase greater than warfarin[64]. The incidence of major GIB, indeed, was comparable between apixaban 5 mg bid and warfarin in the ARISTOTLE trial[64].

A meta-analysis of phase 3 registration studies in patients with atrial fibrillation (AF) showed that DOACs increase, although barely significantly, the risk of major GIB by 23%-25% in comparison to warfarin[65]. In patients treated with DOACs, in comparison to standard anticoagulant therapy, the overall OR for GIB was 1.45 in another meta-analysis; among the DOACs, only dabigatran (OR: 1.58) and rivaroxaban (OR: 1.48) were associated with a significantly increased risk of bleeding[66]. In a recent meta-analysis[67] including 28 RCTs, the risk of major GIB for DOACs was equal to that of warfarin; after accounting for dose, rates of major GIB were higher *vs* warfarin (rivaroxaban 20 mg, dabigatran 300 mg, and edoxaban 60 mg daily: + 47%, + 40%, and + 22%, respectively); in contrast, apixaban 5 mg bid was associated with a

Table 1 Antiplatelet drugs and gastrointestinal bleeding in the real world

Ref.	Setting	Main results
Casado Arroyo <i>et al</i> [49], 2012	Spanish observational register with 1219 patients undergoing PTA, 96.7% of whom were in DAPT with LDA and clopidogrel, and 76.6% on PPI therapy	Eight patients developed GIB during hospitalization, and 27 during follow-up (1.52 bleeds per patient/year). Most GIB cases (81.4%) occurred during the first year. Overall, 84.6% of patients were on long-term PPI at the time of the bleed; lower GIB occurred more frequently than upper GIB (74% <i>vs</i> 26%)
Tsai <i>et al</i> [50], 2012	Observational study aiming to investigate the characteristics of endoscopic findings in clopidogrel or aspirin users undergoing endoscopy for upper gastrointestinal symptoms	Gastroduodenal haemorrhagic spots were more common in clopidogrel users than in aspirin users (10.1% <i>vs</i> 25.5%, $P = 0.004$). Gastroduodenal erosions were more common in aspirin users than clopidogrel users (53.2% <i>vs</i> 38.7%; $P = 0.04$), whilst gastroduodenal peptic ulcers were more common in clopidogrel users than in aspirin users (38.7% <i>vs</i> 23.9%; $P = 0.027$)
de Abajo <i>et al</i> [51], 2013	Case-control study involving 669115 patients assessed the incidence of GIB, evaluating the age of the patients and use of different treatments	The incidence of bleeding observed was 76 per 100000 people/year, with a prevalence higher in men than in women (109 <i>vs</i> 49 per 100000 people/year; OR: 2.23; 95%CI: 1.99-2.50), and with a progressive increase of incidence with age. The risk was significantly higher in patients with a previous episode of GIB (RR: 11.27; 95%CI: 8.35-15.20), in those using aspirin (medium-high doses: RR: 3.29; 95%CI: 1.42-7.62; low doses: RR: 1.74; 95%CI: 1.37-2.21), and other antiplatelet agents (RR: 1.73; 95%CI: 1.27-2.36)
Lanas <i>et al</i> [26], 2015	Case-control study	Non-aspirin antiplatelet agents (mostly clopidogrel) were associated with an increased risk of upper GIB that was similar to that observed with aspirin
Alexopoulos <i>et al</i> [52], 2016	Prospective, observational multicentre cohort trial (GRAPE), performed in patients with ACS undergoing PTA-48% of whom treated with clopidogrel, 18% with prasugrel, and 35% with ticagrelor in dual therapy with LDA	The rate of MACEs was lower in prasugrel treated patients (4.4%) than in clopidogrel treated patients (10.1%) (HR: 0.53; 95%CI: 0.30-0.91), although not significantly different between ticagrelor (6.8%) and clopidogrel groups (HR: 0.78; 95%CI: 0.54-1.12). Any type of bleeding was more frequent in prasugrel-treated patients (51.2%) than in clopidogrel-treated patients (37.6%) (HR: 1.61; 95%CI: 1.33-1.95), and more frequent in ticagrelor-treated patients (56.9%) than in clopidogrel-treated patients (HR: 1.81; 95%CI: 1.55-2.10), but there was no significant difference for fatal events
Sahlén <i>et al</i> [53], 2016	Swedish register SWEDEHEART, where 45073 patients with ACS were enrolled	At 24 mo, the risk of ischemic events, death, and MI was lower with ticagrelor than with clopidogrel (11.7% <i>vs</i> 22.3%, aHR 0.85, 95%CI: 0.78-0.93; 5.8% <i>vs</i> 12.9%, aHR 0.83, 95%CI: 0.75-0.92; 6.1% <i>vs</i> 10.8%, aHR 0.89, 95%CI: 0.78-1.01; respectively). However, re-admission with bleeding was lower in patients taking ticagrelor as compared to those taking clopidogrel: 5.5% <i>vs</i> 5.2%; aHR: 1.20; 95%CI: 1.04-1.40. Furthermore, in a subset of patients undergoing PCI, the PCI-related in-hospital bleeding was higher in patients on ticagrelor compared to those on clopidogrel (7.0% <i>vs</i> 2.7%, aOR: 1.57, 95%CI: 1.30-1.90)
Sehested <i>et al</i> [54], 2019	Danish registry on 46301 patients hospitalized with a MI (35% of whom were at high risk of GIB) treated with clopidogrel (76.2%), ticagrelor (20.3%), or prasugrel (3.5%)	At 12 mo, an episode of digestive bleeding occurred in 1.0% (95%CI: 0.9-1.1) of patients with low risk of bleeding, and in 1.7% (95%CI: 1.5-2.0) of those at high risk. In patients receiving PPIs, the absolute risk of bleeding was overall reduced by 0.44% (95%CI: 0.39-0.48), and by 0.47% (95%CI: 0.43-0.51%) in those at high risk
Nishtala <i>et al</i> [55], 2019	Study performed in New Zealand on 66500 patients aged ≥ 65 yr	No significant change in the incidence of GIB in patients using aspirin (ARR: 0.84; 95%CI: 0.79-0.89), or clopidogrel (ARR: 0.97; 95%CI: 0.87-1.08) in monotherapy, while DAPT resulted in an increased rate of bleeding (aRR: 1.34, 95%CI: 1.14-1.57). In addition, the incidence of bleeding was increased when an anticoagulant therapy was associated with aspirin (aRR: 1.79; 95%CI: 1.30-2.46), clopidogrel (aRR: 6.36; 95%CI: 2.24-18.03), or DAPT (aRR: 4.85; 95%CI: 1.51 to 15.57)
Vidyanti <i>et al</i> [56], 2019	Retrospective study on 1119 ischemic stroke patients	The HR for GIB was significantly in favour of clopidogrel (HR: 2.60; 95%CI: 2.82-3.70)
Zheng <i>et al</i> [57], 2019	Meta-analysis of 13 trials-with a median age of trial participants of 62 yr (range, 53-74)	Aspirin use was associated with an increased risk of bleeding events compared with no aspirin (23.1 per 10000 participant-years with aspirin and 16.4 per 10000 participant-years with no aspirin-HR: 1.43; absolute risk increases 0.47%)

ACS: Acute coronary syndromes; aHR: Adjusted hazard ratio; aOR: Adjusted odds ratio; aRR: Adjusted relative risk; CI: Confidence interval; DAPT: Double antiplatelet therapy; GIB: Gastrointestinal bleeding; HR: Hazard ratio; LDA: Low dose aspirin; MACEs: Major adverse cardiovascular events; MI: Myocardial infarction; OR: Odds ratio; PCI: Percutaneous coronary intervention; PPI: Proton pump inhibitor; PTA: Percutaneous transluminal angioplasty; RR: Relative risk.

lower rate of major GIB than dabigatran 300 mg and rivaroxaban 20 mg daily. Finally, in another very recent meta-analysis[68] on 37 RCTs, in comparison to conventional therapy, no DOACs increased the risk of major GIB; however, the major GIB risk was different among various DOACs: Apixaban 10 mg daily reduced the major GIB risk more than edoxaban 60 mg, rivaroxaban ≥ 15 mg, and dabigatran etexilate 300 mg. The major GIB risk associated with edoxaban 30 mg daily was lower than that of rivaroxaban 10 mg daily: No differences were observed between apixaban 5 mg, edoxaban 30 mg, and dabigatran etexilate 220 mg. However, there are no RCTs comparing directly the different DOACs.

DOACs, besides, can affect GIB at different sites[59,60]. Dabigatran, in 53% of cases, is associated with bleeding events affecting the lower digestive tract[69]. The incomplete absorption of the drug in the upper GI tract and the greater availability of dabigatran in the colon, where it would induce bleeding from pre-existing lesions, may be some causes of this phenomenon[59-60]. In contrast, rivaroxaban-associated bleeding is more frequent in the upper GI tract; edoxaban 60 mg/d, finally, may cause indifferently upper and lower bleeding[69]. Rivaroxaban, being administered once-daily, may cause a higher blood peak of the drug than administration of apixaban and dabigatran administered bid[2,59,64,70].

RISK OF GIB WITH ORAL ANTICOAGULANT AGENTS IN THE REAL WORD

The “real world” evidence from observational studies and post-marketing pharmacovigilance data[70-74] shows a different incidence of GIB with some DOACs compared to warfarin (Table 2)[32,35,75-78].

PHARMACOLOGICAL AND CLINICAL INTERACTIONS BETWEEN PPIs AND ANTIPLATELET AGENTS

Several studies have suggested that PPIs may reduce the antiplatelet effects of clopidogrel and/or aspirin, possibly leading to cardiovascular events.

Regular PPI use reduced by 90% the likelihood of overt upper GIB in aspirin-users aged ≥ 70 years[79]. However, it has recently been reported that long-term use of PPIs can mitigate the anti-aggregating effect of ASA[80]. ASA absorption depends on gastric pH, and PPIs decrease gastric acid secretion by blocking the gastric H⁺/K⁺-adenosine triphosphatase via covalent binding to cysteine residues[81,82], but the combination of 30 mg lansoprazole and 100 mg aspirin does not cause a decrease in antiaggregant activity evaluated by the impedance aggregometry method[83].

In 2009, in patients treated with both clopidogrel and PPIs, an increased risk (+ 40%) of recurrent MI has been reported [84]. It was hypothesized that several PPIs, inhibiting the cytochrome P450C19 (CYP2C19) that transforms clopidogrel into its active metabolites, might reduce its effect[85]. After this study, the clinical implications of potential interactions between PPIs and clopidogrel have been debated, with conflicting results, for over a decade. In a Swedish nationwide cohort study including 99836 patients who received clopidogrel after primary percutaneous coronary intervention (PCI), compared to non-users, PPI users had increased adjusted HRs of the main outcome MI (+ 23%) and the secondary outcomes coronary heart disease (+ 28%), stroke (+ 21%), and death due to coronary heart disease (+ 52%)[86]. In 947 patients at high risk of upper GIB following aspirin-related bleeding for secondary MACE prevention, compared with aspirin treatment, clopidogrel showed an increased risk of MACEs (+ 65%), any cause of mortality (+ 4.8%), and upper GIB (+ 25%), but without statistical significance in propensity score-matched cohort analysis[87]. Using the National Health Insurance Research Database to conduct a retrospective cohort study on patients with diabetes treated with clopidogrel after bare-metal stent deployment, Lee *et al*[88] showed that patients who received PPIs had no significant increase in adverse cardiovascular events compared to those without PPIs within 1 year (-40%). In a nested case-control study conducted within the Cerner Corporation’s Health Facts® database, adjusted OR for PPI use *vs* non-use among clopidogrel users was not significant: A positive association between combined use of clopidogrel/PPIs and increased risk of MI was seen only in the group aged 80-89 years (+ 26%)[89]. Intermittent use of PPIs, compared with sustained use, was associated with lower risks of stroke, MACEs, and net adverse clinical events in a retrospective study on patients with coronary heart disease treated with clopidogrel for at least 1 year[90].

Indeed, the data of meta-analyses were conflicting, too. An increased incidence (+ 39%) of MACEs, stent thrombosis, and MI in patients taking clopidogrel and PPIs was confirmed by Bundhun *et al*[91], but not by Cardoso *et al*[92]. A meta-analysis by Mo *et al*[93], evaluating ten RCTs, showed that PPIs decreased the risk of LDA-associated upper GI ulcers (- 84%) and bleeding (-73%) compared with control. For patients treated with DAPT (LDA and clopidogrel), PPIs were able to prevent the LDA-associated GI bleeding (-64%) without increasing the risk of MACEs. Pang *et al*[94] included 15 RCTs in their meta-analysis, showing that in patients treated with clopidogrel, the risk of MACEs (-18%), MI recurrence (-28%), stroke (-28%), stent thrombosis (-29%), and TVR (-23%) was significantly lower in the non-PPI group than in the added PPI group. The risks of all cause death, cardiovascular death, and bleeding events were similar in the two groups[94]. Another meta-analysis of three RCTs and four cohort studies showed that, overall, there was a significantly lower risk of GIB events in the PPI group compared to the no PPI group (OR: 3.06)[95]; in three RCT studies, there was also a significantly lower risk of GIB events in the PPI group compared to the no PPI group. Overall, there was no significant difference in MACE events between the PPI group and the no PPI group[95].

Besides, action of PPIs on CYP2C19 is not class-specific[96]. Omeprazole and esomeprazole seem having a more marked inhibiting effect on CYP2C19 than pantoprazole[97]. Random-effects meta-analyses of six studies comparing the safety of individual PPIs in patients with coronary artery disease taking clopidogrel revealed, in contrast, an increased risk for adverse cardiovascular events for those taking pantoprazole (HR: 1.38), lansoprazole (HR: 1.29), or esomeprazole (HR: 1.27) compared with patients on no PPI; this association, in contrast, was not significant for omeprazole[15].

The COGENT trial was the only prospective study in this field. It showed, in patients at high risk, that omeprazole significantly reduces composite GI events, without observing any increase in the composite cardiovascular events[98]. The trial was terminated, however, prematurely; therefore, the absence of interaction between omeprazole and clopidogrel could not be considered as a definitive finding.

The P2Y₁₂ receptor inhibitor Ticagrelor does not require biotransformation; thus, no drug interactions with PPIs may be assumed. Surprisingly, in the PLATO study, MACEs were equally higher both with ticagrelor and with clopidogrel among patients treated with PPIs[99]; for this reason, it was hypothesized that treatment with PPIs should be considered as a marker rather than a cause of MACEs. In the Netherlands, an observational registry on patients with acute coronary syndrome (ACS) treated with PPIs, showed a reduction in cardiac death or MI (adjusted HR: 0.27) and cardiac death, MI, or stroke (adjusted HR: 0.33), but this was not observed in subgroup analyses in clopidogrel- or ticagrelor-treated patients. Besides, treatment with PPIs was not associated with a reduction of GIB[100]. In patients undergoing PCI after ACS and receiving clopidogrel or ticagrelor, an international multicentre registry showed no association between PPI treatment and the primary composite endpoint (total mortality, reinfarction, and severe bleeding)[101]; patients treated with PPIs were more often female, older, and with more comorbidities. In a single-center prospective sub-study of a randomized trial on 231 patients completing 1-year antiplatelet therapy after coronary aortic bypass graft (CABG), severe

Table 2 Oral anticoagulant drugs and gastrointestinal bleeding in the real world

Ref.	Setting	Main results
Abraham <i>et al</i> [70], 2015	Retrospective study; the risk of GIB was assessed in a cohort of 92816 patients taking anticoagulants (9.2% patients on dabigatran, 17.5% on rivaroxaban, and 73.2% on warfarin)	Using a propensity score matched model, the risk of GIB with DOACs was similar to that with warfarin in AF patients (dabigatran <i>vs</i> warfarin: HR: 0.79; 95%CI: 0.61-1.03; rivaroxaban <i>vs</i> warfarin: HR: 0.93; 95%CI: 0.69-1.25) and in non-AF patients (dabigatran <i>vs</i> warfarin: HR: 1.14; 95%CI: 0.54 to 2.39; rivaroxaban <i>vs</i> warfarin: HR: 0.89; 95%CI: 0.60-1.32). The risk of bleeding increased with age, so that in patients aged ≥ 76 yr, the risk exceeded that with warfarin among AF patients taking dabigatran (HR: 2.49; 95%CI: 1.61-3.83) and in patients with and without AF taking rivaroxaban (HR: 2.91; 95%CI: 1.65-4.81; and HR: 4.58; 95%CI: 2.40-8.72; respectively)
Brodie <i>et al</i> [71], 2018	Retrospective evaluation of electronic medical records of patients with GIB ($n = 8496$) from 2010-2016 identified 61 patients with GIB episodes while treated with DOACs (rivaroxaban, dabigatran, or apixaban) and 123 patients with GIB while taking warfarin. The DOAC and warfarin groups were similar in terms of age and underlying comorbidity	After adjusting for differences in baseline variables, the DOAC group had fewer hospitalizations and required fewer transfusions than the warfarin group. The DOAC and control groups were not statistically different for all outcomes despite significantly greater concomitant aspirin use in the DOAC group compared with warfarin users
Ray <i>et al</i> [35], 2018	Retrospective cohort study in Medicare patients, during 754389 treatment person-years without PPI co-therapy	The adjusted incidence of upper GIB hospitalizations was 115 (95%CI: 112-118) per 10000 person-years. The incidence for rivaroxaban (1278 hospitalizations/114168 person-years) was 144 (136-152) per 10000 person-years, significantly greater than that for apixaban (279/43970, RR: 1.97, 1.73-2.25), dabigatran (629/79739, RR: 1.19, 1.08-1.32), and warfarin (4933/516512, RR: 1.27, 1.19-1.35). The incidence for apixaban was significantly lower than that for dabigatran (RR: 0.61, 0.52-0.70) and warfarin (RR: 0.64, 0.57-0.73)
Yanagisawa <i>et al</i> [72], 2018	Data from 218 patients receiving oral anticoagulants (73 DOAC users, 145 warfarin users) and 218 patients not receiving any antithrombotics (age- and sex-matched controls) who underwent polypectomy	Bleeding rate was significantly higher in warfarin users and DOAC users compared with controls (13.7% and 13.7% <i>vs</i> 0.9%, $P < 0.001$), but was not significantly different between rivaroxaban (13.2%), dabigatran (11.1%), and apixaban (13.3%) users
Tang <i>et al</i> [32], 2021	Retrospective review of medical records of 626 patients taking warfarin for at least 2 wk	Variables that increase the likelihood of bleeding in warfarin users included aspirin, PPI, history of previous GIB, CRF, and elevated prothrombin time/international normalized ratio values. Concomitant antiplatelet use showed a slight increase in GIB but this was not statistically significant ($P = 0.082$). Patients who are on PPI and warfarin simultaneously are more likely to be on aspirin or have a history of GIB or CRF, all of which are associated with increased incidences of GIB. Although concomitant use of warfarin and PPI appears to be associated with an increased incidence of GIB, these patients are more likely to have other risk factors that also increase the risk of a GIB outcome
Scibelli <i>et al</i> [73], 2021	Retrospective study using the HCA Healthcare Enterprise Data Warehouse to analyse 13440 patients aged > 18 yr that were admitted with an upper GIB from 2017 to 2019. The patients were categorized based on oral anticoagulant (<i>i.e.</i> , rivaroxaban, apixaban, dabigatran, and warfarin). The control group was patients admitted with an upper GIB not on oral anticoagulation	Patients on a DOAC without home PPI have a mortality (OR: 3.066, 95%CI: 1.48-6.26, $P < 0.05$) compared to patients on a DOAC and home PPI. Patients on warfarin and no home PPI have a mortality (OR: 5.55, 95%CI: 1.02-30.35, $P < 0.05$) compared to those on warfarin with home PPI use. In the no anticoagulation group, those not on PPI have an OR of 3.28 (95%CI: 2.54-4.24, $P < 0.05$) of death compared to home PPI users. Overall, patients taking the DOACs or warfarin had no statistically significant increase in RBC transfusions, length of stay, shock, acute renal failure, or mortality rate compared to patients who were not on oral anticoagulation. Home PPI use was shown to lower odds of mortality in patients on anticoagulation who presented with upper GIB
Lee <i>et al</i> [74], 2021	In the Korean National Health Insurance Service claims database, covering the entire Korean population, among patients initiating oral anticoagulants (warfarin and DOACs, during 2013-2017, those concomitantly prescribed PPIs were identified ($n = 19851$))	Overall, DOACs were associated with lower upper GIB risk after adjustment for age, sex, comorbidities, and concomitant medications (aHR: 0.78, 95%CI: 0.65-0.94), compared to warfarin. There was no significant difference in upper gastrointestinal bleeding risk among the individual DOACs
Kwon <i>et al</i> [75], 2021	In the Korean claims database on 42048 patients with prior GIB, DOAC users were compared with warfarin users by balancing covariates	Lower risks of ischemic stroke, major bleeding, and the composite outcome were associated with DOAC use than with warfarin use (weighted HR: 0.608; 95%CI: 0.543-0.680)
Lip <i>et al</i> [76], 2021	Retrospective cohort study including patients with NVAF who were 75 yr and older; had stage III to V CKD; had an HAS-BLED score of 3 or greater; used corticosteroids, antiplatelets, or NSAIDs; or had GI conditions. Data were collected from the Centers for Medicare & Medicaid Services and 4 commercial insurance databases between January 1, 2012 and September 30, 2015	All NOACs were associated with a lower risk of stroke and/or systemic embolism <i>vs</i> warfarin (apixaban: HR: 0.60; 95%CI: 0.52-0.68; dabigatran: HR: 0.75; 95%CI: 0.64-0.88; rivaroxaban: HR: 0.79; 95%CI: 0.73-0.86). Compared with warfarin, apixaban and dabigatran were associated with a lower risk of major GIB (apixaban: HR: 0.59; 95%CI: 0.56-0.63; dabigatran: HR: 0.78; 95%CI: 0.70-0.86), while rivaroxaban was associated with a higher risk (HR: 1.11; 95%CI: 1.05-1.16)
Moudallel <i>et al</i> [77], 2023	Pharmacovigilance data based on spontaneous reports of GIB with DOACs reported to EudraVigilance	Dabigatran is more frequently involved in GIB events than the other DOACs
Ingason <i>et al</i>	Data on all patients in Iceland who received a	Warfarin was associated with higher rates of upper GIB (1.7 events per 100 person-

[78], 2021	prescription for oral anticoagulation from 2014 to 2019 were collected and their personal identification numbers linked to the electronic medical record system of the National University Hospital and the 4 regional hospitals	years <i>vs</i> 0.8 events per 100 person-years; HR: 2.12; 95%CI: 1.26-3.59) but similar rates of lower GIB compared with DOACs. Specifically, warfarin was associated with higher rates of upper GIB compared with apixaban (HR: 2.63; 95%CI: 1.35-5.13), dabigatran (HR: 5.47; 95%CI: 1.87-16.05), and rivaroxaban (HR: 1.74; 95%CI: 1.00-3.05)
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AF: Atrial fibrillation; aHR: Adjusted hazard ratio; CI: Confidence interval; CRF: Chronic renal failure; DOAC: Direct oral anticoagulants; GIB: Gastrointestinal bleeding; HR: Hazard ratio; OR: Odds ratio; PPI: Proton pump inhibitor; RR: Relative risk.

upper GI mucosal lesions were more frequently observed in patients treated with ticagrelor plus aspirin and aspirin monotherapy than in patients treated with ticagrelor monotherapy[102]. In a prospective study[103], patients with acute MI who underwent PCI and treated with ticagrelor were divided into four groups: Pantoprazole, omeprazole, ranitidine, and no gastroprotective treatment. No significant differences were found in infarction related artery perfusion indexes, incidence of stent thrombosis, platelet indicators, platelet activation and aggregation, myocardial necrosis biomarkers and brain natriuretic peptide levels, and incidence of ischemic endpoint events and other tissue and organ bleeding events [103]. A sub-analysis of the randomized GLOBAL LEADERS trial[104] compared the experimental antiplatelet arm (23-mo ticagrelor monotherapy following 1-mo DAPT) with the reference arm (12-mo aspirin monotherapy following 12-mo DAPT) after PCI. In the reference group, the use of PPIs was independently associated with Patient Oriented Composite Endpoints (POCEs: All-cause mortality, MI, stroke, or repeat revascularization; HR: 1.27) and its individual components, whereas it was not in the experimental arm. Thus, in contrast to conventional antiplatelet strategy, there is no evidence suggesting the interaction between ticagrelor monotherapy and PPIs on increased cardiovascular events[104].

Prasugrel, like clopidogrel, is transformed by CYP2C19 into active metabolites, too[85]. However, a lower incidence of MI has been observed in patients treated with PPIs and prasugrel (HR: 0.61) compared to clopidogrel[105]. No associations with MI were observed for PPI use *vs* non-use among prasugrel or ticagrelor users[89].

A meta-analysis[81] including four RCTs and eight controlled observational studies reviewed clinical outcomes in patients taking DAPT with aspirin and clopidogrel, with and without concomitant PPIs; overall, patients taking PPIs had statistical differences in MACE (OR: 1.17), GIB (OR: 0.58), stent thrombosis (OR: 1.30), and revascularization (OR: 1.20), compared with those not taking PPIs. There were no significant differences in MI, cardiogenic death, or all-cause mortality[81]. Another meta-analysis[106] from 40 studies found no association between the risk of adverse clinical outcomes and the combination of PPI and DAPT in patients with coronary heart disease based on the RCT data. In contrast, observational studies showed an increased risk of adverse clinical outcomes due to the use of PPIs in patients treated with DAPT (risk ratio: 1.26), although the heterogeneity of these studies was high[106]. The running "Proton Pump Inhibitor Preventing Upper Gastrointestinal Injury in Patients on Dual Antiplatelet Therapy after CABG" (DACAB-GI-2) study will assess the rate of gastroduodenal erosions and ulcers evaluated by esophagogastroduodenoscopy in subjects on DAPT (clopidogrel plus aspirin or ticagrelor plus aspirin) for 12 mo immediately after CABG randomized to either a 12-mo pantoprazole treatment arm or a 1-mo treatment arm[107].

A prospective population-based cohort study[108] of patients with transient ischemic attacks (TIA), ischaemic stroke, and MI treated with antiplatelet drugs, evaluated hospital care costs associated with bleed management during 10-year follow-up. In secondary prevention with aspirin-based antiplatelet treatment without routine PPI use, the long-term costs of upper GIB at age ≥ 75 years are much higher than those at younger age and are at least 10-fold greater than the drug cost of routine co-prescription of PPI[108]. Besides, in patients aged ≥ 60 years treated with antiplatelet agents, a recent Dutch study showed that therapy with PPIs is cost-effective in reducing GIB[109].

PHARMACOLOGICAL AND CLINICAL INTERACTIONS BETWEEN PPIs AND ANTICOAGULANT AGENTS

As regards patients receiving oral anticoagulants, the preventive role of PPIs on GIB risk appears still controversial due to lack of evidence from RCTs. A large retrospective observational study[34] showed that, in patients treated with warfarin, PPI co-therapy significantly reduced the risk of upper GIB hospitalizations [HR: 0.55; number needed to treat (NNT): 78] among those concurrently using antiplatelet drugs, but not in the absence of a concurrent use of antiplatelet drugs[34]. Another recent cohort study compared the data of 754389 person-years on anticoagulant treatment without PPIs with those of 264447 person-years in co-therapy with PPIs[31]. In patients receiving warfarin, after adjustment for numerous covariates, including use of antiplatelet agents, the incidence of GIB hospitalizations was significantly reduced in those treated with PPIs compared to the group not treated with PPIs (74 *vs* 113 episodes per 10000 person-years)[35]. PPIs may have a pharmacological interaction with warfarin due to their liver metabolism. Thus, in patients taking VKAs, we should monitor INR when initiating or discontinuing PPI therapy[33].

The pharmacokinetics of DOACs is different from that of warfarin. Among DOACs, dabigatran etexilate differs as it is administered as a prodrug and has a low bioavailability. Dabigatran capsules are intended for a release in the acidic environment of stomach, and the drug is absorbed in the distal small intestine. When PPIs are co-administrated with dabigatran, the latter has a lower solubility and its absorption decreases about 30%; its clinical efficacy, however, does not change[58,60,110,111].

Patients on triple therapy (DAPT plus OAT), *e.g.*, those with AF following PCI, are particularly at risk of GIB. The question is: Could the addition of a PPI reduce the risk of bleeding in patients requiring triple therapy? The RE-DUAL PCI trial[112] randomized patients with AF post-PCI, treated with clopidogrel or ticagrelor, to dabigatran 110/150 mg

twice daily dual therapy or to warfarin triple therapy. Dual therapy, regardless of PPI use, reduced the risk of major bleeding events or clinically relevant non-major bleeding events *vs* warfarin triple therapy; the composite efficacy endpoint was comparable. For GIB, no interaction was observed between study treatment and PPI use[112]. Thus, PPIs in patients in triple therapy should be used regardless of anticoagulant chosen treatment.

The impact of gastroprotective agents is modest with rivaroxaban[90]. The COMPASS study, a 3 × 2 partial factorial double-blind trial, randomized patients with stable cardiovascular disease and peripheral arterial disease to receive pantoprazole 40 mg daily or placebo, as well as rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg alone for 3 years[113]. No significant differences have been observed in clinical events (overt upper GIB, bleeding of presumed occult upper GI tract origin with documented decrease in Hb ≥ 2 g/dL, GI pain with underlying multiple gastroduodenal erosions, symptomatic gastroduodenal ulcer, and upper GI obstruction or perforation). In a *post-hoc* analysis with a broadened definition, pantoprazole therapy significantly reduced overt bleeding of gastroduodenal origin (HR: 0.45), gastroduodenal ulcer (HR: 0.46), and multiple gastroduodenal erosions (HR: 0.33), particularly in patients treated with ASA[114]. PPIs used routinely in patients with stable cardiovascular disease receiving low-dose anticoagulation and/or aspirin may reduce bleeding from gastroduodenal lesions, but does not reduce upper gastrointestinal events[114]. In a retrospective cohort study, when OAC treatment with PPI co-therapy was compared to that without PPI cotherapy, risk of upper GIB hospitalizations was lower for each anticoagulant: Apixaban (IRR = 0.66); dabigatran (IRR = 0.49); rivaroxaban (IRR = 0.75); warfarin (IRR = 0.65)[35]. Therefore, PPI co-treatment might be able to reduce the risk of upper GIB in patients taking OACs regardless of the presence of risk factors. Obviously, more studies are needed in this field. The incidence of upper GIB hospitalization was most pronounced for dabigatran, potentially resulting from direct mucosal injury by the drug's tartaric acid core[35]. Using a nationwide claims database, in OAC-naïve patients with AF and a history of upper GIB before initiating OAC treatment, compared to the patients without PPI use, PPI co-therapy was associated with a significantly lower risk of major GIB, by 40% and 36%, in the rivaroxaban and warfarin groups, respectively; in dabigatran, apixaban, and edoxaban users, PPI co-therapy did not show a significant reduction in the risk of major GIB[115]. In a meta-analysis of ten studies, OAC and PPI co-therapy was associated with a lower odds of total and major GIB (OR: 0.67 and 0.68, respectively)[116]. PPI co-therapy was related to a lower GIB odds by 24%-44% for all kinds of OACs, except for edoxaban; the protective effect of PPIs was more significant in concurrent antiplatelet drug users and in patients with a previous GIB history, HAS-BLED ≥ 3, or underlying gastrointestinal diseases (conditions at high bleeding risk)[116].

ROLE OF *H. PYLORI* INFECTION IN THE RISK OF UPPER GIB IN PATIENTS TREATED WITH ANTIPLATELET AND/OR ANTICOAGULANTS AGENTS

H. pylori infection is, together with the use of aspirin, one of the main risk factors in the pathogenesis of peptic ulcer disease (PUD)[117]. This disease, however, does not develop in all *H. pylori*-positive patients or those taking aspirin; individual susceptibility to the infection and drug toxicity, therefore, are critical factors to the initiation of mucosal damage[2,117]. A systematic review aimed to determine the influence of *H. pylori* infection on the risk of upper GIB in patients taking ASA; it did not allow for strong conclusions due to the heterogeneity of the studies and the controversial results[118]. *H. pylori* infection has an additive effect with NSAID use, whilst no interaction was shown with LDA use [117]. *H. pylori* infection could have a synergistic or antagonistic interaction with LDA use in adverse gastroduodenal events depending on gastric acid secretion, which shows considerable geographic variation at the population level. While gastric acid secretion levels were not decreased and were well-preserved in most patients with *H. pylori* infection from Western countries, the majority of Japanese patients with *H. pylori* infection exhibited decreased gastric acid secretion [119]. A meta-analysis showed that the risk of gastroduodenal ulcers during LDA therapy increased by approximately 70% in patients with *H. pylori* infection[120]. The risk of upper GIB in patients taking LDA was greater in *H. pylori*-positive patients (OR: 2.32), as shown in another meta-analysis[121]; however, the NNT to prevent one bleeding event/year was between 100 and more than 1000. Therefore, the possible cost-effectiveness of test and treatment strategies for *H. pylori* in all patients receiving LDA is debatable, also considering the increasing primary resistance to antimicrobial agents [122]. In addition, in patients taking LDA with an average risk of GIB, *H. pylori* eradication was never adequately evaluated as a first-line strategy to prevent PUD. Incidence rates of GIB were not significantly different between patients with previous PUB in whom *H. pylori* was eradicated and an average-risk cohort (*i.e.*, LDA-naïve patients without a history of ulcer and with unknown infection status)[123]. Sostres *et al*[117] proposed to classify patients taking LDA into two groups (low and high bleeding risk), eradicating *H. pylori* only in the latter. Indications to eradicate always the infection are a previous peptic disease[2], older age, and the concomitant use of NSAIDs, oral anticoagulants, non-aspirin antiplatelet agents, and corticosteroids[117].

There are limited data in the literature as regards the relationship between *H. pylori* and non-aspirin antiplatelet agents or oral anticoagulants. A recent cohort study demonstrated an increased (OR: 4.37) risk of haemorrhagic peptic disease in *H. pylori*-positive patients taking non-aspirin antiplatelet agents, while the risk was not increased in infected patients taking OACs[31]. In *H. pylori*-eradicated patients, new users of DOACs had a significantly lower risk of upper GIB than new warfarin users[124].

Nearly all the available evidence is prone to bias with case-control or cohort studies; thus, more well-designed RCTs are needed, as well as pharmaco-economic evaluations assessing the risk-benefit ratio of *H. pylori* eradication in LDA, non-aspirin antiplatelet agent, and oral anticoagulant users. In the recent Helicobacter Eradication Aspirin Trial, there was a significant reduction in incidence of the primary outcome in the active eradication group in the first 2.5 years of follow-up compared with the control group, but it was lost with longer follow-up (HR: 1.31) in the period after the first

2.5 year[125].

ARE THERE ALTERNATIVES TO PPIs?

H₂RAs decrease gastric acid secretion by reversibly binding to histamine H₂ receptors located on gastric parietal cells, thereby inhibiting the binding and action of the endogenous ligand histamine[82]. Their use is not significantly associated with ischemic stroke or MI[4,89]; however, PPIs are superior to H₂RAs in preventing GI bleeding in patients treated with antiplatelet agents, both as monotherapy and DAPT[126]. Two RCTs demonstrated that PPIs are superior over misoprostol and ranitidine in the prevention of gastroduodenal ulcers and/or erosions induced by NSAIDs[127,128]. The protective action of ranitidine on the gastroduodenal mucosa decreased significantly within 4 wk from the start of treatment; at 6 mo, it was significantly less effective than PPIs[127]. Another study, besides, clearly showed that the effects of ranitidine in reducing gastric acid secretion is almost halved already on the third day of treatment[129]. It is likely that this phenomenon depends on the onset of tachyphylaxis, typical of H₂RA, but not of PPIs. When long-term antiplatelet treatment is needed, this aspect cannot be disregarded[33]. Ranitidine, besides, significantly interferes with the antiplatelet activity of the LDA, probably reducing its intestinal absorption, although it does not seem to attenuate the antiplatelet power of clopidogrel *in vitro*[130,131]. The incidence of GIB events in the PPI group was significantly lower than that in controls in patients treated with ticagrelor, whereas in the H₂RA group no significant difference was observed [103]. In a study, LDA users with a history of peptic ulcers who did not have gastroduodenal mucosal breaks at initial endoscopy were randomly assigned to receive famotidine (20 mg bid) or omeprazole (20 mg qd) for 6 mo. The incidence of gastroduodenal mucosal breaks was 33.8% among the patients receiving famotidine, and 19.8% among those receiving omeprazole. The two patient groups had comparable incidence rates of gastroduodenal ulcers and bleeding. Multivariate analysis showed that use of the PPI was an independent protective factor (OR: 0.47)[132]. In the PROTECT trial, after 600-mg clopidogrel loading for elective PCI, clopidogrel-sensitive patients were recruited and randomly assigned to add rabeprazole 20 mg daily or famotidine 40 mg daily. Baseline platelet measures performed with light transmittance aggregometry and VASP-P assay did not differ significantly between the groups. At the 30-d follow-up, the incidence of high platelet resistance was similar between the famotidine and rabeprazole groups[133].

Misoprostol, compared to PPIs, is also significantly less effective in prolonged gastroprotective treatment, and is more frequently burdened by adverse events (diarrhoea and abdominal pain)[109]. Besides, there are possible negative implications for patient compliance and costs, as it requires the administration of at least 1-2 tablets twice daily, compared to the single administration of PPIs.

Vonoprazan is the first molecule of a new class of drugs, the potassium-competitive acid blockers (P-CABs), capable of effectively reducing gastric acid secretion. These drugs could be useful in preventing gastroduodenal mucosal lesions induced by antiplatelet agents. In a RCT, in patients with a history of PUD requiring long-term LDA therapy for cardiovascular and cerebrovascular protection, peptic ulcer recurrence rates were significantly lower with vonoprazan 10 mg than with lansoprazole 15 mg[134]. *In vitro*, no effect of vonoprazan on the platelet-aggregating inhibitory activity of aspirin was shown, and *in vivo* there is no significant interaction between the two drugs[135]. Data on the potential interaction of vonoprazan with other antiplatelet agents and oral anticoagulants, however, are not yet available.

Potential NSAID gastroprotectors, including allantoin and rebamipide, are being evaluated. The latter was found to be as effective as misoprostol[136] but not in patients treated with naproxen[137], and better tolerated. However, there is still no evidence about their efficacy in preventing gastrointestinal damage from antiplatelet agents or anticoagulants.

Concomitant therapy with both PPIs and H₂RAs was associated with a 50% reduction of risk of GIB in patients treated with anticoagulants, with the maximum effect when both drugs were used in association[138]. Being mediated by the bleeding reduction from pre-existing gastroduodenal ulcers, this protective effect seems confined to the upper GI tract, and to patients with previous peptic disease or GIB[59].

RECOMMENDATIONS OF THE GUIDELINES AND REGULATORY INDICATIONS

Several guidelines or position papers by various American[139-142], Asiatic[143], European[144-147], and Italian[33,148,149] Societies of Cardiology, Gastroenterology, Pharmacology, and General Practitioners (Table 3) deal with gastroprotection in patients taking antiplatelet and/or oral anticoagulant treatment.

GASTROPROTECTION IN THE REAL WORLD: UNDERPRESCRIPTION AND OVERPRESCRIPTION

Prophylactic PPI use in patients at risk of GIB is still largely ignored by physicians, despite many studies and recommendations. In a Danish study on 46000 patients treated with DAPT after an acute MI, an under-utilisation of gastroprotection with PPIs was shown, notwithstanding an annual risk of GIB of about 1% in the general population, and of 1.7% in patients at high risk[54]. This phenomenon was also documented in Italy[150]. In Spain, a retrospective study on patients hospitalized for ACS showed that, at discharge, most patients received gastroprotective agents, mainly PPIs [151]; however, in only one every three cases of patients treated with clopidogrel, the recommendation of the Food and Drugs Administration and of the European Medicine Agency was not followed as omeprazole or esomeprazole was prescribed[151]. A study retrospectively evaluated patients with upper GIB diagnosis who had taken NSAIDs,

antiaggregants, or anticoagulants; of them, 86% had moderate to high risk for GIB, but 81% of these patients were not actually using PPIs. In patients with a previous history of peptic ulcer bleeding, PPI prophylaxis was not provided in one every four cases[152]. A Danish nationwide register-based study identified citizens at an increased ulcer bleeding risk and showed only 44.4% concomitantly treated with PPIs[153]. From a database, elderly patients (> 64 years old) who were chronic (> 3 mo) users of LDA and had an indication for PUD prophylaxis as per the ACG-ACCF-AHA guideline document were identified. Overall, only 40% of patients received a PPI[154]. In another retrospective drug utilization study, in China, the prescribing pattern of LDA revealed a poor awareness of preventing GI injury with combined protective medications[155]. Under-prescription is frequent also in very high-risk patients. A retrospective study included patients on combined antithrombotic therapy receiving PPIs, reporting an overall rate of PPI co-therapy of 40.9%, with only 22.3% of patients receiving PPIs for GIB prophylaxis[156].

There are, however, some positive findings. In the All Nippon AF In the Elderly (ANAFIE) Registry[157], a prospective, observational study among elderly (aged > 75 years) Japanese non-valvular AF patients in the real-world clinical setting, PPIs were used in 36.9% of patients. Compared with the PPIs- group, the PPIs+ group included a greater proportion of female patients and had significantly higher CHA2DS2-VASc and HAS-BLED scores, as well as higher prevalence of several comorbidities. In the PPIs+ group, 54.6% of patients did not have GI disorders and were likely prescribed a PPI to prevent GIB events. Compared with patients not receiving anticoagulants, a significantly higher proportion of patients receiving anticoagulants received PPIs. For patients receiving anticoagulants, antiplatelet drugs, and both drugs, rates of PPI use were 34.1%, 44.1%, and 53.5%, respectively ($P < 0.01$). These data suggest that PPIs were actively prescribed in high-risk cases. In a Dutch monocentric observational registry on ACS patients, besides, from 2010 to 2014 PPI prescription at discharge significantly increased from 34.7% to 88.7%[100].

On the other hand, overprescription has also been observed. In a Dutch primary care database[158] with all new PPI prescriptions, valid PPI indications at initiation were seen only in 44% of PPI users. Predictors of inappropriately initiated PPI use were older age and use of non-selective NSAIDs, COX-2 inhibitors, and LDA. An inappropriate indication was found in more than half of PPI users in primary care (one of the leading causes was unnecessary ulcer prophylaxis related to drug use)[158]. An observational study on a large insurance claims database showed that the incidence of potentially inappropriate PPI prescriptions significantly increased from 4.8% in 2013 to 6.4% in 2017 (age, male gender, multimorbidity, and use of drugs with bleeding risk being independent determinants)[159]. The main predictor of inappropriate PPI use is the number of received medications[160]. We particularly need efforts, thus, to deprescribe PPIs after interruption of antithrombotic therapies.

CONCLUSION

In patients at thrombotic risk, antiplatelet and anticoagulant drugs are effective for primary and secondary prevention of cardiovascular events. Antithrombotic drugs, unfortunately, can cause GIB, sometimes with a fatal outcome[23,45,53,161]. Besides, GIB, in turn, may often require treatment discontinuation, and this may have harmful consequences in the medium and long term on ischemic events[162]. Therefore, gastroprotection is required in patients at increased bleeding risk[163]. PPIs are often prescribed, regardless of the bleeding risk, in patients with many CVDs such as ACS, mechanical or surgical revascularizations, ischemic strokes, and TIAs. The prescription of these drugs should be based on the presence of stents and the need for DAPT, as well as on the GIB risk profile of the patients (age > 65 years, previous upper GIB events, concomitant therapy with anticoagulants or NSAIDs, and *H. pylori* infection).

In patients treated with single antiplatelet therapy for the first time, standard dose of PPIs should be used only in the presence of GIB risk factors[2,23,33,54,126]. There is currently no evidence to recommend one PPI agent as gastroprotection for the risk of upper GIB in the absence of any risk factors[1,28,31,51,57]. Choosing a PPI lacking interference with the hepatic CYP450 enzymes might be preferred in patients treated with clopidogrel[33,84,91,92]. Among patients with a history of aspirin-induced upper GIB, the use of a standard dose of PPI in association with LDA should be preferred to substitution with clopidogrel to reduce the risk of upper GIB recurrence[43,44,139]. Currently, available data do not allow answering the question about the differences between individual PPIs in their impact on the risk of adverse cardiovascular events due to the small number of such studies, design heterogeneity, and differences in the inclusion criteria and endpoints, as well as in the rate of administration of individual PPIs.

As for antiplatelet therapy, the most effective gastroprotection in patients treated with oral anticoagulants, when necessary, is that with standard PPI dosage[58-60]. For VKAs, INR monitoring is required when starting or stopping PPI therapy[33]. For DOACs, PPI use is recommended in the presence of risk factors[36,37]. We recommend to use standard dose of PPIs in patients treated with DAPT, or with double or triple antithrombotic treatment[139,145]. Specific recommendations are dedicated to patients with cirrhosis[60,64,165]. Obviously, PPIs are not effective against bleeding from the small intestine or from the colon[33].

The interaction between antiplatelet therapy and *H. pylori* infection remains also controversial[31,113,120,121], requiring randomized prospective studies. Finally, there is no evidence that other gastroprotective drugs are more effective than PPIs[109,130,134,135,137].

In conclusion, in patients treated with antiplatelet therapy with an increased risk of GIB, use of PPIs should be considered mandatory[33,141,144]. In other cases, the decision to use PPIs in patients treated with thienopyridines or anticoagulant agents should be based on risk-benefit ratio, assessing both cardiological and gastroenterological risks in order to balance them. Validated therapies to prevent bleeding risk from VKAs and DOACs are not available[139,142]. Recent studies seem to demonstrate a benefit of the PPI treatment also in patients taking anticoagulants[34,35,90,113,138]. We need further prospective, randomized studies to accurately evaluating the protective role of PPIs during OAC

Table 3 Main guideline and consensus documents on gastroprotection in patients under antithrombotic treatment

Guideline/consensus documents	Year	Main recommendations
The joint United States guidelines of the American College of Cardiology Foundation, the American College of Gastroenterology, and the American Heart Association[139]	2008	Recommended the use of PPIs only in patients taking warfarin in combination with antiplatelet therapy and/or NSAIDs. It did not recommend the substitution of clopidogrel for LDA in high-risk patients to reduce the risk of recurrence ulcer bleeding
Focused update of the joint United States guidelines of the American College of Cardiology Foundation, the American College of Gastroenterology, and the American Heart Association[141]	2010	Recommended use of PPIs in patients taking DAPT and in those who have multiple risk factors for GIB
Position paper issued by Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners[33]	2016	Recommended the use of standard doses of PPIs for those taking antiplatelet agents (individually or in association) only if at least one risk factor is present (age > 65 yr, concomitant use of steroids or anticoagulants, previous history of peptic ulcer). In addition, the use of pantoprazole or rabeprazole was suggested if clopidogrel was used, while there were no restrictions on the choice of PPIs with prasugrel and ticagrelor
The ESC guidelines on DAPT[145]	2017	Recommended gastroprotection with PPIs in all patients
Maastricht/Florence Consensus report on management of <i>Helicobacter pylori</i> infection[146]	2017	Search for <i>H. pylori</i> should be performed in patients with a history of peptic disease who take NSAIDs or aspirin. However, there were no specific recommendations on LDA since the evidence was considered controversial; no recommendations were provided for non-aspirin antiplatelet agents and/or oral anticoagulants
Consensus of the American College of Gastroenterology on treatment of <i>Helicobacter pylori</i> infection[140]	2017	Suggested searching for the infection in patients starting aspirin therapy, even if it was emphasized that the basis for this recommendation was weak. No specific recommendations regarding non-aspirin antiplatelet agents and/or oral anticoagulants
ESC guidelines on non-ST-segment elevation acute coronary syndrome[144]	2020	Recommended (class I, level of evidence A), for pharmacological long-term management, concomitant use of PPIs in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of GIB. They suggested as a strategy to reduce bleeding risk related to percutaneous coronary intervention the use of PPIs in patients on DAPT at higher-than-average risk of gastrointestinal bleeds (<i>i.e.</i> , history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use, or two or more of: Age ≥ 65 yr; dyspepsia; gastro-oesophageal reflux disease; <i>H. pylori</i> infection; chronic alcohol use)
2020 ESC guidelines on the management of AF [147]	2020	Apixaban or dabigatran 110 mg bid is not associated with an excess of gastrointestinal bleeding compared with warfarin. It suggests the use of apixaban in patients with AF at high risk of bleeding from the GI tract
The Korean guidelines for the Clinical Guidelines for Drug-related Peptic Ulcer, revised under the Korean College of Helicobacter and Upper Gastrointestinal Research in 2020[143]	2020	Treatment for <i>Helicobacter pylori</i> infections is recommended in patients with a history of peptic ulcers and receiving long-term LDA therapy to prevent peptic ulcers and complications. The maintenance of anti-ulcer drugs, such as PPIs, is also recommended after <i>H. pylori</i> eradication if patients require other antiplatelet agents or anticoagulants. Regardless of <i>H. pylori</i> eradication, when patients with a history of peptic ulcer take long-term LDA, the concomitant use of a PPI according to the severity of the peptic ulcer is recommended
Gastroprotection in patients on antiplatelet and/or anticoagulant therapy: A position paper of the National Association of Hospital Cardiologists and the Italian Association of Hospital Gastroenterologists and Endoscopists [148]	2021	PPIs are recommended: In single antiplatelet therapy in presence of risk factors; in DAPT; in dual and triple antithrombotic therapy; in single anticoagulant therapy in presence of risk factors

H. pylori: *Helicobacter pylori*; AF: Atrial fibrillation; DAPT: Double antiplatelet therapy; DAT: Double antithrombotic therapy; GIB: Gastrointestinal bleeding; GI: Gastrointestinal; LDA: Low dose aspirin; OAC: Oral anticoagulant; PPI: Proton pump inhibitor; TAT: Triple antithrombotic therapy.

Table 4 Summary statements

No. PPIs are recommended	
1	In single antiplatelet therapy in presence of risk factors (history of peptic disease; concomitant treatment with non-steroidal anti-inflammatory drugs or steroids; two of the following: Age > 65 yr, dyspeptic symptoms, and gastrointestinal reflux symptoms)
2	In double antiplatelet therapy
3	In dual and triple antithrombotic therapy
4	In single anticoagulant therapy in presence of risk factors (at least one of the following: Age > 75 yr; history of peptic disease; concomitant use of non-steroidal anti-inflammatory drugs)
Searching for <i>Helicobacter pylori</i> infection could be useful in patients starting aspirin therapy	

therapy, considering the stratification of both thrombotic and haemorrhagic risk and potential long-term consequences. Meanwhile, physicians should both be aware of potential issues related to long-term use of PPIs and weigh benefits of PPI therapy along with the likelihood of the potential risks. Discussing evidence behind the reported side effect profile will help clarify the growing concerns over PPI therapy[166]. Table 4 synthesizes some suggestions on this topic.

FOOTNOTES

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Use of intravascular lithotripsy in non-coronary artery lesions

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Abstract

BACKGROUND

Intravascular lithotripsy (IVL) is a novel technique increasingly used for plaque modification and endovascular revascularization in patients with severe calcification and peripheral artery disease. However, much of the available literature on IVL is focused on its use in coronary arteries, with relatively limited data on non-coronary artery use.

AIM

To analyze the safety and efficacy of current IVL use in non-coronary artery lesions, as reported in case reports and case series.

METHODS

We searched EMBASE, PubMed, and *Reference Citation Analysis* databases for case reports and case series on IVL use in peripheral artery disease. We then extracted variables of interest and calculated the mean and proportions of these variables.

RESULTS

We included 60 patients from 33 case reports/case series. Ninety-eight percent of the cases had IVL usage in only one blood vessel, while four had the IVL used in two vessels (2.0%), resulting in 64 Lesions treated with IVL. The mean age of the patients was 73.7 (SD 10.9). IVL was successfully used in severe iliofemoral artery stenosis (51.6%), severe innominate, subclavian, and carotid artery stenosis (26.7% combined), and severe mesenteric vessel stenosis (9.4%). Additionally, IVL was successfully used in severe renal (7.8%) and aortic artery (4.7%) stenosis. There were complications in 12% of the cases, with dissection being the commonest.

CONCLUSION

IVL has successfully used in plaque modification and endovascular revascularization in severely calcified and challenging lesions in the iliofemoral, carotid, subclavian, aorta, renal, and mesenteric vessels. The most severe but transient complications were with IVL use in the aortic arch and neck arteries.

Key Words: Intravascular lithotripsy; Peripheral artery disease; Non-coronary artery

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Core Tip: Intravascular lithotripsy (IVL) has emerged as a novel endovascular therapy for treating severe vascular calcifications. In this review of case reports, we assessed the efficacy and safety of IVL in treating calcified lesions in non-coronary artery vessels and the various situations in which IVL was used in these vessels. We found that IVL has successfully facilitated treating severely calcified and challenging lesions in the iliofemoral, carotid, subclavian, aorta, renal, and mesenteric vessels.

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INTRODUCTION

The global prevalence of peripheral artery disease (PAD) is estimated to be over 230 million[1]. This prevalence was higher in high-income countries than in low- and middle-income countries (LMICs). As per data published in 2021, approximately 6.5 million people in the United States aged 40 and above suffer from PAD[2]. A vast majority of these conditions are due to atherosclerosis.

Intravascular lithotripsy (IVL) is a novel technique successfully used for plaque modification and endovascular revascularization in patients with severe calcification and PAD. Severe vascular calcifications are statistically correlated with poor clinical outcomes and increased mortality rates. In addition, they present technical challenges during the revascularization process and increase complications like stent thrombosis or stent fracture following endovascular revascularization[3-6]. Atherectomy, a treatment modality for debulking calcifications, has been reported as not being selective to the calcified plaque lesions and disrupting the vessel's intimal healthy soft tissue[7]. In addition, this procedure has been associated with higher complications. During the EASE trial, the dissection and perforation rate was estimated at around 6%[8], while the DEFINITIVE Ca++ trial reported a major adverse event rate of 6.9%[9].

IVL is based on a similar concept of shockwave lithotripsy deployed to treat nephrolithiasis. The selected single-use balloon catheter's diameter is 1.1 times that of the reference vessel diameter, embedded with lithotripsy emitters, capable of disrupting both superficial and embedded calcification with the advantage of controlled dilatation[10]. After the successful apposition of the balloon with the vessel wall, pulses are first generated at 50 atmospheres. Once calcification has been disrupted, the balloon is inflated to fully expand the vessel at 6 atmospheres, reducing stenosis rates and procedural complications[11,12]. Much of the available literature on IVL is focused on its use in coronary arteries, with relatively limited data on non-coronary artery use. This systematic review of case reports of IVL in non-coronary artery lesions aims to analyze the safety and efficacy of current IVL use in non-coronary artery lesions.

MATERIALS AND METHODS

Articles were obtained by searching PubMed, EMBASE, and *Reference Citation Analysis* databases with the keywords peripheral artery intravascular lithotripsy. We exclusively selected case reports or case series. Two authors independently reviewed the titles and abstracts to determine the studies that met our inclusion criteria. Our inclusion criteria include: (1) The study must be a case report or case series; and (2) the study must be regarding intravascular lithotripsy on non-coronary arteries. In addition, we excluded studies that were not written in English. The next phase was reviewing the full text of the studies that met the inclusion criteria and data extraction into a data spreadsheet. The extracted data included the country of publication, the age and gender of patients, the vessels in which IVL was used, and the complications reported. We assessed the quality of the studies using The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports. The checklist evaluates the quality of case reports using an eight items list[13,14].

We did a qualitative and quantitative analysis. In the qualitative analysis, we summarized the use of IVL in different vessel groups in the body, such as the mesenteric, lower extremity, upper trunk, and neck, *etc.* In the quantitative analysis, we used means, standard deviations, and percentages to describe the statistics of the patients in the study, the vessels in which IVL was used, and the complications reported.

RESULTS

Identification of relevant studies

Our search identified 185 articles, of which 114 were unique after removing duplicate publications. Two researchers independently reviewed the abstracts to assess if they met our study's inclusion and exclusion criteria. Articles excluded include a description of IVL (25), coronary artery IVL (42), and review articles ($n = 15$). We included 60 patients from 33 case reports/case series (Figure 1; Table 1).

Quality of studies assessment

Our assessment showed that ninety-seven percent of the case reports (32 of 33) were high quality and well-written. They included pertinent information about the patient's demographics, clinical symptoms, procedures performed, and outcomes. One of the case reports (3%) did not include patients' demographic information and history, although it was a conference abstract. However, it had information about the procedure outcomes and complications. Twenty-one percent of the studies (7 of 33) did not comment on the presence or absence of adverse events or complications from the procedure (Supplementary Table 1).

Quantitative result

Most patients had the IVL used in only one vessel (98%), while four had the IVL used in two vessels (2%), resulting in 64 lesions treated with IVL. The mean age of the included population was 73.7 (SD 10.9), with 56% males. The majority of the published cases were from the United States (54%), followed by Italy (18.8%) and France (12.5%). The baseline demographic and procedural characteristics are shown in Table 2. IVL was successfully used in severe iliofemoral artery stenosis (51.6%), severe innominate, subclavian, and carotid artery stenosis (26.7% combined), and severe mesenteric vessel stenosis (9.4%) (Table 3). Additionally, IVL was successfully used in severe renal (7.8%) and aortic arteries (4.7%) stenosis. There were complications in 12% of the cases. The reported complications include dissections, perforation, a transient ischemic attack, an acute blindness post-carotid artery IVL successfully treated with tissue plasminogen activator (TPA), and transient hypotension, which improved with fluids and inotropes.

DISCUSSION

IVL use in the iliofemoral artery

IVL use in iliofemoral arteries was mainly for treating heavily calcified and symptomatic peripheral artery disease[15,16] and providing large-bore vascular access for cardiovascular procedures such as transcatheter aortic valve replacement in patients with heavily calcified lesions[17,18].

IVL was used to improve vessel compliance and predilection before stent placement[16]. Several authors reported the use of IVL for severely calcified vessels before stent placement[16,19] or before treatment with drug-coated balloon angioplasty[20]. IVL was also used in severely calcified vessels as a stand-alone treatment without stent placement. Nasiri reported IVL use in the distal right anterior tibial artery as a stand-alone therapy with resolution of the slow blood flow [16].

Furthermore, IVL was used in treating patients with heavily calcified iliofemoral artery in-stent restenosis. Honton *et al* [15] described the use of IVL in treating severe common iliac artery stent restenosis caused by underlying eccentric severely calcified stenosis. This led to the device under expansion and inadequate stent deployment. An intrastent IVL was successfully deployed to disrupt the calcified lesion resulting in stent expansion.

In summary, IVL was successfully used without complication in heavily calcified iliofemoral arteries before stent placement, as a stand-alone treatment without stent placement, and in in-stent restenosis.

IVL use in the aortic arch and necks arteries

The use of IVL was also reported in the aortic arch vessels, including the carotid, subclavian and innominate vessels. Though IVL is not yet approved for use in these vessels, Case *et al*[21] reported the use of IVL in two cases of heavily calcified carotid artery lesions in patients who were not candidates for carotid endarterectomy. Both patients had post-radiation necks and were determined by the vascular surgeons to be non-surgical candidates. IVL was successfully used before the placement of stents. Unfortunately, despite using distal embolic protection, one of the patients developed temporary right eye blindness, likely secondary to emboli to the central retinal artery. The patient was treated with non-selective delivery of tPA at the ostium of the right ophthalmic artery and intravenous heparin for 48 h with the resolution of the blindness[21].

IVL was also successfully used in two patients with severe calcified subclavian artery stenosis[21]. One of the cases was *de-novo* totally occluded left subclavian artery at the ostium. The patient was symptomatic, and the decision was made to open up the artery for symptomatic relief. IVL was used for the severely calcified lesion, and a stent was successfully placed with no significant residual stenosis. The second case was a left subclavian artery in-stent restenosis in which IVL was successfully used. In both cases, no complications were reported, and the patients did well at one year of follow-up.

In summary, although IVL is not approved for use in patients with heavily calcified aortic arch arteries, IVL was successfully used to treat *de-novo* calcified arteries and in-stent restenosis. However, it is essential to ensure that distal embolic protections are used with aortic arch arteries IVL to prevent emboli to the brain.

Table 1 Studies included in the review

Ref.	Country	Age	Sex	Iliac-femoral	Popliteal and infra-popliteal	Carotid, subclavian, innominate	Celiac, superior mesenteric	Renal	Radial	Aorta
Honton <i>et al</i> [15], 2020	France	75	M	1						
Nasiri <i>et al</i> [16], 2022		82	M	1						
Nasiri <i>et al</i> [16], 2022		70	M	1						
Nasiri <i>et al</i> [16], 2022		75	M	1						
Nasiri <i>et al</i> [16], 2022		59	F							1
Nasiri <i>et al</i> [16], 2022	United States	74	F		1					
Tayal <i>et al</i> [17], 2021		78	F	1						
Riley <i>et al</i> [18], 2019		78	F	1						
Rosseel <i>et al</i> [19], 2020		69	F	1						
Golamari <i>et al</i> [20], 2019		66	M	1	1					
Case <i>et al</i> [21], 2020	United States	56	M			1				
Case <i>et al</i> [21], 2020	United States	72	M			1				
Case <i>et al</i> [21], 2020	United States	73	M			1				
Case <i>et al</i> [21], 2020	United States	82	M			1				
Case <i>et al</i> [21], 2020	United States	54	M			1				
Cheng <i>et al</i> [23], 2021	United States	79	F				1			
Khan <i>et al</i> [24], 2020	United States	73	F				1			
Khan <i>et al</i> [24], 2020	United States	65	F				1			
Schnupp <i>et al</i> [28], 2020	Germany	76	M					1		
Lee <i>et al</i> [29], 2020	United States	85	F					1		
Chag <i>et al</i> [32], 2021	India	67	F							1
Bellini <i>et al</i> [33], 2019	Italy	65	M			1				
Donas <i>et al</i> [34], 2022		74	M	1						
Napoli <i>et al</i> [35], 2023		37							1	
Yousif <i>et al</i> [36], 2021	Bahrain	72	F					1		
Cereda <i>et al</i> [37], 2020	Italy	86	M	1						
Kumar <i>et al</i> [38], 2022		76	M	1						

Kumar <i>et al</i> [38], 2022		75	F	1		
Price <i>et al</i> [39], 2021	United States	97	M	1		
Price <i>et al</i> [39], 2021	United States	71	M	1		
Price <i>et al</i> [39], 2021	United States	82	M	1		
Price <i>et al</i> [39], 2021	United States	75	F	1		
Price <i>et al</i> [39], 2021	United States	83	F	1		
Price <i>et al</i> [39], 2021	United States	83	F	1		
Price <i>et al</i> [39], 2021	United States	59	M	1		
Price <i>et al</i> [39], 2021	United States	81	M	1		
Price <i>et al</i> [39], 2021	United States	83	F	1		
Ahsan <i>et al</i> [40], 2022	United States	74	F			1
Amor <i>et al</i> [41], 2022	France				1	
Amor <i>et al</i> [41], 2022	France				1	
Amor <i>et al</i> [41], 2022	France				1	
Amor <i>et al</i> [41], 2022	France				1	
Amor <i>et al</i> [41], 2022	France				1	
Harada <i>et al</i> [42], 2022	United States	86	F			1
Shah <i>et al</i> [43], 2022	India	80	F	1		1
Fazzini <i>et al</i> [44], 2022	Italy			1		
Fazzini <i>et al</i> [44], 2022	Italy			1		
Fazzini <i>et al</i> [44], 2022	Italy			1		
Fazzini <i>et al</i> [44], 2022	Italy			1		
Fazzini <i>et al</i> [44], 2022	Italy			1		
Balboa <i>et al</i> [45], 2021		67	M		1	
Kiron <i>et al</i> [46], 2021	India	75	M		1	
Varotto <i>et al</i> [47], 2022	Italy	83	M		1	
Henry <i>et al</i> [48], 2021	United States	73	M		1	
Henry <i>et al</i> [48], 2021	United States	81	M		1	
Misztal <i>et al</i> [49], 2020	Poland	82	M		1	

Spaccarotella <i>et al</i> [50], 2020	Italy	82	M	1	
Hamandi <i>et al</i> [51], 2020	United States	42	F	1	
Rehman <i>et al</i> [52], 2020	United States	80	M	1	
Sogomonian <i>et al</i> [53], 2021		75	F		1

Table 2 Descriptive statistics of study participants

	Number	Percentage
Age (yr)	73.7 (SD 10.9)	
Gender		
Male	28	56%
Female	21	44%
Country		
Bahrain	1	2.1%
Denmark	1	2.1%
France	6	12.5%
Germany	1	2.1%
India	3	6.3%
Italy	9	18.8%
Poland	1	2.1%
United States	26	54.2%

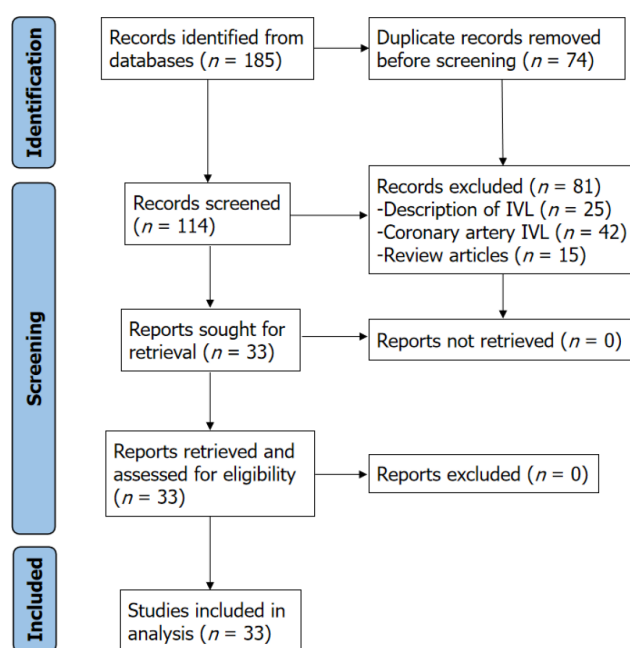
Table 3 Vessels where intravascular lithotripsy was used and complications reported

Artery	Percentage	Complication reported
Iliofemoral, popliteal, and tibial	51.6% (33/64)	Dissection (3/33), perforation (1/33)
Carotid, subclavian, and innominate arteries	25.0% (16/64)	Transient ischemic attack (1/16), acute blindness that resolved with TPA (1/16), transient hypotension, which improved with fluids and inotropes (1/16)
Mesenteric vessels, including celiac and superior mesenteric artery	9.4% (6/64)	None
Renal	7.8% (5/64)	None
Aorta	4.7% (3/64)	None
Radial	1.6% (1/64)	None

TPA: Tissue plasminogen activator.

IVL use in mesenteric arteries

IVL was successfully used to treat heavily calcified lesions in the splanchnic circulation. Endovascular revascularization has become an alternative to open surgical repair of stenotic splanchnic lesions, especially in elderly patients and patients with comorbidities[22]. Endovascular revascularization results in lower short-term mortality compared to surgical intervention but have decreased long-term primary patency compared to surgical repair[22]. One major limitation of endovascular revascularization is the presence of heavily calcified lesions, resulting in under-expanded stents[23]. Cheng *et al*[23] reported the use of IVL in a symptomatic elderly patient with a heavily calcified celiac artery that failed prior percutaneous endovascular intervention. IVL was safely used to modify the calcified lesion allowing a stent to be successfully deployed. Khan *et al*[24] also reported IVL use in treating severely calcified *de novo* superior mesenteric artery stenosis and celiac artery in-stent restenosis. In both cases, IVL was successfully used without complications. In



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Figure 1 Preferred reporting items for systematic review and meta-analyses guidelines flowchart of the selection process. IVL: Intravascular lithotripsy.

summary, IVL has been used without complications in treating *de novo* stenosis and in-stent restenosis of heavily calcified mesenteric arteries.

IVL use in renal arteries and aorta

Angioplasty of renal arteries with or without stent placement has not been found to be superior to medical therapy in patients with atherosclerotic renal artery stenosis[25,26]. However, revascularization is a reasonable option in patients with hemodynamically significant atherosclerotic renal artery stenosis with flash pulmonary edema, recurrent unexplained congestive heart failure, progressive chronic kidney disease, and resistant hypertension[27]. Angioplasty of the renal artery could be challenging due to the large diameter, and heavily calcified plaques make it more challenging [28]. Lee *et al*[29] reported a heavily calcified bilateral renal artery stenosis successfully treated with IVL and stenting. The initial attempt at percutaneous transluminal renal angioplasty was unsuccessful due to severely calcified lesions. Schnupp *et al*[28] also reported safely using IVL in heavily calcified renal artery stenosis with successful stent placement. In summary, IVL has been successfully used in heavily calcified renal artery stenosis.

Efficacy of IVL procedures

We found 100% clinical and angiographic success in patients with heavily calcified non-coronary artery lesions treated with IVL. While we cannot rule out a publication bias because authors are more likely to publish successful IVL cases, previous systematic reviews of IVL in lower extremity peripheral artery disease have reported high success rates. A systematic review and meta-analysis involving nine studies with 681 patients showed a diameter stenosis reduction of 59.3% in lower extremity lesions post-IVL[30]. Similarly, another study of 336 patients who underwent endovascular revascularization of lower extremity peripheral artery lesions with IVL demonstrated a significant diameter stenosis reduction of 55.1% post-IVL[31].

Complications of IVL procedures

In our study, complications were reported in 12% of the cases. The reported complications include dissections (4.7%), perforation (1.6%), a transient ischemic attack (1.6%), an acute blindness post-carotid artery IVL (1.6%) that was successfully treated with TPA and transient hypotension (1.6%), which improved with fluids and inotropes. In the subgroup analysis, complications were more likely to occur in the IVL involving the aortic arch and necks arteries (18.7%), followed by IVL of lower extremity arteries (12.1%). However, none of the complications was associated with permanent disability or in-hospital mortality.

The reported complication rates in the lower extremities in our sub-group analysis are similar to those reported in previous systematic reviews of IVL use in lower extremity peripheral artery disease. For example, Madhavan *et al*[31] reported dissection with IVL in 14.5% of the procedures, but the flow-limiting dissection or type D/E/F dissection was in only 0.9% of the 328 cases. Similarly, Wong *et al*[12] reported flow-limiting dissection of the lower extremity vessels in 1.25% of the 681 patients in their meta-analysis.

Limitations of the study

One major limitation of the study is the small sample sizes provided by case reports. Additionally, authors might be more likely to publish cases with successful outcomes leading to publication bias. Therefore, there is a need for more extensive studies to evaluate the safety and efficacy of these procedures in different non-coronary artery vessels.

CONCLUSION

Heavily calcified lesions present a challenge in endovascular procedures, and IVL has been shown to safely and effectively address the calcified lesions and improve vessel compliance[16]. One advantage of IVL is that it does not typically lead to distal emboli like many atherectomy procedures, and distal protection is usually unnecessary[16,24]. An exception is the atherectomy of the carotid arteries, where distal protection is still necessary due to the severe consequences of an embolus[21]. Furthermore, compared to atherectomy of a calcified lesion, IVL is a relatively quicker procedure, easy to learn, has a lower risk of vascular injuries such as vessel rupture or dissection, and more uniform plaque disruption[16,24]. In summary, we found that IVL was safely and successfully used in plaque modification and endovascular revascularization in severely calcified and challenging lesions in the iliofemoral, carotid, subclavian, aorta, renal, and mesenteric vessels. The most severe but transient complications were with IVL use in the aortic arch and neck arteries.

ARTICLE HIGHLIGHTS**Research background**

Peripheral arterial disease (PAD) is a common manifestation of atherosclerotic disease globally, and heavy calcifications in peripheral artery diseases reduce the success of endovascular therapy for PAD. Intravascular lithotripsy (IVL) has emerged as a technique for plaque modification of severely calcified artery lesions.

Research motivation

Most of the focus of IVL has been on treating coronary artery diseases, and its use in peripheral arteries has not been extensively studied.

Research objectives

To analyze the use of IVL in the peripheral arteries, its safety, and efficacy, as reported in case reports.

Research methods

We searched and extracted cases from PubMed, EMBASE, and *Reference Citation Analysis* databases. Then, we did a quantitative and qualitative analysis of case reports on IVL use in peripheral artery diseases.

Research results

IVL was successfully and safely used in heavily calcified lesions in the iliofemoral artery, aortic arch and necks arteries, mesenteric arteries, renal arteries, and aorta, with the iliofemoral artery being the commonest site reported. Adverse effects were minimal, but the most severe was reported in IVL use in the neck arteries.

Research conclusions

IVL has been safely used in a broadening array of complex, severely calcified peripheral artery disease lesions.

Research perspectives

More extensive studies are needed to assess the safety of IVL in peripheral artery vessels, such as the aortic arch and necks arteries, where it is not currently approved for use.

FOOTNOTES

Author contributions: All authors conceptualized and revised the study design; Stratton A, Wagner T, Saigal S, Sood K, Dhawan R, and Wagner C extracted the data; Umeh CA analyzed the data; Umeh CA and Gupta R wrote the first draft of the paper; Ching THS, Kumar S, Obi J, Gupta R, and Umeh CA reviewed and revised the paper; Stratton A led and coordinated the research and writing of the manuscript; Scottie C, Gupta R, and Umeh CA supervised the project; and all authors have read and approved the final manuscript.

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Spontaneous coronary artery dissection-associated takotsubo syndrome: A systematic review of case reports

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Abstract

BACKGROUND

Spontaneous coronary artery dissection (SCAD) is underdiagnosed and requires comprehensive angiographic findings. Few SCAD occurrences have a comparable clinical appearance as takotsubo syndrome (TTS) or exist simultaneously, making it challenging for clinicians to treat and manage. Case reports lack consolidated

data. We examined SCAD-TTS case reports.

AIM

To conduct a systematic review of available case reports on SCAD in order to investigate its potential association with TTS.

METHODS

SCAD-associated TTS case reports were reviewed after thoroughly screening PubMed, EMBASE, Scopus, and Google Scholar databases till January 2023. Case reports described demographics, comorbidities, imaging, management, and results.

RESULTS

Twelve articles about 20 female patients were analyzed. 30% of patients ($n = 6$, > 60 years) were elderly (mean age 56.2 ± 9.07 years, range 36-70 years). Canada has 9 cases, United States 3, Australia 3, Sweden 2, Japan, Denmark, and France 1. Only 5 reports identified emotional stressors in these cases while 4 reports showed physical triggers for TTS. Nine had hypertension, 2 had hyperlipidemia, and 1 had prediabetes. 5 patients (25%) smoked. 10 (50%) troponin-positive myocardial infarction patients reported chest discomfort. 11 (55%) of 20 instances had TTS/SCAD. 12 (60%) of 20 patients exhibited ST elevation and 3 (15%) had T wave inversion on electrocardiogram. 19/20 patients had elevated troponin. 9 (45%) of 20 people had apical akinesis with TTS ballooning on cardiac imaging. All 20 exhibited echocardiographic wall motion abnormalities. 19 (95%) of 20 coronary angiography cases had SCAD. 10 of 19 SCAD patients had left anterior descending, 2 diagonal, and 2 left circumflex coronary artery involvement. 7 of 20 patients had left ventricular ejection fraction (LVEF) data. LVEF averaged $38.78 \pm 7.35\%$. 5 (25%) of the 20 cases underwent dual antiplatelet therapy. Three (15%) of 20 cases experienced occasional ectopic ventricular complexes, Mobitz II AV block, and paroxysmal atrial fibrillation. All 20 cases recovered and survived.

CONCLUSION

Given the clinical similarities and challenges in detecting TTS and SCAD, this subset needs more research to raise awareness and reduce morbidity.

Key Words: Spontaneous coronary artery dissection; Takotsubo syndrome; Takotsubo cardiomyopathy; Systematic review; Coronary angiography; Cardiology

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Core Tip: This study highlights the coexistence and clinical similarities of takotsubo syndrome and spontaneous coronary artery dissection, therefore emphasizing the importance of further research, awareness as well as comprehensive angiographic testing for effective diagnosis and management.

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INTRODUCTION

Takotsubo syndrome (TTS), also known as "broken heart syndrome," mimics a myocardial infarction and is typically caused by an abrupt surge of stress hormones, such as catecholamines, in reaction to mental or physical stress[1]. These hormones can produce a transitory weakening of the heart's contractile cells, resulting in myocardial stunning and a specific pattern of wall motion abnormalities[2]. The exact pathophysiological process behind this syndrome is not completely understood. In addition, endothelial and microvascular dysfunction can produce abrupt constriction or spasms of the coronary arteries, resulting in reduced blood supply to the cardiac muscle and precipitating the symptoms of TTS[3]. Spontaneous coronary artery dissection (SCAD) and TTS have similar causes and prevalence. Stress causes both conditions, which affect women more. However, there are differences between these conditions. A rupture in the inner layer of the coronary artery wall can block or restrict blood flow and cause SCAD. SCAD may result from arterial defects, hormones, and genetics. TTS, a type of transient heart failure, can cause chest pain, shortness of breath, and other heart attack-like symptoms. TTS may be caused by the sympathetic nervous system's "fight or flight" response.

SCAD has been reported in patients with TTS despite these differences. Genetic, hormonal, and environmental factors may be involved. SCAD and TTS affect predominantly women, particularly postmenopausal women. There may be a hormonal component to both of these conditions. SCAD and TTS share comparable pathophysiology, symptoms, triggers,

prevalence, and etiology but have distinct prognoses. Recent studies suggest a possible link between the two. TTS and SCAD have similar symptoms and etiologies, but their prognoses and outcomes are distinct. The majority of TTS patients recover without lasting effects. Cardiogenic shock, left ventricular rupture, and malignant arrhythmias are potentially lethal conditions. Patients with TTS are more likely to experience recurrent episodes and cardiovascular complications. SCAD causes myocardial infarction, heart failure, and sudden cardiac death. The severity, location, and presence of CAD influence the outcomes of SCAD. Patients with SCAD require medication, invasive procedures, and prolonged hospitalizations. This systematic review examines the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients. TTS patient case reports with SCAD imaging are reviewed. This review discusses the pathogenesis, causes, and potential links between these two cardiovascular disorders. The review examines patient data to identify trends that may improve the diagnosis, management, and outcomes of TTS and SCAD.

MATERIALS AND METHODS

Literature review, Screening Titles/Abstracts and Population Selection Until January 2023, a comprehensive search of PubMed/Medline, EMBASE, Scopus, and Google Scholar was conducted to identify case reports and case series linked with spontaneous coronary artery dissection SCAD and TTS using relevant keywords such as Takotsubo syndrome, Takotsubo cardiomyopathy, broken heart syndrome, apical ballooning syndrome, stress-induced cardiomyopathy and spontaneous coronary artery dissection. The search was restricted to articles written in English only and with full text.

Search strategy

The systematic review comprised case reports and case series on the clinical presentation, diagnosis, and treatment of TTS with imaging evidence of SCAD. The exclusion of studies lacking sufficient TTS or SCAD-related information or failing to meet diagnostic criteria. Before retrieving the full-text papers for further evaluation, two reviewers evaluated the abstracts and titles of identified publications. To resolve conflicts, agreement or discussion with a third reviewer was sought.

Detailed search methodology

Up to January 2023, a thorough search as shown in PRISMA flow diagram (Figure 1) was carried out in the PubMed, Scopus, EMBASE and Google Scholar databases. "Spontaneous coronary artery dissection" (in title or abstract), "Takotsubo Syndrome" OR "Takotsubo Cardiomyopathy" OR "Broken Heart Syndrome" OR "apical ballooning syndrome" OR "stress-induced cardiomyopathy" (in title or abstract), and a publication date filter from 2000 to January 31, 2023, were all included in the search strategy. Publications classified as "editorial," "review," "comment," "meta-analysis," or "systematic review" were omitted; only case reports were included.

Inclusion criteria

(1) Case studies describing the connection between TTS and SCAD; (2) Publications published from 2000 to January 31, 2023; and (3) Reports that detail the demographics, comorbidities, imaging results, management, and outcomes of SCAD-TTS cases.

Exclusion criteria

(1) Publications labeled as "editorial," "review," "comment," "meta-analysis," or "systematic review"; (2) Studies that fail to mention how SCAD and TTS are related; (3) Publications released after January 31, 2023, but before 2000; and (4) Non-English articles. The search method was designed to locate pertinent case reports that satisfy the requirements for a thorough analysis of TTS related to SCAD.

Data extraction and quality assessment

From the included studies, we retrieved patient demographics (country of origin, age, gender), presenting complaints, comorbidities, medical interventions during hospitalization, imaging findings of SCAD, management, and outcomes. Using the Joanna Briggs Institute's critical appraisal criteria for case reports, the studies' quality was appraised.

Synthesis and data analysis

It was determined that a meta-analysis was not viable due to the expected heterogeneity of the included studies. Instead, a narrative synthesis of the data with minimal descriptively pooled analysis, consisting of a systematic review and summary of findings, was performed. The clinical characteristics, imaging findings, treatment, and outcomes of TTS associated with SCAD were examined descriptively and presented in tabular format. Categorical data were displayed as numbers or percentages, whereas continuous data were displayed as means with standard deviations or medians with interquartile ranges. Excel was utilized for every descriptive statistic.

Synthesis of data

The data were synthesized by summarizing the features of the included studies, including the number of patients, gender distribution, age range, and the presence of co-morbidities. In addition, the imaging findings of SCAD, treatment, and results of TTS were presented.

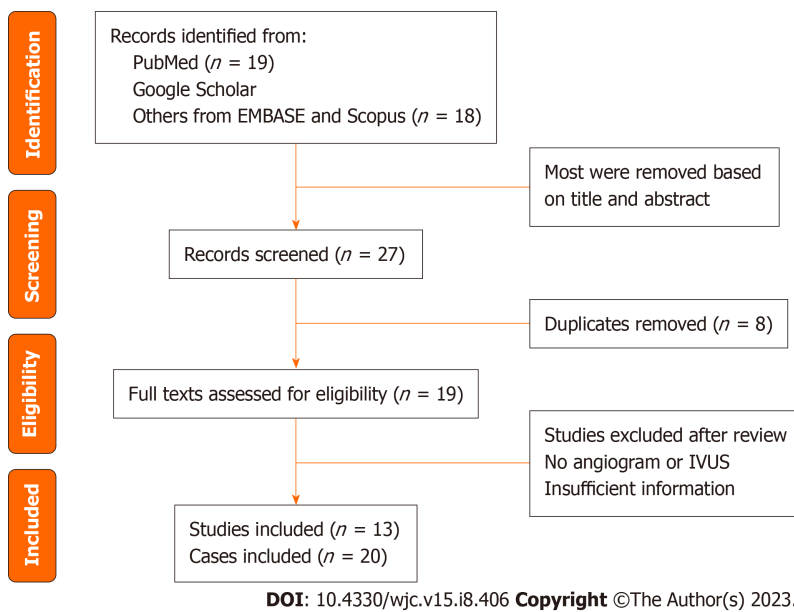


Figure 1 PRISMA flow diagram. IVUS: Intravascular ultrasound.

Quality assessment

The quality of the included studies was evaluated using the Joanna Briggs Institute's checklist for critical appraisal of case reports. Two reviewers examined the papers separately, and disagreements were resolved through consensus or contact with a third reviewer. Considering this is a systematic study of previously published case reports, ethical approval was not mandatory.

RESULTS

Twelve articles describing 20 female patients for the analysis were selected[4-15]. The mean age of the reported patients was 56.2 ± 9.07 years (range 36-70 years) out of which 40% of patients were elderly ($n = 8$, > 60 years). Out of the reported cases, 9 cases were from Canada, 3 cases each from USA, and Australia, 2 cases from Sweden and while Japan, Denmark and France contributed 1 case each. Only 5 reports identified emotional stressors in these cases while 4 reports showed physical stressors for TTS (Table 1).

Out of 20 cases, cardiovascular comorbidities were reported in 10 cases (hypertension in 9, hyperlipidemia in 2), and prediabetes in 1 case. 5 (25%) patients showed a history of smoking. The most common presenting symptom noticed was chest pain and discomfort in 9 cases (45%) and 10 (50%) cases presented with troponin-positive myocardial infarction. In 11 (55%) out of 20 cases, TTS and SCAD coexisted. Electrocardiogram was done in all 20 patients out of which 12 (60%) patients showed ST elevation and 3 (15%) showed T wave inversion. The baseline troponin level was measured in 19 cases and was elevated in all.

Out of 20, 9 (45%) cases showed apical akinesis and ballooning patterns of TTS on cardiac imaging. All 20 cases reported wall motion abnormalities on Echocardiography. In 19 (95%) out of 20 cases, SCAD was reported on coronary angiography. Out of 19 patients with SCAD, 10 showed involvement of left anterior descending (LAD) coronary artery, 2 showed diagonal artery, 2 showed left circumflex coronary (LCx) artery involvement, 2 showed marginal artery, 2 showed posterolateral artery, and a patient had a coexisting right coronary artery and LAD lesions. Out of 20 cases, data on left ventricular ejection fraction (LVEF) was reported in only 7 cases. The mean LVEF was $38.78 \pm 7.35\%$. Out of 20, 5 (25%) cases were treated with dual antiplatelet therapy. Only 3 (15%) cases out of 20 reported complications with 1 case each of occasional ectopic ventricular complexes, Mobitz II AV block, and ventricular fibrillation. All 20 cases survived and recovered (Table 2).

DISCUSSION

The coexistence of SCAD and TTS is rare and unclear[16]. The occurrence of the two is not coincidental and is mostly related to one another. SCAD was noted in many cases after a careful angiographic review of patients with TTS as the initial diagnosis[17]. SCAD rarely causes acute coronary syndrome and on the contrary, TTS shows ACS-like symptoms with left ventricular wall motion abnormality (LVWMA) without any obstructive lesions[18]. However, according to the recent update in the criteria of International Takotsubo Diagnostic criteria, TTS is diagnosed in patients with pre-existing SCAD. 2.5% of the cases diagnosed with TTS with coronary angiography (CAG) met the criteria for diagnosis of SCAD in a retrospective review.

Table 1 Baseline characteristics and presentation of cases with spontaneous coronary artery dissection and takotsubo syndrome

Ref.	Country	Age	Clinical presentation	Cardiovascular comorbidity	Prediabetes (Yes/No)	Smoker (Yes/No)
VI Chou <i>et al</i> [5], 2015	Canada	59	Troponin positive MI	Yes	No	No
VII Chou <i>et al</i> [5], 2015	Canada	60	Troponin positive MI	No	No	No
VIII Chou <i>et al</i> [5], 2015	Canada	50	Troponin positive MI	Yes	No	No
IX Chou <i>et al</i> [5], 2015	Canada	50	Troponin positive MI	Yes	No	No
Y-Hassan <i>et al</i> [14], 2016	Sweden	61	Sudden onset of chest pain	No	No	No
Ghafoor <i>et al</i> [9], 2020	United States	52	Chest pain, Palpitations	No	Yes	No
Takeuchi <i>et al</i> [13], 2021	Japan	36	Left arm discomfort and convulsions	Yes	No	No
Blazak <i>et al</i> [4], 2022	Australia	65	Severe chest pain	Yes	No	No
Y-Hassan <i>et al</i> [15], 2018	Sweden	67	Chest pain, nausea, dyspnea	Yes	No	Yes
Fitouchi <i>et al</i> [7], 2022	France	49	Retrosternal chest pain radiating to the left arm	No	No	No
Johnson <i>et al</i> [10], 2018	United States	66	Chest pain, headache, and pain in her left jaw, left arm numbness	-	-	-
Desai <i>et al</i> [6], 2020	United States	67	Chest discomfort, shortness of breath	Yes	No	No
Frederiksen <i>et al</i> [8], 2020	Denmark	57	Left arm pain, chest discomfort, dyspnea, palpitation, elevated Bp	No	No	Yes
Sugito <i>et al</i> [12], 2020	Australia	56	Central chest pain	No	No	No
McGhie <i>et al</i> [11], 2020	Australia	56	Inferior STEMI	Yes	No	Yes

Common factors which contribute to the development of SCAD include extreme physical activity, drugs, fibromuscular dysplasia, multiparity, connective tissue disorders, hormonal therapy, and inflammatory conditions[19]. The reasons for their co-existence might be because SCAD and TTS have a common predilection in younger women[10,14]. Both are preceded by significant psychological or physiological stress and share similar findings clinically. Acute chest pain caused by SCAD can trigger physical stress leading to TTS. Post-ischemic myocardial stunning caused by SCAD extending beyond the dissected coronary artery supply region resulting in the consequent LVWMA is consistent with TS. Typically, both present with ACS - chest pain, ischemic electrocardiographic abnormalities, biomarker positivity, and wall motion abnormalities that subsequently normalize.

Interestingly, TTS and SCAD have congruent diagnostic, imaging, and histopathological findings post-ischemia[19]. Patients with TTS and SCAD both report having abnormal electrocardiogram findings initially with either ST elevation, T wave inversion, or both[15,20]. In addition, although the peak values are substantially lower in comparison to acute coronary syndrome, both disorders have elevated troponin levels similar to those in acute coronary syndrome[20]. Of the 20 cases included in the study, 12 were reported with ST elevation and 3 with T wave inversion and 19 of them reported a surge in baseline troponin levels. One of the most crucial diagnostic techniques for recognizing SCAD is invasive CAG which helps distinguish SCAD in three angiographic patterns, type 1 with the presence of a double lumen, type 2 with lumen narrowing, and type 3 with abrupt lumen narrowing mimicking an atherosclerotic lesion[21,22].

Echocardiography is one the most used imaging tool where the regional wall motion abnormalities are assessed that help differentiate between these two conditions[19,20]. The regional LVWMA with a distinctive circumferential pattern is the distinguishing feature of TTS that results in the ballooning of the left ventricle during the systole, besides, the coronary artery supply regions are discordant with the LVWMA in TTS[22]. Left ventricular ballooning can be characterized by an apical, mid-ventricular, basal, or localized pattern in TTS[22]. In SCAD, main lesions are observed in the LAD and its branches rather than the right coronary artery (RCA) or left circumflex artery (LCX)[17]. However, SCAD is argued to not have classical apical ballooning observed in TTS and the wall akinesia corresponds to only the regions supplied by the affected dissected artery which leads to reversible myocardial stunning[5]. This occurs because apical ballooning, a crucial hallmark of TTS, cannot be described by the dissection in LAD as it does not wrap around the cardiac apex instead the diagonal branches, LCX and RCA, correspond to the other locations coexistent in SCAD and TTS

Table 2 Investigations, complications, and outcomes of spontaneous coronary artery dissection takotsubo syndrome cases

Ref.	ECG	Troponin elevated?	Lesion & dissection involved which vessel?	LVgram	LVEF	DAPT (Yes/No)	SCAD and TTS coexist?	Complications	Final outcome
I Chou <i>et al</i> [5], 2015	STEMI	Yes	RPLA	N/A	-	No	-	No	Survived
II Chou <i>et al</i> [5], 2015	STEMI	Yes	1st obtuse marginal and 1st Dx	N/A	-	No	-	No	Survived
III Chou <i>et al</i> [5], 2015	Antero-lateral TWI	Yes	Distal LAD	N/A	-	No	-	No	Survived
IV Chou <i>et al</i> [5], 2015	NSVT	Yes	Distal LPL	N/A	-	No	-	No	Survived
V Chou <i>et al</i> [5], 2015	Antero-lateral TWI	Yes	1st Dx	N/A	-	No	-	No	Survived
VI Chou <i>et al</i> [5], 2015	STEMI	Yes	1st mid-Dx	N/A	-	No	-	No	Survived
VII Chou <i>et al</i> [5], 2015	Antero-lateral STD, TWI	Yes	Distal LAD, 3rd Dx	N/A	-	No	-	No	Survived
VIII Chou <i>et al</i> [5], 2015	VT	Yes	Distal LAD	N/A	-	No	-	No	Survived
IX Chou <i>et al</i> [5], 2015	STEMI	Yes	Distal LAD	N/A	-	No	-	No	Survived
Y-Hassan <i>et al</i> [14], 2016	STEMI	Yes	Dx	LV apical ballooning	-	None	Coexist	No	Survived
Ghafoor <i>et al</i> [9], 2020	STEMI	Yes	RCA and Distal LAD	Apical akinesis	50-55%	Yes	Coexist	Occasional ectopic ventricular beats	Survived
Takeuchi <i>et al</i> [13], 2021	STEMI	Yes	Middle to distal LAD	Apical ballooning	39%	Yes	Coexist	No	Survived
Blazak <i>et al</i> [4], 2022	NSTEMI	Yes	Dx	Apical akinesis	28%	None	Coexist	No	Survived
Y-Hassan <i>et al</i> [23], 2018	STEMI	Yes	Peripheral marginal branch	Circular mid-apical ballooning	26%	None	Coexist	No	Survived
Fitouchi <i>et al</i> [7], 2022	Sinus tachycardia	Yes	LAD	LV apical ballooning	45%	Yes	Coexist	No	Survived
Johnson <i>et al</i> [10], 2018	STEMI	Yes	-	Apical akinesis	41%	None	Coexist	V. fib	Survived
Desai <i>et al</i> [6], 2020	STEMI	N/A	Typical TTS pattern	Apical ballooning	N/A	None	Coexist	No	Survived
Frederiksen <i>et al</i> [8], 2020	NSTEMI	Yes	-	Apical akinesis	40%	Yes	Coexist	No	Survived
Sugito <i>et al</i> [12], 2020	STEMI	Yes	Typical TTS pattern	Circular mid-apical ballooning	N/A	None	Coexist	3:1 Mobitz II	Survived
McGhie <i>et al</i> [11], 2020	STEMI	Yes	Typical TTS pattern	LV apical ballooning	-	Yes	Coexist	N/A	Survived

ECG: Electrocardiogram; STEMI: ST-Segment Elevation Myocardial Infarction; NSTEMI: Non-ST-Elevation Myocardial Infarction; TTS: Takotsubo syndrome; LV: Left ventricle; RCA: Right coronary artery; LAD: Left anterior descending (LAD), DX diagonal branches; N/A: Not applicable.

[17]. In this review, cardiac imaging revealed apical ballooning and akinesia in 9 cases (45%), and 19 (95%) out of 20 cases, were diagnosed as SCAD on CAG. In a case series by Chou *et al* [5], several of these patients (particularly those with a long wrap-around LAD artery) with implicated mid to distal LAD artery, SCAD was found to have a large-segmental akinesia comparable to typical TTS (anterolateral, apical, and inferior akinesia/dyskinesia). The authors of the case series determined that the LVWMA in these 9 patients was consistent with the regions supplied by the dissected coronary arteries, and all 9 SCAD cases were misinterpreted as TTS[22].

Furthermore, because both the SCAD and TTS present as ACS, the majority of the SCAD and TTS are treated with a similar treatment of ACS (beta blockers, aspirin, angiotensin-converting enzymes, and/or angiotensin receptor blockers, and diuretics)[5]. Although the idea of using dual platelet therapy is controversial in SCAD, it is continued to be used in concern to the presence of thrombus within the blood vessel[21]. The majority of the lesions found in both SCAD and TTS culminate in 'restitution and integrum'[15].

The spontaneous resolution of LVWMA in hours to weeks is a defining trait of TTS[23]. In contrast to TTS, where angiographic abnormalities are frequently unchanged from prior investigations, SCAD exhibits acute and dynamic angiographic findings that resolve with time[5]. Interestingly in our review of the cases series, all 20 cases survived and recovered well with only one patient undergoing cardiac intervention and 3 cases reporting complications (case each of occasional ectopic ventricular complexes, Mobitz II AV block, and paroxysmal atrial fibrillation).

Several limitations should be acknowledged when evaluating the results of this systematic review. First, the evidence is based on case reports, which are susceptible to publication bias and may not reflect all patients with SCAD-associated TTS. Second, the quality of reporting in case reports is inconsistent and may not give comprehensive data on patient characteristics, comorbidities, and management. Thirdly, the small number of cases included in this analysis limits the findings' applicability to the larger population of patients with TTS or SCAD. Lack of established diagnostic criteria for SCAD and TTS may have led to misdiagnosis or underreporting of cases. The use of different imaging modalities in different investigations may have influenced the diagnostic precision and the reporting of the findings. In the absence of a control group, it is difficult to demonstrate a causal relation between SCAD and TTS. Further research with larger, more representative samples and established diagnostic criteria is required to confirm the results of this systematic review.

CONCLUSION

In conclusion, TTS and SCAD have peculiar similarities in clinical presentation, diagnosis, imaging findings, and management, thus, are misdiagnosed often. However, because of similar precipitant factors (physical and emotional stressors), both conditions can even co-exist. The angiographic and echocardiographic findings of SCAD can help differentiate between both conditions if interpreted with the familiarity of SCAD variants. Therefore, to avoid misdiagnosis and underreporting of SCAD, there is a need for further scientific literature to bring awareness and improve uncalled morbidity in the cohort.

ARTICLE HIGHLIGHTS

Research background

Takotsubo syndrome (TTS) and spontaneous coronary artery dissection (SCAD) have similar symptoms and etiologies, but their prognoses and outcomes are distinct. This systematic review examines the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients.

Research motivation

To examine the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients.

Research objectives

Our objective is to conduct a systematic review of available case reports on SCAD in order to investigate its potential association with TTS.

Research methods

SCAD-associated TTS case reports were reviewed after thoroughly screening PubMed, EMBASE, Scopus, and Google Scholar databases till January 2023. Case reports described demographics, comorbidities, imaging, management, and results.

Research results

Key findings include: Elderly patients constituted 30% of the sample, with a mean age of 56.2 years. Canada had the most cases (9), followed by the United States (3), Australia (3), and other countries. Emotional stressors were identified in only 5 cases, while physical triggers were observed in 4 cases. Half of the patients experienced chest discomfort, while a quarter were smokers. Over half of the cases (55%) had both TTS and SCAD. All 20 cases recovered and had a favorable prognosis.

Research conclusions

This study highlights the coexistence and clinical similarities of TTS and SCAD, therefore emphasizing the importance of further research, awareness as well as comprehensive angiographic testing for effective diagnosis and management.

Research perspectives

Further research with larger, more representative samples and established diagnostic criteria is required to confirm the results of this systematic review.

FOOTNOTES

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Real-time cardiovascular magnetic resonance-guided radiofrequency ablation: A comprehensive review

Konstantinos Tampakis, Sokratis Pastromas, Alexandros Sykiotis, Stamatina Kampanarou, Georgios Kourgiannidis, Chrysa Pyrpiri, Maria Bousoula, Dimitrios Rozakis, George Andrikopoulos

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Abstract

Cardiac magnetic resonance (CMR) imaging could enable major advantages when guiding in real-time cardiac electrophysiology procedures offering high-resolution anatomy, arrhythmia substrate, and ablation lesion visualization in the absence of ionizing radiation. Over the last decade, technologies and platforms for performing electrophysiology procedures in a CMR environment have been developed. However, performing procedures outside the conventional fluoroscopic laboratory posed technical, practical and safety concerns. The development of magnetic resonance imaging compatible ablation systems, the recording of high-quality electrograms despite significant electromagnetic interference and reliable methods for catheter visualization and lesion assessment are the main limiting factors. The first human reports, in order to establish a procedural workflow, have rationally focused on the relatively simple typical atrial flutter ablation and have shown that CMR-guided cavotricuspid isthmus ablation represents a valid alternative to conventional ablation. Potential expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact, taking into consideration the widespread use of substrate-based strategies. Importantly, all limitations need to be solved before application of CMR-guided ablation in a broad clinical setting.

Key Words: Interventional cardiac magnetic resonance; Image-guided ablation; Substrate ablation; Cavotricuspid isthmus; Catheter ablation; Tracking

Core Tip: Technologies and platforms for performing electrophysiology procedures in a cardiac magnetic resonance (CMR) environment have been developed and several human studies have demonstrated that CMR-guided catheter ablation is feasible for typical atrial flutter ablation. Expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact, taking into consideration the widespread use of substrate-based strategies. Importantly, several limitations need to be solved before application of CMR-guided ablation in a broad clinical setting. This article reviews the clinical implementation of real-time CMR-guided catheter ablation and discusses the potential benefits, challenges and future perspectives of this approach in the treatment of cardiac arrhythmias.

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) has progressively evolved to become an important tool in imaging for cardiac arrhythmias and its implementation is increasingly used[1-3]. By enabling cardiac visualization with augmented temporal and spatial resolution and detailed tissue characterization, CMR imaging identifies both atrial and ventricular arrhythmogenic substrates[1-3]. Accurate scar tissue characterization has been shown to enable prediction of catheter ablation outcome[3], selection of ablation targets for substrate-based procedures[4,5] and identification of gaps in previous ablation lines[5-7]. Moreover, magnetic resonance (MR) imaging may facilitate ablation by providing a detailed anatomical description as pulmonary venous drainage pattern while pre-procedural imaging has also been used for image integration[8,9]. Recent innovations permit visual assessment through a variety of approaches including late gadolinium enhancement, T1 and T2 mapping.

Increased attempts have been performed to use CMR for the guidance of invasive procedures[10]. CMR-imaging could enable major advantages when guiding in real-time cardiac electrophysiology (EP) procedures offering high-resolution anatomy, arrhythmia substrate, and ablation lesion visualization in the absence of ionizing radiation. Scar tissue characterization has a high correlation with the electroanatomic maps (EAM) obtained during the ablation procedures while CMR provides delimitation within the entire myocardial thickness compared with endocardial or epicardial surface electroanatomic maps alone[11,12]. Over the last decade, technologies and platforms for performing electrophysiology procedures in a CMR environment have been developed. To date, human reports on interventional CMR are limited to typical atrial flutter ablation as several limitations have not permitted a routine clinical use.

The aim of this article is to review the clinical implementation of real-time CMR-guided catheter ablation and to discuss the challenges and limitations in this early stage of this approach as well as the potential benefits and the future perspectives in the treatment of cardiac arrhythmias.

TECHNICAL ASPECTS

Performing procedures in a CMR environment and outside the conventional fluoroscopic laboratory posed technical, practical and safety concerns[13]. A number of limiting factors should be overcome as the development of magnetic resonance imaging (MRI) compatible ablation systems, the recording of high-quality electrograms despite significant electromagnetic interference and reliable methods for catheter visualization and lesion assessment.

Interventional CMR suite

To transform the pre-existing magnetic resonance imaging environment into an interventional cardiac MRI suite, all standard EP (recording system, displays and catheters) and anesthetic instruments should be replaced with non-ferromagnetic alternatives to avoid potential risks and adverse incidences of both patient and health care personnel (Figure 1)[13]. Ferromagnetic instruments that cannot be replaced, as the non-MRI compatible radio frequency (RF) generators should therefore positioned outside the scanner room (Figure 1E)[13,14]. Communication between the operators and the radiologist at the MRI console may be facilitated by a compatible wireless communication system.

Additionally, modifications are probably required to the electrical installation to comply with safety guidelines that include to a touch-voltage less than 10 mV, isolation transformers for all wall power outlets, and a 'protected earth' connection for every device[13].

Patient preparation, including femoral vein access and possible intubation, is performed in an adjacent zone outside the scanner room[13]. Importantly, a detailed procedural workflow should have been established for the safe



Figure 1 Full transformation of the pre-existing magnetic resonance imaging environment into an interventional cardiac magnetic resonance imaging suite. A: Pre-existing diagnostic magnetic resonance imaging (MRI) scanner room; B: Pre-existing diagnostic MRI control room; C: Transformed interventional cardiac magnetic resonance (iCMR) suite; D: Transformed iCMR control room. E: The non-MR compatible RF generator including cooling-pump positioned in the iCMR control room. EP, electrophysiological; iCMR, interventional cardiac MRI. Citation: Bijvoet GP, Holtackers RJ, Smink J, Lloyd T, van den Hombergh CLM, Debie LJB, Wildberger JE, Vernooij K, Muhl C, Chaldoupi SM. Transforming a pre-existing MRI environment into an interventional cardiac MRI suite. *J Cardiovasc Electrophysiol* 2021; 32: 2090-2096 [PMID: 34164862 DOI: 10.1111/jce.15128]. Epub 2021 Jul 4. Copyright © 2021 The Authors. *Journal of Cardiovascular Electrophysiology* published by Wiley Periodicals LLC. (Reproduced with permission)[13].

performance of the procedure and recognition and management of potential complications. Notably, CMR enables an early recognition of complications as pericardial effusion.

Catheter visualization

Catheter location in conventional EAM systems is visualized using magnetic-based sensing or impedance-based tracking and displayed on approximate geometries of cardiac chambers[15]. MR conditional diagnostic and ablation catheters are similar in appearance and function to conventional catheters, but include proprietary components to reduce MR-induced heating[16]. MR conditional catheters were initially created using a polyether block amide plastic body, copper wires and platinum electrodes[17] while the currently approved ablation catheter incorporates gold tip electrodes for energy delivery, recording of electrograms and pacing (Figure 2). During CMR-guided electrophysiology procedures, there are two methods of catheter visualization and intra-procedural guidance, active and passive catheter tracking.

Passive catheters are discerned by local susceptibility artifacts that are induced by para- or ferromagnetic materials placed near the tip of the catheter[18-20]. Optimized imaging protocols using a steady-state free precession imaging sequence at frame rates of 4-8 frames per second provide an adequate temporal resolution[18-20]. However, passive tracking permits a single plane real-time visualization[18,20]. Therefore, manipulation of the catheter requires a continuous manual selection of the appropriate image plane and a constant communication between the operator and the radiologist at the MR imaging console being time-consuming and prone to localization errors.

In contrast to passive tracking that is based on local susceptibility artifacts, active tracking uses integrated receiver lumenless solenoid micro-coils at the tip of the catheter to determine its location (Figure 2)[16,21,22]. These micro-coils act as point-source detectors of MR signals. Locating these coils is accomplished by acquiring the MR signal in the presence of applied magnetic field gradient and identifying the position of the most intense frequency-domain signal[16,22]. The main advantage of this technique is that enables automation of the tracking of the catheter for the localization of its position controlling the MRI scan plane in real-time (Supplementary material and Video). Moreover, high spatial resolution is provided using tracking rates up to 50 frames per second[16].

Electrogram fidelity in the MRI environment

Distortion of the electrograms within the magnetic field can make interpretation of both the surface electrocardiogram (ECG) and intra-cardiac electrograms (EGMs) unreliable[14,23,24]. Although hardware development over recent years has enabled ECG and EGMs acquisitions during MRI examination, interpretation and analysis of waveforms is limited. Signals are severely distorted during MRI scans due to the effects of magnetohydrodynamic (MHD) voltages, RF pulses and fast-switching gradient magnetic fields (Figure 3)[23,24].

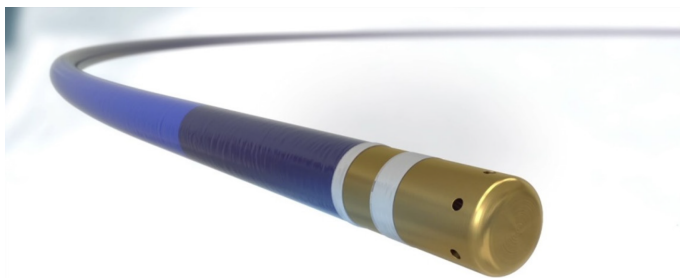
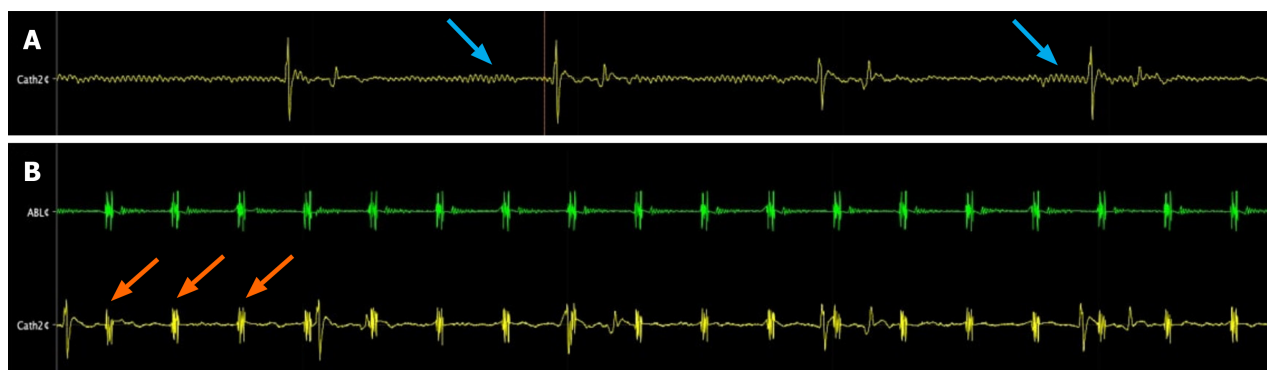


Figure 2 9 Fr. bipole irrigated-tip ablation catheter with two magnetic resonance receive coils in the distal end for active magnetic resonance tracking. (Reproduced with permission from <https://imricor.com>).



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Figure 3 Distortion of the electrograms within the magnetic field. A: Baseline noise of intra-cardiac electrograms recorded with the coronary sinus catheter (blue arrows indicate the maximally distorted signal); B: Gradient-induced artifacts that cause high frequency peaks during magnetic resonance scanning (orange arrows). ABLc: Ablation catheter; CATH2c: Coronary sinus catheter.

The MHD (or magnetofluid dynamic) effect is a result of the static magnetic field and the movement of charge carriers that induces a voltage across the blood vessels[23,24]. This induced voltage superimposes on the signals and appears primarily during the S-T phase of the cardiac cycle as it has been related to the blood ejection through the aortic arch which is perpendicular to the magnetic field and coincides with the occurrence of the T-wave of the ECG. The RF pulses (64-128 MHz) and the fast-switching gradients (33-50 mT/m, 20-100 T/m/s), which are required for MRI, both disturb the signals because of the voltages induced on the electrodes, wires and patient's body.

Passing electrograms through several levels of filtering limited the noise on EGMs, in a previous study[25]. In detail, low-pass RF filters to reduce the 64-MHz RF signal from the MRI scanner were combined with a series of active filters (a low pass filter of 300 Hz, a high-pass filter of 30 Hz and a 60-Hz notch filter) to reduce gradient signal-induced noise[23]. For low-pass filtering, the highest-quality EP signals was obtained at the frequency of 120 Hz despite lower peak-to-peak signal amplitude[26]. Algorithms that overcome the limitations of state-of-the-art methods and enable suppression of MR gradient artifacts and improve signal denoising quality have also been described including adaptive noise cancellation and non-linear Bayesian filtering[23,27].

Signal distortion should be taken into consideration especially for interpretation of EGMs after previous ablation attempts as double potentials (for typical flutter ablation) or abnormal potentials of low-amplitude as late potentials (for ventricular tachycardia ablation), although previous reports have presented detection of these ambiguous electrograms [21,28,29]. Moreover, as interpretation of surface ECG leads recording (that are usually connected to the recorder for rhythm monitoring and early detection of complications) may be impeded, additional monitoring should be used as pulse waveform.

Ablation lesion assessment

Lesions of radiofrequency catheter ablation can be visualized with CMR imaging[30,31]. The failure to create contiguous and durable transmural lesions has been held largely responsible for high recurrence rates[8,9]. Changes in tissue electrical impedance, electrode tissue contact and delivered power during conventional ablation techniques may not strongly correlated with the actual lesion size[32]. Electrical isolation may also be observed despite the presence of gaps in myocardial tissue after ablation that can be identified with MRI[6,7]. Thus, real-time lesion imaging is attractive as it could assess the ablation results and potentially provide a procedural endpoint.

Imaging with T2 mapping detects inflamed edematous tissue (Figures 4 and 5)[33]. However, T2-derived edema also corresponds to reversible lesions and is poorly correlated to long-term outcome as edema subsides progressively leading to electrical reconnections[34]. Several studies have reported on the extent of post-ablation T2-weighted signal that is greater in extent than delayed enhancement and overlaps with the areas of irreversible injury[30,31].

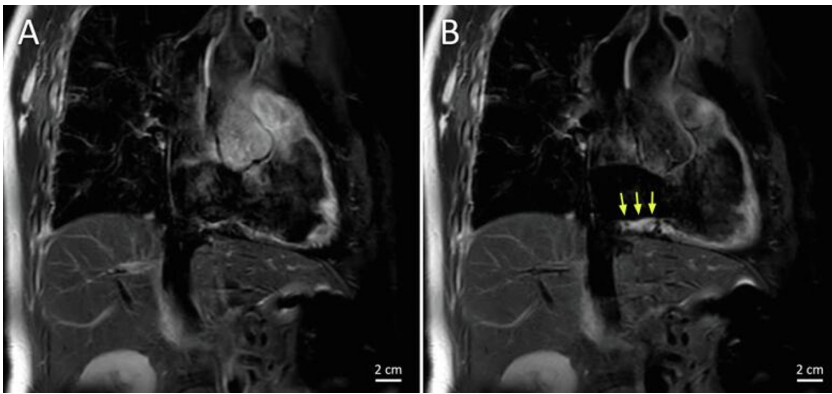


Figure 4 Imaging with T2 mapping detects inflamed edematous tissue. A and B: T2-weighted magnetic resonance images of the cavotricuspid isthmus in the RAO view before (A) and after (B) ablation showing edema in the ablation lesions, indicated by the yellow arrows. Citation: Bijvoet GP, Holtackers RJ, Nies HMJM, Muhl C, Chaldoupi SM. The role of interventional cardiac magnetic resonance (iCMR) in a typical atrial flutter ablation: The shortest path may not always be the fastest. *Int J Cardiol Heart Vasc* 2022; 41: 101078. [PMID: 35800043 DOI: 10.1016/j.ijcha.2022.101078]. Copyright © 2022 The Authors. Published by Elsevier B.V. (Reproduced under the terms of the Creative Commons CC-BY license)[44].

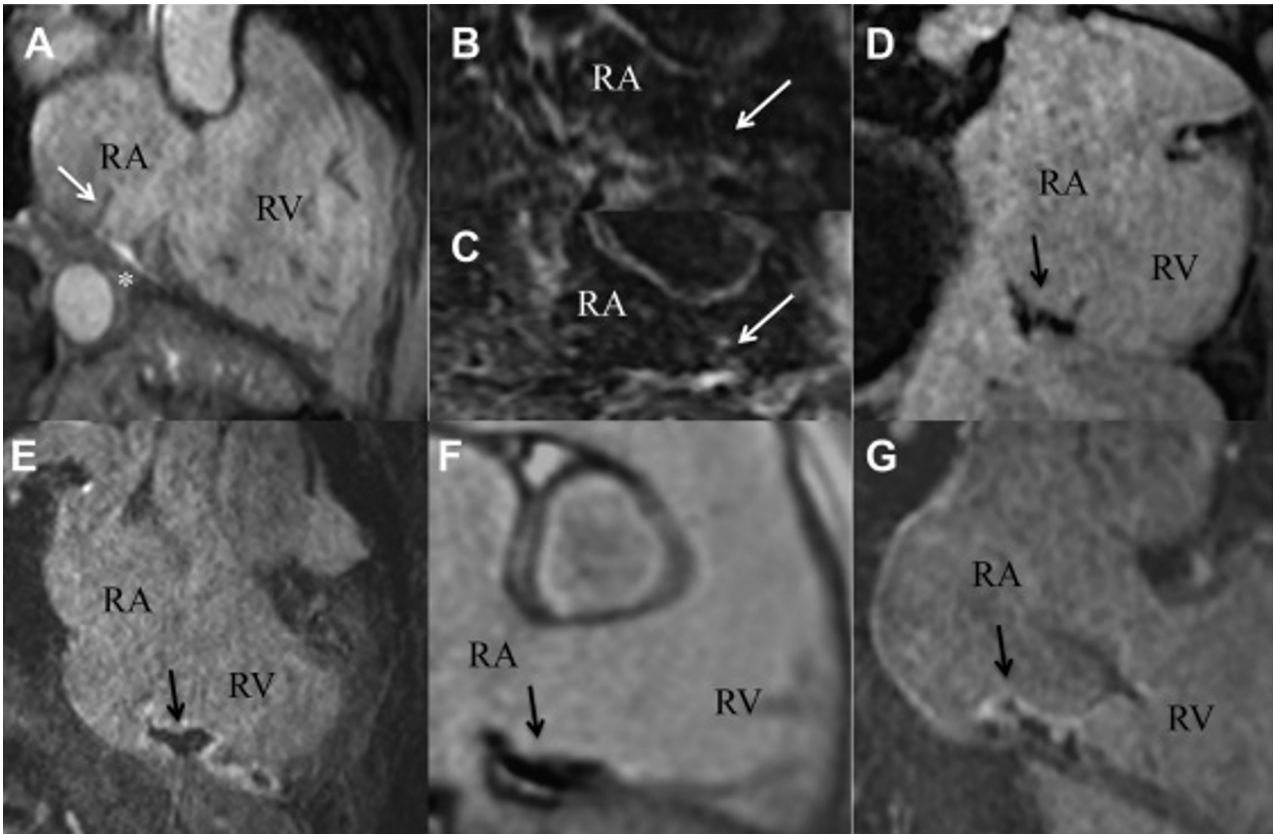


Figure 5 Acute lesion after radiofrequency ablation of the right cavotricuspid isthmus. A: Balanced steady-state free precision sequence image of the cavotricuspid isthmus (CTI) immediately after ablation. White asterisk indicates pericardial effusion. White arrow indicates a prominent eustachian valve; B and C: T2-weighted images preablation (B) and postablation (C) showing signal intensity enhancement of the isthmus line (white arrows); D: Noncontrast enhanced T1-weighted image of the CTI depicts acute necrotic lesions as signal intensity loss (black arrow); E: Postcontrast early enhancement image shows hypoenhanced myocardium localized at the CTI, known as a microvascular obstruction as an acute ablation lesion sign; F: Phase-sensitive inversion recovery image depicts acute ablation lesion in terms of black, hypoenhanced myocardium; G: Postcontrast late gadolinium enhancement images led to partially enhanced radiofrequency ablation lesions (white edge) with black necrotic core (black arrow). Citation: Ulbrich S, Huo Y, Tomala J, Wagner M, Richter U, Pu L, Mayer J, Zedda A, Krafft AJ, Lindborg K, Piorkowski C, Gaspar T. Magnetic resonance imaging-guided conventional catheter ablation of isthmus-dependent atrial flutter using active catheter imaging. *Heart Rhythm* 2022; 3: 553-559 [PMID: 36340492 DOI: 10.1016/j.hrro.2022.06.011]. Copyright © 2022 Heart Rhythm Society. Published by Elsevier Inc. (Reproduced under the terms of the Creative Commons CC-BY license)[40].

Late contrast-enhancement is used to detect lesion necrosis and T1-weighted imaging is thought to reflect true procedural success determining reversibility of lesions (Figure 5)[33]. However, the use of gadolinium-based techniques has significant disadvantages related to wash-in and wash-out kinetics of this contrast agent[35]. Late contrast-enhanced imaging demonstrates higher contrast-to-noise ratio between normal myocardium tissue and the lesion. However, edematous tissues as well as previous fibrotic areas can also become enhanced, impeding identification of gaps between lesions. Furthermore, estimation of complete delayed enhancement is time-consuming. Measurements during the initial phase of contrast void overestimate the transmural extent of lesions while regions of micro-vascular obstruction acquired approximately 26 min after contrast administration to accurately predict the chronic lesion volume in a previous report [30,36]. Finally, repeated injections of gadolinium-based agents in a single session is limited by clinical restrictions in their dosage, as well as effects on imaging from accumulated contrast agent.

In this way, there has been interest in the development of intrinsic (non-contrast)-based methods for ablation lesion assessment[30]. Imaging with non-contrast-enhanced T₁-weighted pulse sequence with long inversion time was demonstrated to produce images of ablation lesions with readily visible contrast between the lesion core and normal myocardium and improved image quality for visualization of both lesions and anatomy (Figure 5)[30]. Importantly, unlike contrast-enhanced imaging, in which enhancement pattern changes over time, non-contrast based techniques can be repeated multiple times during a procedure.

MR thermometry is a technique for the monitoring of thermal treatments that utilizes the temperature dependent proton resonant frequency shift that occurs in water molecules[37]. MR thermometry has been shown to provide a direct assessment of ablation lesion extent in the myocardium[37]. The dimensions of the thermal lesions measured on thermal dose images were correlated with T1-weighted images acquired immediately after the ablation and at gross pathology in an animal study, although prediction of the lesion durability remains unclear[37].

Procedural workflows for real-time CMR-guided ablation of the cavotricuspid isthmus (CTI) have been proposed[21, 38,39]. Pre-ablation balanced steady-state free precession three dimensions (3D) whole heart (bSSFP-3DWH) sequences without contrast provide the anatomy of cardiac cavities and large thoracic vessels with a selected acquisition window in ventricular diastole. Segmentation techniques may be used to derive the right atrial contour of this acquisition for integration into a navigation system. As a baseline for post-ablation imaging, T2-weighted images are also acquired prior to ablation. For guidance of the ablation catheter, the optimal planes are selected for the visualization of the CTI. A four-chamber view depicts the tricuspid valve and the distance to the interatrial septum while a long axis view the entire CTI length[38]. Views similar to the standard fluoroscopy views may also be used[39]. During active tracking, a dedicated sequence permits detection of the tip of the catheter and enables its manipulation along the CTI. A catheter is also placed into the coronary sinus for pacing maneuvers in order to verify isthmus block. For post-procedural imaging, the above-mentioned methods have been described. Imaging with non-contrast-enhanced T1-weighted pulse sequence with long inversion time can be performed multiple times in case of identified gaps. Gadolinium may also be administered in the end of the procedure for lesion assessment.

CLINICAL IMPLEMENTATION OF CMR-GUIDED ABLATION

Over the last two decades, substantial progress has been achieved in real-time CMR-guided electrophysiology studies and ablation procedures. In Tables 1 and 2, reported animal and human studies are presented. Following successful experimental reports, several human studies have demonstrated that CMR-guided catheter ablation is feasible without fluoroscopic guidance and enables the concurrent visualization of the targeted anatomical structure and substrate as well as the ablation lesion. The first human reports, in order to establish a procedural workflow, have rationally focused on typical atrial flutter ablation taking into consideration the relatively simple access to the right atrium and CTI[18,21,28,38, 40].

Cavotricuspid isthmus dependent atrial flutter ablation

Reports of conventional radiofrequency catheter ablation of CTI-dependent atrial flutter have revealed a high acute success rate up to 95% and a low recurrence rate[41,42]. Moreover CTI-ablation is a relatively safe procedure with low risk of complications. However, difficult cases of initial failed ablation and persistent CTI conduction are occasionally encountered. A complex isthmus anatomy has been considered as a cause of failure to achieve a complete ablation line [43]. Isthmus pouches that are frequently present, a prominent Eustachian ridge and large pectinate muscles may impede catheter stability and navigation to target sites leading to poor tissue contact and low RF energy delivery (Figures 5A and 6). CMR-guidance provides visualization of these anatomical obstacles and enables the optimal target ablation line selection taking also into consideration the length and thickness of the lateral, medial and septal CTI portion[44].

Despite initial difficulties due either to technical issues or to unachievable procedural endpoint and requirement of ablation completion under fluoroscopic guidance[18,21,28], the most recent and larger studies have shown that CMR-guided CTI ablation represents a valid alternative to conventional ablation with an acute success rate of 93% to 100%[38, 40]. Procedural times were comparable with fluoroscopy-guided treatment with similar results with regards to direct procedural success and short-term follow-up in a comparative study[38]. A steep learning curve was also demonstrated with a small number of procedures needed to achieve a level of competency and a meaningful gradual reduction of procedural duration[38].

Future perspectives

To date, no human studies have evaluated the use of real-time CMR-guided ablation apart from procedures performed

Table 1 Published animal studies on real-time cardiac magnetic resonance guided ablation

Ref.	n	Subject	Cardiac chamber/site	Procedure type
Lardo <i>et al</i> [31], 2000	6	Mongrel dog	RV apex	Ablation
Nazarian <i>et al</i> [25], 2008	10	Mongrel dog	RA, His bundle, RV	EP study
Nordbeck <i>et al</i> [60], 2009	8	Swine	RA, RV, AV node	Ablation
Hoffmann <i>et al</i> [61], 2010	20	Swine	CTI	Ablation
Nordbeck <i>et al</i> [62], 2011	9	Swine	CTI	Ablation
Vergara <i>et al</i> [63], 2011	6	Swine	RA, LA	Ablation
Ranjan <i>et al</i> [6], 2011	7	Mongrel dog	RA	Ablation
Ganesan <i>et al</i> [64], 2012	11	Sheep	PV, CTI	Ablation
Grothoff <i>et al</i> [65], 2017	14	Swine	RA, LA, AV node	Ablation
Krahn <i>et al</i> [33], 2018	12	Swine	LV	Ablation
Mukherjee <i>et al</i> [58], 2018	6	Swine	LV epicardium	Ablation
Chubb <i>et al</i> [21], 2017	5	Swine	CTI	Ablation
Lichter <i>et al</i> [53], 2019	8	Canine	PV, SVC, focal	(Cryo)ablation

AV: Atrioventricular; CTI: Cavotricuspid isthmus; EP: Electrophysiology; LA: Left atrium; PV: Pulmonary veins; SVC: Superior vena cava; RV: Right ventricle; RA: Right atrium.

Table 2 Published human studies on real-time cardiac magnetic resonance guided ablation

Ref.	n	Cardiac chamber/site	Procedure type
Nazarian <i>et al</i> [25], 2008	2	RA	EP study
Sommer <i>et al</i> [20], 2013	5	RA	EP study
Grothoff <i>et al</i> [18], 2014	10	CTI	Ablation
Hilbert <i>et al</i> [28], 2016	6	CTI	Ablation
Chubb <i>et al</i> [21], 2017	10	CTI	Ablation
Paetsch <i>et al</i> [38], 2019	30	CTI	Ablation
Ulbrich <i>et al</i> [40], 2022	15	CTI	Ablation

CTI: Cavotricuspid isthmus; EP: Electrophysiology; RA: Right atrium.

for typical atrial flutter. Broadening the application in the field of ventricular tachycardia (VT) would be of essential impact considering the widespread use of substrate-based strategies in VT ablation[45-47]. In the context of structural heart disease, surviving myocardium within areas of scar provide a substrate for reentry circuits[48]. Substrate-based ablation strategies have been shown to be as equally effective as activation mapping, which is often limited by haemodynamic instability and non-inducibility[49]. Even substrate ablation based only on the integration of pre-procedural CMR has been shown to be feasible and efficient while recent studies have shown improved VT recurrence-free survival compared to standard ablation[50,51]. Importantly, the information obtained from the CMR shows the wall distribution of the scar within the entire myocardial thickness[11]. Therefore, implementation of real-time CMR-guidance could increase the efficacy of VT ablation contributing also to deciding on the optimal approach during the procedure (endocardial, epicardial or combined). The VISABL-VT, a prospective, single-arm, multi-center trial will investigate the safety and efficacy of RF ablation of ventricular tachycardia associated with ischemic cardiomyopathy in the CMR environment (ClinicalTrials.gov Identifier: NCT05543798).

Towards the application of CMR-guided ablation in the field of atrial fibrillation, an MRI-compatible cryoablation system has been developed by removing all ferromagnetic components (as the circular mapping catheter) of a commercially available cryoballoon, implementing a compatible steering mechanism for balloon deflection and placing the console for the system outside the scanner room[52]. A recent animal study has shown that the real-time CMR-guided cryoablation of the pulmonary veins is feasible and provides the ability to visualize the freeze-zone formation during the freeze cycle[53]. Pulmonary vein reconnection has been reported as the main cause of arrhythmia recurrence and thus, durable isolation has been a key determinant of clinical outcome in patients undergoing catheter ablation for atrial fibril-

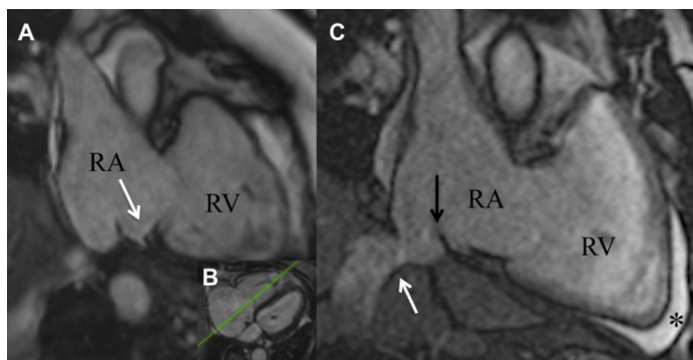


Figure 6 Isthmus pouches that are frequently present, a prominent Eustachian ridge and large pectinate muscles may impede catheter stability and navigation to target sites leading to poor tissue contact and low radio frequency energy delivery. A and B: Septal pouch (white arrow) of the cavotricuspid isthmus in a balanced steady-state free precision sequence image [as visualized in the transversal plane (B)]; C: Kinking of the vena cava inferior junction in the right atrium (white arrow) and a eustachian valve (black arrow) was found. Anterior to the right ventricular apex, a pre-existing pericardial effusion was located (asterisk). Citation: Ulbrich S, Huo Y, Tomala J, Wagner M, Richter U, Pu L, Mayer J, Zedda A, Krafft AJ, Lindborg K, Piorkowski C, Gaspar T. Magnetic resonance imaging-guided conventional catheter ablation of isthmus-dependent atrial flutter using active catheter imaging. *Heart Rhythm* O2 2022; 3: 553-559 [PMID: 36340492 DOI: 10.1016/j.hrroo.2022.06.011]. Copyright © 2022 Heart Rhythm Society. Published by Elsevier Inc. (Reproduced under the terms of the Creative Commons CC-BY license)[40].

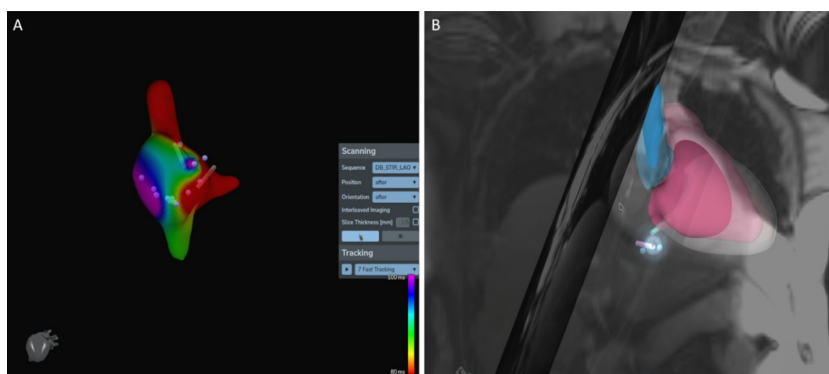


Figure 7 Electroanatomic mapping systems compatible for use inside a magnetic resonance scanner have been developed. A: 3D electroanatomical activation mapping; B: Integration with real-time cardiac magnetic resonance imaging planes. (Reproduced with permission from <https://imricor.com>).

lation[54]. It has also been demonstrated that electrical isolation may be observed due to local tissue architecture and/or anisotropy despite the presence of gaps in myocardial tissue and the recovery of conductivity can potentially lead to arrhythmia recurrence[6]. MRI has been shown to be able to identify gaps in ablation lines[54] while a report using real-time MR thermometry and thermal dosimetry demonstrated a strong correlation between thermal lesion and post-ablation T1-w images as well as with measurements at gross pathology[37]. Although further investigation is warranted, if MRI is able to assess lesion quality and durability, real-time CMR-guidance could improve effectiveness of catheter ablation.

However, several limitations should be solved before an extended application of CMR-guided ablation including the requirement of compatible tools as defibrillators and trans-septal needles, the scarce clinical data and safety concerns posed by performing procedures with high complication rate outside the conventional environment. Custom-made actively tracked needles (incorporated a receiver antenna) have been described to enable transseptal puncture under real-time CMR guidance[55]. Recently, a deflectable intracardiac MRI-compatible guiding-sheath was developed to accelerate imaging during CMR-guided electrophysiological interventions while real-time CMR-guided pericardiocentesis using commercially available passive access titanium needles has also been described[56,57].

EAM systems compatible for use inside an MR scanner have been developed (Figure 7)[58,59]. The achievement of active tracking opened up all the strengths of fast EAM, including activation and voltage mapping[21]. Integration with real-time imaging of cardiac anatomy, arrhythmia substrate and ablation lesions permits a combination of electrophysiological and anatomic information. However, further innovation of these tools may be warranted in order to be comparable to the conventional mapping systems including signal fidelity and modules for correction of annotation.

CONCLUSION

Real-time CMR-guided ablation could offer a number of benefits including not only radiation-sparing procedures, but also evaluation of cardiac anatomy and substrate as well as assessment of ablation lesion formation, although further research is warranted for confirming the above-mentioned potential advantages. The feasibility of CMR-guided CTI ablation has already been demonstrated and potential expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact. However, several limitations need to be solved before application of CMR-guided ablation in a broad clinical setting, including signal fidelity and compatible tools, while innovations in EAM integration could enable the combination of the advantages of conventional electrophysiological and substrate-based approaches.

FOOTNOTES

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Retrospective Study

Remdesivir, dexamethasone and angiotensin-converting enzyme inhibitors use and mortality outcomes in COVID-19 patients with concomitant troponin elevation

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Abstract

BACKGROUND

There are indications that viral myocarditis, demand ischemia, and renin-angiotensin-aldosterone system pathway activation play essential roles in troponin elevation in coronavirus disease 2019 (COVID-19) patients. Antiviral medications and steroids are used to treat viral myocarditis, but their effect in patients with elevated troponin, possibly from myocarditis, has not been studied.

AIM

To evaluate the effect of dexamethasone, remdesivir, and angiotensin-converting enzyme (ACE) inhibitors (ACEI) on mortality in COVID-19 patients with elevated troponin.

METHODS

Our retrospective observational study involved 1788 COVID-19 patients at seven hospitals in Southern California, United States. We did a backward selection Cox multivariate regression analysis to determine predictors of mortality in our study population. Additionally, we did a Kaplan Meier survival analysis in the subset of patients with elevated troponin, comparing survival in patients that received dexamethasone, remdesivir, and ACEI with those that did not.

RESULTS

The mean age was 66 years (range 20-110), troponin elevation was noted in 11.5% of the patients, and 29.9% expired. The patients' age [hazard ratio (HR) = 1.02, $P < 0.001$], intensive care unit admission (HR = 5.07, $P < 0.001$), and ventilator use (HR = 0.68, $P = 0.02$) were significantly associated with mortality. In the subset of patients with elevated troponin, there was no statistically significant difference in survival in those that received remdesivir (0.07), dexamethasone ($P = 0.63$), or ACEI ($P = 0.8$) and those that did not.

CONCLUSION

Although elevated troponin in COVID-19 patients has been associated with viral myocarditis and ACE II receptors, conventional viral myocarditis treatment, including antiviral and steroids, and ACEI did not show any effect on mortality in these patients.

Key Words: Coronavirus disease 2019; Troponin elevation; Remdesivir; Ace inhibitor; Steroids

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Core Tip: Myocarditis from direct viral injury or related to angiotensin-converting enzyme (ACE) II downregulation with subsequent hyperactivity of the renin-angiotensin-aldosterone system plays an essential role in troponin elevation in coronavirus disease 2019 (COVID-19) patients. However, the effect of antiviral medications and steroids used to treat viral myocarditis has not been well-studied in patients with elevated troponins, which this study sought to address. We found no significant difference in survival rates in COVID-19 patients with elevated troponin that received remdesivir, dexamethasone, or ACE inhibitors vs those that did not. The implication for practice is that treatment with various medications that could be beneficial in viral myocarditis did not show any mortality benefit in our study for COVID-19 patients with troponin elevation.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection continues to have a devastating global impact, with over 640 million confirmed infections, including 6.6 million deaths worldwide as of December 3, 2022[1]. The virus's predilection for the pulmonary system is a well-studied effect of its pathogenicity, evidenced in the 2003 outbreak in Southern China. Cardiac involvement has also been a widely observed sequela of the COVID-19 infection, conferring a worse prognosis on those with underlying cardiovascular disease[2,3]. Several studies have discussed the usefulness of measuring cardiac troponins (cTn) as a measure of myocardial injury and also as a method to stratify at-risk individuals. Myocardial injury is defined as an elevation in cTn above the 99% of the upper reference limit (URL). It is considered acute if there is a subsequent rise and/or fall of cTn values[2,4].

Recent literature has revealed the cytopathic, inflammatory, and thrombotic effects of COVID-19 suggesting the important role of inflammatory markers in disease progression and severity[5,6]. Particularly important is the correlation of the severity of the hyper-inflammatory response with a higher level of cTn, increasing the risk of mortality and complications in patients[2,7-9]. In addition, elevated C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, immunoglobulin G-induced protein 10, chemokine ligand 3 and tumor necrosis factor in COVID-19 patients, have been associated with cardiac injury and increased mortality[2,7-10].

Several mechanisms of myocardial injury leading to troponin elevation have been postulated. One such mechanism is direct virus-induced myocardial injury leading to myocarditis. In the initial phase, the virus facilitates its damage to the myocardium by direct lysis of cardiac myocytes[11]. This is typically followed by an intensified T-cell response, leading to further immune mediated myocyte injury and ventricular dysfunction[11]. Since 2005, it has been known that the SARS-CoV virus infects cells through the angiotensin-converting enzyme (ACE) II receptor. ACE II receptors are highly expressed in vascular endothelium, cardiac pericytes, and alveolar cells, which has lent support to this proposed mechanism of myocardial damage[11,12]. This observation has now sparked interest in evaluating whether medications such as ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) would benefit or harm those infected with SARS-CoV-2. In addition, SARS-CoV-2's indirect effects on the cardiovascular system have been studied extensively concerning ACE II downregulation leading to activation of the renin-angiotensin-aldosterone system (RAAS)[11]. Furthermore, ACE II catalyzes the conversion of angiotensin II to angiotensin I, a process that directly opposes the innate immune system's subsequent release of proinflammatory cytokines, vasoconstriction, pro-oxidants, pro-proliferative and profibrotic actions[11]. As such, there is interest in examining if inhibition of the ACE II enzyme with widely used antihypertensives, including ACEI and ARBs, would benefit COVID-19 patients as it stimulates the innate immune system, thus facilitating a more robust response to combat the underlying infection.

In summary, there are indications that viral myocarditis, demand ischemia, and RAAS pathway activation play essential roles in troponin elevation in COVID-19 patients. Antiviral medications and steroids are used to treat viral myocarditis, but their effect in patients with elevated troponin, possibly from myocarditis, has not been studied. Additionally, there is a lack of studies on the impact of ACEI use in patients with elevated troponin. Therefore, this

multicenter retrospective study aims to evaluate the effect of dexamethasone, remdesivir, and ACEI on mortality in COVID-19 patients with elevated troponin.

MATERIALS AND METHODS

We conducted a multicenter retrospective observational study at seven hospitals in Southern California, United States. The study enrolled 1788 consecutive COVID-19 patients admitted to the seven hospitals between March 2020 and August 2021 who had a troponin test on admission. All patients were confirmed to have COVID-19 infection through a positive polymerase chain reaction nasopharyngeal swab. We extracted relevant deidentified patient data using a SQL program from the electronic medical record, which included: Age, race, gender, comorbidities, date of hospital admission, date of discharge, laboratory results on admission, medications they received while on admission, heart rate, and disposition at discharge. Our primary outcomes were the predictors of troponin elevation in COVID-19 patients and the effect of dexamethasone, remdesivir, and ACEI on mortality in COVID-19 patients with elevated troponin. Elevated cTn diagnostic of myocardial infarction is when the levels exceed the 99th percentile of a normal, healthy reference population (URL). This value is determined for each specific troponin assay with appropriate quality control in each laboratory[13]. Based on our laboratory assay, a troponin I (cTnI) level above 0.4 ng/mL was considered elevated for our study.

We performed a univariate analysis of the independent variables, including patients' age, gender, race, length of hospital stay, comorbidities, the medication patients received while in the hospital, and laboratory results using means and percentages. Furthermore, we performed a bivariate analysis of the relationship between troponin elevation and different study variables using chi-square and *t*-test, with a *P* value of 0.05 considered significant. We then did a backward selection logistic regression to determine the factors associated with troponin elevation. Additionally, we did a backward selection Cox multivariate regression analysis using mortality as a dependent variable. For the logistic and Cox regression analysis, we initially included statistically significant or biologically plausible variables from the bivariate analysis, such as patients' age, sex, body mass index, comorbidities, intensive care unit (ICU) admission, and mechanical ventilation, as independent variables in the multivariate model. The effect was expressed in odds and hazard ratios (HRs) for the logistic and Cox regression, respectively. Hypothesis testing was done using a two-sided test, and an alpha value of 0.05 indicated statistical significance.

In the second phase of our analysis, we did the Kaplan Meier survival analysis in the subset of patients with elevated troponin comparing survival in patients that received dexamethasone, remdesivir, and ACEI with those that did not. Statistical analysis was done using IBM SPSS version 27. The WIRB-Copernicus Group institutional review board approved the study.

RESULTS

Descriptive statistics

Tables 1 and 2 show the descriptive statistics of continuous and categorical variables of the study population, including length of stay, age, body mass index (BMI), and gender. The mean age was 66 years and ranged from 20-110 years, and 58% were males. Patients' race was categorized into white, Asian, black, and others, with 64.4%, 6.1%, 4.5%, and 24.9%, respectively. The patients had underlying comorbidities, including hypertension (42.3%), diabetes (19.2%), chronic kidney disease (CKD) (24%), and congestive heart failure (CHF) (18.8%). The patients received different medications while on admission, including dexamethasone (68.2%), remdesivir (50.9%), and ACEI (19.4%). Troponin was elevated in 11.5% of the study subjects and 29.9% of the total study population expired.

Bivariate analysis

In the bivariate analysis of continuous variables, length of hospital stay (*P* = 0.007), CRP (*P* < 0.001), lactate dehydrogenase (LDH) (*P* < 0.001), ferritin (*P* = 0.03), creatine phosphokinase (CPK) (*P* = 0.01), platelet count (*P* = 0.02), white blood cell count (*P* < 0.001), potassium (*P* < 0.001) and total bilirubin were significantly associated with troponin elevation. Patients with elevated troponin were more likely to have increased inflammatory markers, including CRP, LDH, ferritin, and CPK. The length of stay was also higher in patients with elevated troponin. There was no difference in age, BMI, and oxygen saturation in patients with or without elevated troponin (Table 3).

In the bivariate analysis of categorical variables, mortality (*P* < 0.001), ventilator use (*P* < 0.001), ICU admission (*P* < 0.001), CKD (*P* < 0.001), and CHF (*P* < 0.001) were significantly associated with elevated troponin. Patients with elevated troponin were more likely to die, be admitted to ICU, or be placed on a ventilator. Additionally, those with CHF or CKD were more likely to have elevated troponin (Table 4).

Multivariate analysis

In the multivariate logistic regression analysis, elevated levels of LDH [odd ratio (OR) = 1, *P* = 0.004], underlying CHF (OR = 2.7, *P* < 0.001), and ICU admission (OR = 3.6, *P* < 0.001) were independently associated with elevated troponin. Additionally, in the Cox regression multivariate analysis, age (HR = 1.02, *P* < 0.001), ICU admission (HR = 5.07, *P* < 0.001), and ventilator use (HR = 0.68, *P* = 0.02) were significantly associated with mortality. However, Troponin elevation (HR = 1.25, *P* = 0.1) was not independently associated with mortality after adjusting for age, comorbidities like CHF, ICU admission, and inflammatory markers (Tables 5 and 6).

Table 1 Descriptive statistics of continuous variables

	<i>n</i>	Minimum	Maximum	Mean	SD
Length of stay	1788	1	117	11.77	11.73
Age	1788	20	110	66.36	16.36
Body mass index	1741	14.14	83.12	30.07	8.69
C-reactive protein	1575	0.05	54.38	14.60	9.57
Lactate dehydrogenase	1384	55	8180	487.45	525.15
Ferritin	1240	5.1	47560.8	1038.56	2187.49
Troponin	1788	0.01	32.78	0.49	2.41
Creatine phosphokinase	979	10	88961	755.30	4495.43
Platelet	1786	37	1176	328.47	138.68
White blood cell count	1787	2.4	80.7	16.12	9.05
Potassium	1513	2.70	8.50	4.82	0.84
Total bilirubin	1780	0.2	27.8	1.01	1.16

Subgroup analysis

In the Kaplan-Meier survival analysis of the subset of 205 patients with elevated troponin, the median survival in patients that received remdesivir (18 d) was higher than those that did not (14 d). However, this was not statistically significant ($P = 0.07$) (Figure 1A). Similarly, the median survival in patients receiving dexamethasone (16 d) was higher than in those not (14 d), but this was not statistically significant ($P = 0.63$) (Figure 1B). Finally, the median survival in patients on ACEI (16 d) was the same as those without ($P = 0.8$) (Figure 1C).

Furthermore, we did a Kaplan Meier analysis in the subset of patients with elevated concomitant troponin, CPK, and LDH, which would be expected in patients with significant myocarditis. However, similar to our analysis in those with elevated troponin, we found no difference in mortality between those that received dexamethasone ($P = 0.88$), ACEI ($P = 0.83$), or remdesivir ($P = 0.93$) and those that did not in this sub-group of patients.

DISCUSSION

COVID-19 has been reported to cause direct myocardial injury and myocarditis in some patients[14,15]. COVID-19 patients with myocarditis have increased troponin and non-specific ST-segment and T-wave changes. Echocardiogram typically shows global hypokinesis and pericardial effusion[14]. Thus, myocarditis mimics acute coronary syndrome, but the coronary arteries are usually normal on coronary angiogram. The gold standard for diagnosing myocarditis is histopathology of endomyocardial biopsy, an invasive procedure not often performed in clinical practice. Cardiac magnetic resonance imaging (MRI) is often used to diagnose myocarditis[14,16]. Antiviral medications, intravenous immunoglobulins, and immunosuppressants such as steroids and azathioprine have been used in treating viral myocarditis with limited evidence of benefit[16]. In our study, we did not do cardiac MRI to determine the proportion of patients with elevated troponin that have myocarditis. However, our Kaplan Meier analysis did not show any statistically significant difference in mortality in patients with elevated troponin who received steroids and those that did not. The role of steroids in myocarditis caused by COVID-19 is unclear, and the lack of steroid efficacy on mortality in patients with elevated troponin in our study could suggest that steroids may not play any significant role in COVID-19 induced myocarditis. However, we do not know the proportion of patients in our study with myocarditis, and the role of steroids in COVID-19 myocarditis needs to be further investigated.

Furthermore, studies have suggested a possible relationship between increased viral load and myocardial injury in COVID-19 patients. For example, in a study of hospitalized COVID-19 patients, those with detectable viremia were significantly more likely to have elevated troponin and myocardial injury than those without viremia[17]. Although another study did not find any relationship between the initial viral load and the incidence of myocardial injury in hospitalized COVID-19 patients, high viral load and myocardial injury were independent predictors of in-hospital mortality [18]. Remdesivir, a viral RNA polymerase inhibitor, significantly reduced the median recovery time of COVID-19 patients compared to placebo in the adaptive, randomized controlled Adaptive COVID-19 Treatment Trial-1 study[19]. However, there is limited data on how Remdesivir impacts cardiac injury. In the Kaplan-Meier survival analysis of the subset of patients with elevated troponin in our study, the median survival in patients that received remdesivir (18 d) was higher than those that did not (14 d). However, this was not statistically significant ($P = 0.07$). The lack of statistical significance could be due to our sub-group analysis being underpowered to detect a difference.

SARS-CoV-2 binds to the ACE II receptor (ACE II), which is highly expressed in the lungs and myocardium, and this has been postulated as a mechanism through which the virus causes direct damage to cardiac cells[20]. ACEI have been shown to upregulate the expression of ACE II in lung cells in animal studies. The mechanism is unclear but is possibly

Table 2 Descriptive analysis of categorical variable

	Frequency	Percent
Gender		
Female	749	41.9%
Male	1039	58.1%
Race		
Asian	109	6.1%
Black	81	4.5%
White	1152	64.4%
Others	446	24.9%
Expired		
No	1254	70.1%
Yes	534	29.9%
Ventilator use		
No	1352	75.6%
Yes	436	24.4%
Intensive care unit		
No	1328	74.3%
Yes	460	25.7%
Remdesivir		
No	853	49.1%
Yes	883	50.9%
Dexamethasone		
No	568	31.8%
Yes	1220	68.2%
Angiotensin converting enzyme inhibitor		
No	1441	80.6%
Yes	347	19.4%
Diabetes mellitus		
No	1444	80.8%
Yes	344	19.2%
Hypertension		
No	1032	57.7%
Yes	756	42.3%
Chronic kidney disease		
No	1355	76.0%
Yes	427	24.0%
Acute kidney injury		
No	1588	88.8%
Yes	200	11.2%
Congestive heart failure		
No	1451	81.2%
Yes	337	18.8%

Chronic obstructive pulmonary disease		
No	1678	93.8%
Yes	110	6.2%
Bradycardia		
No	823	46.0%
Yes	965	54.0%
Troponin elevation		
No	1583	88.5%
Yes	205	11.5%

Table 3 Bivariate analysis of the relationship between continuous variables and troponin elevation

	Troponin elevation	<i>n</i>	Mean	SD	<i>P</i> value
Length of stay	0	1583	11.46	11.44	0.007
	1	205	14.16	13.52	
Age	0	1583	66.14	16.49	0.08
	1	205	68.13	15.29	
Body mass index	0	1540	30.11	8.62	0.64
	1	201	29.80	9.20	
Oxygen on admission	0	1415	94.47	6.27	0.27
	1	187	94.20	6.69	
C-reactive protein	0	1393	14.23	9.50	< 0.001
	1	182	17.47	9.70	
Lactate dehydrogenase	0	1236	447.71	363.69	< 0.001
	1	148	819.34	1165.85	
Ferritin	0	1099	956.44	1859.08	0.03
	1	141	1678.58	3844.02	
Creatine phosphokinase	0	863	586.10	4245.13	0.01
	1	116	2014.03	5913.58	
Platelet	0	1582	331.24	138.55	0.02
	1	204	307.00	138.15	
WBC	0	1583	15.66	8.97	< 0.001
	1	204	19.76	8.88	
Potassium	0	1341	4.78	0.83	< 0.001
	1	172	5.07	0.92	
Total bilirubin	0	1577	0.95	0.83	0.004
	1	203	1.46	2.48	

WBC: White blood cell.

through decreasing angiotensin II, leading to indirect upregulation of ACE II[21,22]. Thus, there have been concerns that the use of ACEI in patients with COVID-19 will increase the risk of lung and myocardial injury. However, some human studies did not support the hypothesis that ACEI use increases ACE II expression and the risk of lung and myocardial injuries in COVID-19 patients[23]. Furthermore, the Kaplan-Meier analysis in our study showed no difference in survival in patients with elevated troponin who received ACEI and those who did not, suggesting that the use of ACEI should not be withheld even in patients with elevated troponin.

Table 4 Bivariate analysis of the relationship between categorical variables and troponin elevation

Variable	Troponin elevation		P value
	No	Yes	
Gender			
Male	918 (88.4%)	121 (11.6%)	0.78
Female	665 (88.8%)	84 (11.2%)	
Race			
Asia	96 (88.1%)	13 (11.9%)	0.38
Black	72 (88.9%)	9 (11.1%)	
White	1030 (89.4%)	122 (10.6%)	
Others	385 (86.3%)	61 (13.7%)	
Expired			
Yes	415 (77.7%)	119 (22.3%)	< 0.001
No	1168 (93.1%)	86 (6.9%)	
Ventilator			
Yes	334 (76.6%)	102 (23.4%)	< 0.001
No	1249 (92.4%)	103 (7.5%)	
Intensive care unit			
Yes	354 (77.0%)	106 (23.0%)	< 0.001
No	1229 (92.5%)	99 (7.5%)	
Diabetes mellitus			
Yes	314 (91.3%)	30 (8.7%)	0.08
No	1269 (87.9%)	175 (12.1%)	
Hypertension			
Yes	677 (89.6%)	79 (10.4%)	0.25
No	906 (87.8%)	126 (12.2%)	
Chronic kidney disease			
Yes	354 (82.9%)	73 (17.1%)	<0.001
No	1223 (90.3%)	132 (9.7%)	
Congestive heart failure			
Yes	279 (82.8%)	58 (17.2%)	< 0.001
No	1304 (89.9%)	147 (10.1%)	
Chronic obstructive pulmonary disease			
Yes	96 (87.3%)	14 (12.7%)	0.67
No	1487 (88.6%)	191 (11.4%)	
Bradycardia			
Yes	853 (88.4%)	112 (11.6%)	0.84
No	730 (88.7%)	93 (11.3%)	
Use of Remdesivir			
Yes	789 (89.4%)	94 (10.6%)	0.28
No	748 (87.7%)	94 (12.3%)	
Use of dexamethasone			
Yes	1069 (87.6%)	151 (12.4%)	0.08

No	514 (90.5%)	54 (9.5%)
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Table 5 Logistic regression on predictors of increased troponin elevation

	B	SE	Wald	df	Sig	Exp (B)	95%CI for EXP (B)	
							Lower	Upper
Lactate dehydrogenase	0.000	0.000	8.091	1	0.004	1.000	1.000	1.001
Congestive heart failure	0.991	0.239	17.170	1	0.000	2.694	1.686	4.305
Intensive care unit	1.278	0.232	30.359	1	0.000	3.591	2.279	5.659
Constant	-3.154	0.194	264.436	1	0.000	0.043		

95%CI: 95% confidence interval; df: Degree of freedom; SE: Standard error; Sig: Significance.

Table 6 Cox regression analysis showing predictors of mortality in coronavirus disease 2019 patients

	B	SE	Wald	df	Sig	Exp (B)	95%CI for Exp (B)	
							Lower	Upper
Age	0.022	0.004	26.460	1	0.000	1.022	1.014	1.031
Ventilator use	-0.378	0.157	5.830	1	0.016	0.685	0.504	0.931
Intensive care unit admission	1.624	0.164	97.657	1	0.000	5.074	3.677	7.003
Troponin	0.219	0.133	2.705	1	0.100	1.245	0.959	1.616

95%CI: 95% confidence interval; df: Degree of freedom; SE: Standard error; Sig: Significance.

In our study, elevated levels of LDH (OR = 1, $P = 0.004$), underlying CHF (OR = 2.7, $P < 0.001$), and ICU admission (OR = 3.6, $P < 0.001$) were independently associated with elevated troponin. This finding is similar to former studies that showed that elevated troponin, increased age, and co-morbidities are predictors of ICU admission[24]. This was further collaborated by a meta-analysis of 23 studies that showed that patients with elevated troponin had a significantly increased risk of severe disease and ICU admission [risk ratio (RR) = 5.57, 95% confidence interval (95%CI): 3.04 to 10.22, $P < 0.001$; RR = 6.20, 95%CI: 2.52 to 15.29, $P < 0.001$][25]. Furthermore, our study showed that elevated troponin was associated with CHF, similar to previous studies that showed that patients with troponin elevation were older, with more co-morbidities[26].

In our study, there was increased mortality in patients with troponin elevation (HR = 1.25, $P = 0.1$), although this was not statistically significant at a P value of 0.05. The lack of statistical significance could be related to the fact that our study was underpowered to detect a difference. It could also be that patients in our study differ from those in previous studies. For example, while the proportion of patients in our study with elevated troponin was 11%, a meta-analysis of prior studies has shown an average of 31% (range 23%-38%)[27], 22.9%[28], and 27% (range 9%-51%)[29]. Studies have found that elevation of high-sensitivity troponin and traditional troponin assays are associated with increased mortality in COVID-19 patients[27-31]. Patients with elevated troponin had significantly increased odds of death than those with normal troponin independent of elevation in inflammatory markers and cardiovascular co-morbidities[27-31].

Our study has several limitations. Firstly, in the subgroup analysis, we dealt with a small sample size which may limit the overall power of the study. Secondly, troponin was assessed on admission and was not monitored for the duration of the patient's hospital stay, which may impact the lack of association observed between troponin elevation and mortality. Thirdly, in the analysis between ACEI use and troponin elevation, our data only reflects patients placed on an ACEI during their hospital stay. We did not stratify patients on whether they were on the medication previously, and it is possible some patients on ACEI at home might not have been started on it in the hospital. This might have resulted in a misclassification bias and affected the study outcome. Finally, this research is an observational study, and there might have been unmeasurable variables that might have confounded the study outcome. Also we did not conduct cardiac MRI to confirm our findings of myocarditis but based that on inferential analysis.

CONCLUSION

Although elevated troponin in COVID-19 patients has been associated with viral myocarditis, conventional viral myocarditis treatment, including steroids and antiviral, did not affect mortality in these patients. In addition, previous

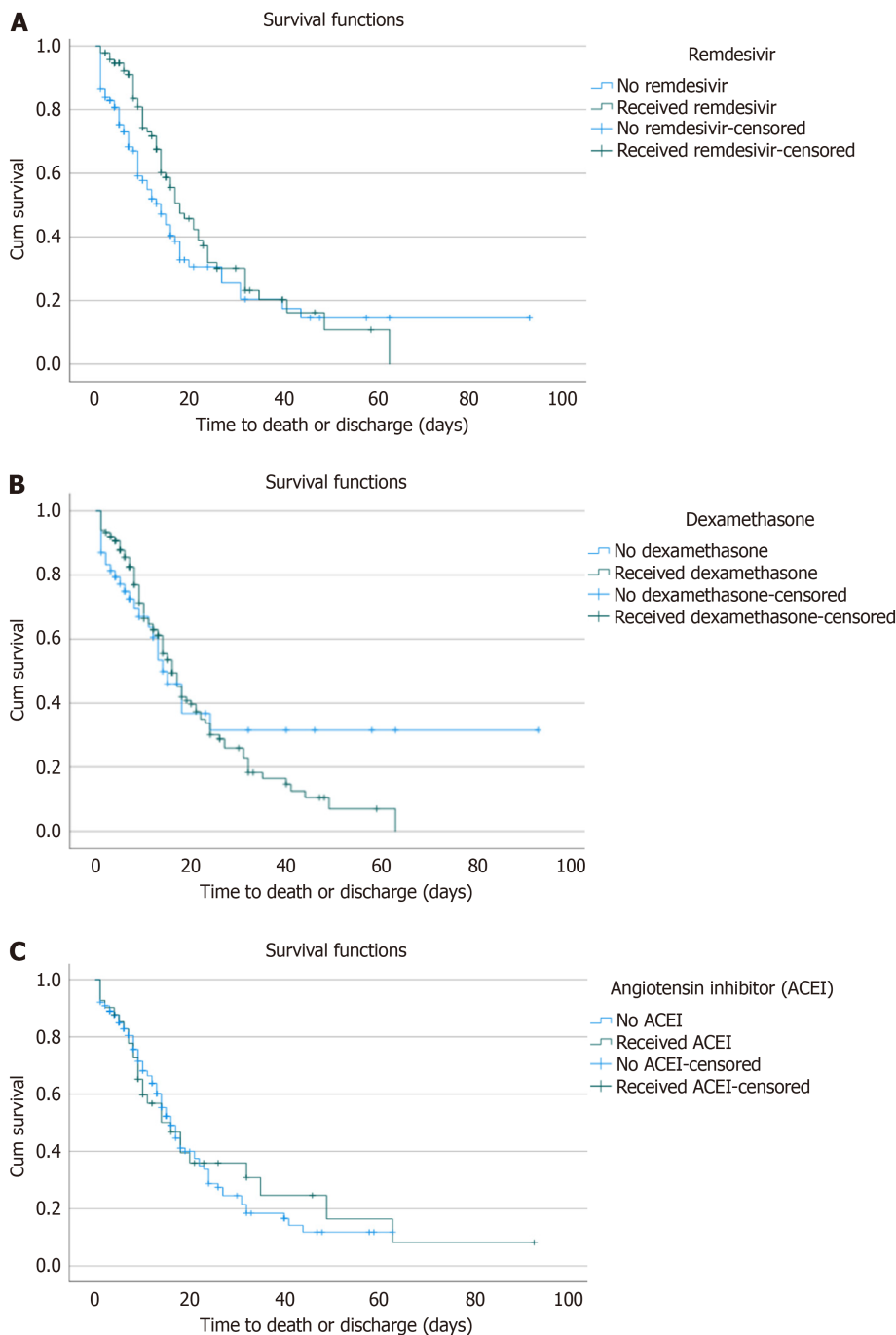


Figure 1 Kaplan Meier. A: Remdesivir use and mortality in patients with troponin elevation; B: Dexamethasone use and mortality in patients with troponin elevation; C: Angiotensin-converting enzyme inhibitors use and mortality in patients with troponin elevation. ACEI: Angiotensin-converting enzyme inhibitors.

studies have suggested a possible association between COVID-19 viral load and myocardial injury; however, we found no statistically significant difference in survival in patients with elevated troponin treated with remdesivir and those that were not. Furthermore, our study suggested that ACEI should not be withheld even in patients with elevated troponin because it did not negatively or positively affect survival.

ARTICLE HIGHLIGHTS

Research background

Several studies have proposed that troponin elevation seen in coronavirus disease 2019 (COVID-19) patients is due to an interplay between viral myocarditis, demand ischemia and renin-angiotensin-aldosterone system pathway activation. This creates the hypothesis that the use of steroids, antivirals and angiotensin-converting enzyme inhibitors (ACEI) in

patients with COVID-19 infection and troponin elevation would impact mortality outcomes.

Research motivation

The COVID-19 pandemic has had a monumental global impact and resulted in several deaths worldwide. The motivation of this study was to analyze if the use of the steroids, antivirals and ACEI would improve survival in patient with COVID-19 infection and troponin elevation.

Research objectives

Our main objective was to analyze any differences in mortality in our subjects, in the hopes of adding to existing knowledge and creating a standardized treatment protocol in patients with COVID-19 and troponin elevation.

Research methods

Our study design was a retrospective observational study consisting of 1788 COVID-19 patients at seven hospitals across Southern California. To determine the predictors of mortality in our subjects, we did a backward selection cox multivariate regression analysis. Furthermore, to analyze survival in the subset of patients with troponin elevation we did a Kaplan Meier analysis comparing those that received treatment with steroids, remdesivir and ACEI and those that did not.

Research results

Though the beneficial role of steroids in the treatment of COVID-19 has been established, our study did not show any statistically significant difference in mortality in patients with elevated troponin who received steroids and those that did not. Therefore, the role of steroids in myocarditis caused by COVID-19 is still unclear and needs further investigation. On the other hand, our study showed improved survival in COVID-19 patients with elevated troponin that received remdesivir, although this was not statistically significant.

Research conclusions

Although the mechanism of troponin elevation in COVID-19 patient has been linked to viral myocarditis and renin-angiotensin-aldosterone system activation, the novel treatments of these subsequent pathologies including steroids, remdesivir and ACEI showed no significant survival benefit in our study. This creates the theory that there are other mechanisms at play guiding this complex interaction.

Research perspectives

Although our study did not show a statistically significant mortality benefit with the use of steroids and remdesivir, our sub-group analysis was limited by a small sample size, so further studies on the effect of remdesivir in the sub-set of COVID-19 patients with elevated troponin using a larger population will be beneficial.

FOOTNOTES

Author contributions: Umeh CA, Maoz H, Obi J, Dakoria R, Patel S, Maity G and Barve P conceptualized and revised the study design; Umeh CA analyzed the data; Maoz H, Umeh CA, Obi J, Dakoria R, Patel S, and Maity G, wrote the first draft of the paper; Barve P and Umeh CA, reviewed and revised the paper; Maoz H led and coordinated the research and writing of the manuscript; Barve P and Umeh CA supervised the project; all authors have read and approved the final manuscript.

Institutional review board statement: The WIRB-Copernicus Group (WCG) institutional review board (IRB) approved the study. IRB approval number: 13410516.

Informed consent statement: Our study was a retrospective observational study which used medical records for data acquisition and analysis and thus does not require informed consent from subjects.

Conflict-of-interest statement: None to declare.

Data sharing statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Retrospective Study

Immediate in-hospital outcomes after percutaneous revascularization of acute myocardial infarction complicated by cardiogenic shock

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Abstract

BACKGROUND

Cardiogenic shock (CS) is a life-threatening complication of acute myocardial infarction with high morbidity and mortality rates. Primary percutaneous coronary intervention (PCI) has been shown to improve outcomes in patients with CS.

AIM

To investigate the immediate mortality rates in patients with CS undergoing primary PCI and identify mortality predictors.

METHODS

We conducted a retrospective analysis of 305 patients with CS who underwent primary PCI at the National Institute of Cardiovascular Diseases, Karachi, Pakistan, between January 2018 and December 2022. The primary outcome was immediate mortality, defined as mortality within index hospitalization. Univariate and multivariate logistic regression analyses were performed to identify predictors of immediate mortality.

RESULTS

In a sample of 305 patients with 72.8% male patients and a mean age of 58.1 ± 11.8 years, the immediate mortality rate was found to be 54.8% (167). Multivariable analysis identified Killip class IV at presentation [odds ratio (OR): 2.0; 95% confidence interval (CI): 1.2-3.4; $P = 0.008$], Multivessel disease (OR: 3.5; 95%CI: 1.8-6.9; $P < 0.001$), and high thrombus burden (OR: 2.6; 95%CI: 1.4-4.9; $P = 0.003$) as independent predictors of immediate mortality.

CONCLUSION

Immediate mortality rate in patients with CS undergoing primary PCI remains high despite advances in treatment strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality. These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly in those with these high-risk characteristics.

Key Words: Acute myocardial infarction; Cardiogenic shock; Primary percutaneous coronary intervention; Mortality; Predictors

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Core Tip: Cardiogenic shock (CS) is a severe form of acute myocardial infarction (AMI) associated with low blood pressure, poor organ perfusion, and high mortality rates. Overall, primary percutaneous coronary intervention (PCI) plays a crucial role in the management of patients with CS by improving blood flow to the heart, restoring cardiac function, and reducing mortality rates. However, the success of primary PCI depends on several factors, including the timeliness of treatment, the skill and experience of the operators performing the procedure, and the patient's overall health status. Therefore, it is essential to identify high-risk patients and provide timely appropriate treatment to achieve the best outcomes. Therefore, we conducted a retrospective analysis of 305 patients with CS complicated AMI undergone primary PCI at our center. It has been observed the immediate mortality rate was unacceptably high at 54.8% with cardiac arrest followed by renal failure, multi-organ dysfunction, sepsis, hypoxic brain injury and cerebrovascular accident as a cause of mortality. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality in multivariable analysis.

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INTRODUCTION

The prevalence of myocardial infarction is estimated to vary by age group, with reported rates of 3.8% among individuals under 60 years of age and a higher prevalence of 9.5% among those aged 60 years and above. Within the context of acute myocardial infarction (AMI), a critical complication known as cardiogenic shock (CS) emerges as a life-threatening concern[1]. This condition stands as the leading cause of mortality associated with AMI, with reported incidence rates ranging from 5% to 15%[2,3]. CS is a medical emergency that occurs when the heart is unable to pump enough blood to meet the body's needs. It can be caused by a variety of conditions, including myocardial infarction (heart attack), cardiomyopathy, and valvular heart disease[3]. Management of CS involves identifying and treating the underlying cause and providing supportive care to stabilize the patient's condition[4]. In AMI, CS is a life-threatening complication with a high morbidity and mortality rate[5]. Primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion strategy in patients with AMI and CS[6]. The main goal of primary PCI in patients with CS is to restore blood flow to the affected area of the heart, which can help to improve cardiac function and reduce mortality rates[4]. Compared to other revascularization strategies, such as thrombolysis or medical therapy alone, primary PCI has been shown to be more effective in restoring blood flow and improving outcomes in patients with CS[7].

Patients with CS are at risk of developing several in-hospital complications, which include; acute kidney injury (AKI) as a result of reduced kidney perfusion due to a decreased cardiac output and low blood pressure[8], arrhythmias such as atrial fibrillation and ventricular tachycardia[9], pulmonary edema due to excessive fluid administration or impaired cardiac function[10], and multi-organ failure due to impaired perfusion to vital organs as a result of prolonged hypotension and decreased cardiac output[10]. Additionally, invasive procedures such as PCI can increase the risk of bleeding complications[11], catheter-related bloodstream infections, and ventilator-associated pneumonia[12]. Also, CS is associated with an increased risk of thromboembolic events, as patients with reduced cardiac output and immobility are at increased risk of developing deep vein thrombosis and pulmonary embolism[10]. The development of these complications can further worsen the prognosis of patients with CS. Therefore, close monitoring and prompt management of these complications are essential in improving patient outcomes.

The management of CS requires a multidisciplinary approach involving cardiology, critical care, and interventional teams. Clinical precautions in the management of CS include several essential considerations. Firstly, early identification and diagnosis of CS is crucial, as early interventions have been shown to improve survival rates[13]. Therefore, healthcare providers should be vigilant for signs and symptoms of CS, such as hypotension, tachycardia, and decreased urine

output. Secondly, revascularization procedures such as PCI and coronary artery bypass grafting are essential in managing CS caused by myocardial infarction[6]. Early revascularization can restore blood flow to the heart muscle and prevent further damage. Thirdly, the use of inotropes and vasopressors should be carefully titrated to avoid complications such as arrhythmias and excessive vasoconstriction[14]. Adequate fluid resuscitation is necessary to maintain blood pressure and cardiac output, but excessive fluid administration can lead to pulmonary edema and worsen CS[14]. Fourthly, mechanical circulatory support devices such as intra-aortic balloon pump (IABP) and extracorporeal membranous oxygenation (ECMO) may be necessary in refractory cases of CS[15]. However, these devices have risks and complications, such as bleeding and infection, which should be carefully monitored and managed[16]. Finally, closely monitoring hemodynamic parameters such as blood pressure, heart rate, and cardiac output is essential to guide management and assess response to therapy[16]. Patients with CS require close attention and frequent assessments to identify and manage any complications that may arise.

The management of patients with CS undergoing primary PCI has evolved significantly over the last few decades. Despite these advances, the mortality rate in this patient population remains high[17]. There is a need to identify factors associated with poor immediate outcomes after primary PCI in patients with CS to help identify high-risk patients and guide treatment decisions[13]. Understanding the predictors of mortality and other immediate outcomes after primary PCI in patients with CS can also provide valuable insights for further refining the management of these patients. Therefore, this study aimed to investigate the immediate mortality rate in patients with CS undergoing primary PCI and identify mortality predictors.

MATERIALS AND METHODS

This retrospective analysis was conducted at the largest tertiary care cardiac hospital in Karachi, Pakistan, after approval from the institutional ethical review committee (ERC/46/2022). For this analysis, the de-identified data were extracted from the hospital records for the consecutive patients with CS who underwent primary PCI at our institution between January 2018 and December 2022. Patients with missing information on study variables were excluded from the analysis, and patients who did not undergo primary PCI were also excluded.

The primary outcome was immediate mortality, defined as mortality within index hospitalization. Baseline demographics, clinical characteristics, and procedural data were collected. Data regarding the hospital course of the patients were also extracted, which included IABP placement, intubation, temporary pacemaker, inotropic support, and in-hospital complications such as sepsis, renal dysfunction, cardiac arrest, cerebrovascular accident, hypoxic brain injury, and multi-organ dysfunction.

Data regarding demographics, clinical characteristics, procedural, and hospital course were compared between the two groups of patients based on immediate survival status with the help of an independent sample t-test/Mann-Whitney U test or Chi-square test/Fisher exact test. Univariate and multivariable binary logistic regression analyses were performed to identify predictors of immediate mortality. All the variables with P value < 0.20 in the univariate analysis were included in the multivariable analysis[18]. All the statistical analyses were formed with the help of IBM SPSS version 21, and $P < 0.05$ was the set criteria for statistical significance.

RESULTS

A total of 305 patients were included, of which 222 (72.8%) were male, and the mean age of the study sample was 58.1 ± 11.8 years. Most patients were in Killip class IV, 186 (61.0%), at the time of presentation. The immediate mortality rate was found to be 54.8% (167). The mean age was 59.4 ± 12.0 vs 56.5 ± 11.5 ; $P = 0.031$, Killip IV at presentation was 68.3% vs 52.2%; $P = 0.004$, and diabetes was present in 54.5% vs 41.3%; $P = 0.022$ among expired and survived patients, respectively (Table 1).

The multivessel disease was observed in 90.4% vs 68.1%; $P < 0.001$, high thrombus burden (grade ≥ 4) in 85.6% vs 67.4%; $P < 0.001$, bifurcations lesion in 29.9% vs 16.7%; $P = 0.007$, intraluminal defect in 89.8% vs 81.9%; $P = 0.045$, need of temporary pacemaker was for 60.5% vs 1.4%; $P < 0.001$, need of intubation for 78.4% vs 2.2%; $P < 0.001$, need of inotropic support was 76.0% vs 1.4%; $P < 0.001$, need of IABP was 48.5% vs 21.7%; $P < 0.001$, and left ventricular dysfunction was observed in 91.0% vs 75.4%; $P < 0.001$ among expired and survived patients, respectively (Table 2).

Multivariate analysis identified Killip class IV at presentation [odds ratio (OR): 2.0; 95% confidence interval (CI): 1.2-3.4; $P = 0.008$], Multivessel disease (OR: 3.5; 95% CI: 1.8-6.9; $P < 0.001$), and high thrombus burden (OR: 2.6; 95% CI: 1.4-4.9; $P = 0.003$) as independent predictors of immediate mortality (Table 3).

A 12.0% (20/167) of the total deaths were deaths on the catheterization table. Cardiac arrest was the most common cause of death observed in 95.8% (160/167). Among other causes, renal failure was observed in 25.1% (42/167), multi-organ dysfunction in 19.8% (33/167), sepsis in 18.0% (30/167), hypoxic brain injury in 6.6% (11/167), and cerebrovascular accident in 0.6% (1/167) patient.

DISCUSSION

CS is a severe complication of AMI associated with low blood pressure, poor organ perfusion, and high mortality rates.

Table 1 Distribution of demographics and clinical characteristics patients with cardiogenic shock stratified by immediate outcome after primary percutaneous coronary intervention

	Total	Immediate outcome		P value
		Mortality	Survived	
Total (n)	305	167	138	
Gender				
Male	222 (72.8)	114 (68.3)	108 (78.3)	0.051
Female	83 (27.2)	53 (31.7)	30 (21.7)	
Age (years)	58.1 ± 11.8	59.4 ± 12	56.5 ± 11.5	0.031
Body mass index (kg/m²)	25.7 ± 2.9	25.6 ± 2.9	25.9 ± 3	0.346
Underweight	2 (0.7)	2 (1.2)	0 (0.0)	0.470
Healthy	150 (49.2)	84 (50.3)	66 (47.8)	
Overweight	131 (43)	71 (42.5)	60 (43.5)	
Obese	22 (7.2)	10 (6)	12 (8.7)	
Killip Class				
III	119 (39)	53 (31.7)	66 (47.8)	0.004
IV	186 (61)	114 (68.3)	72 (52.2)	
Known risk factors				
Diabetes	148 (48.5)	91 (54.5)	57 (41.3)	0.022
Hypertension	181 (59.3)	95 (56.9)	86 (62.3)	0.336
Smoke	80 (26.2)	40 (24)	40 (29)	0.320
Family history	8 (2.6)	4 (2.4)	4 (2.9)	0.784
Dyslipidemia	7 (2.3)	4 (2.4)	3 (2.2)	0.898
Chest pain to ER (min)	240 (120-360)	210 (120-360)	240 (120-360)	0.718
ER to lab time (min)	55 (39-76)	55 (35-70.11)	55 (40-80)	0.337
Total ischemic time (min)	285 (190-415)	280 (180-413)	287 (200-440)	0.672
ST depression in AVR	56 (18.4)	33 (19.8)	23 (16.7)	0.487

ER: Emergency room; AVR: Augmented vector right.

Overall, primary PCI plays a crucial role in managing patients with CS by improving blood flow to the heart, restoring cardiac function, and reducing mortality rates. However, the success of primary PCI depends on several factors, including the timeliness of treatment, the skill and experience of the operators performing the procedure, and the patient's overall health status. Therefore, it is essential to identify high-risk patients and provide timely and appropriate treatment to achieve the best outcomes. Therefore, we conducted a retrospective analysis of 305 patients with CS-complicated AMI who had undergone primary PCI at our center. It has been observed the immediate mortality rate was unacceptably high at 54.8%, with cardiac arrest followed by renal failure, multi-organ dysfunction, sepsis, hypoxic brain injury, and cerebrovascular accident as a cause of mortality. In multivariable analysis, Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality.

Despite advancements in the therapeutic and technical management of CS, the rate of adverse events remains unacceptably high. Studies have reported varying mortality rates in-hospital, short-term, and long-term depending on the definition of CS and follow-up duration. Similar to our study, Hayiroğlu *et al*[5] surveyed 319 CS complicated ST-elevation myocardial infarction (STEMI) patients treated with primary PCI and reported a high in-hospital mortality rate of 61.3%. This study found several predictors of in-hospital mortality, including final thrombolysis in myocardial infarction flow, chronic kidney disease, left ventricular ejection fraction, tricuspid annular plane systolic excursion, blood urea nitrogen level, lactate level, and plasma glucose level. Similarly, other studies, including Wang *et al*[19] and Backhaus *et al*[13], reported 65.3% and 37%-50% in-hospital mortality rates, respectively. The use of IABP has decreased over the years, and improvements in therapeutic management, such as increased use of drug-eluting stents, prasugrel, and ticagrelor, have resulted in better long-term prognosis for these patients[13]. Kawaji *et al*[20] conducted a registry-based study on 466 STEMI patients with CS and reported high 30-d, one-year, and five-year mortality rates of 25.4%,

Table 2 Distribution of angiographic and procedural characteristics patients with cardiogenic shock stratified by immediate outcome after primary percutaneous coronary intervention

	Total	Immediate outcome		P value
		Mortality	Survived	
Total (n)	305	167	138	
Number of involved vessels				
Single vessel disease (SVD)	56 (18.4)	15 (9)	41 (29.7)	< 0.001
Two vessel disease (2VD)	80 (26.2)	43 (25.7)	37 (26.8)	
Three vessel disease (3VD)	145 (47.5)	100 (59.9)	45 (32.6)	
Left main (LM)	2 (0.7)	1 (0.6)	1 (0.7)	
LM + SVD	2 (0.7)	0 (0)	2 (1.4)	
LM + 2VD	7 (2.3)	2 (1.2)	5 (3.6)	
LM + 3VD	13 (4.3)	6 (3.6)	7 (5.1)	
Infarct related artery				
Left anterior descending artery	191 (62.6)	106 (63.5)	85 (61.6)	0.917
Right coronary artery	78 (25.6)	42 (25.1)	36 (26.1)	
Left circumflex	31 (10.2)	17 (10.2)	14 (10.1)	
Left main	5 (1.6)	2 (1.2)	3 (2.2)	
Only LHC done	17 (5.6)	12 (7.2)	5 (3.6)	0.177
Only POBA	32 (10.5)	19 (11.4)	13 (9.4)	0.579
Lesion length (cm)	20 (15-26)	20 (15-26)	20 (15-26)	0.948
Bifurcations lesion	73 (23.9)	50 (29.9)	23 (16.7)	0.007
Side branch	57 (18.7)	37 (22.2)	20 (14.5)	0.087
Pre-procedure TIMI flow				
0	290 (95.1)	152 (91)	138 (100)	0.005
I	8 (2.6)	8 (4.8)	0 (0.0)	
II	6 (2)	6 (3.6)	0 (0.0)	
III	1 (0.3)	1 (0.6)	0 (0.0)	
Post-procedure TIMI flow				
0	14 (4.6)	9 (5.4)	5 (3.6)	0.124
I	9 (3)	7 (4.2)	2 (1.4)	
II	39 (12.8)	26 (15.6)	13 (9.4)	
III	243 (79.7)	125 (74.9)	118 (85.5)	
Tissue Myocardial Perfusion				
0	20 (6.6)	10 (6)	10 (7.2)	0.731
I	18 (5.9)	11 (6.6)	7 (5.1)	
II	62 (20.3)	37 (22.2)	25 (18.1)	
III	205 (67.2)	109 (65.3)	96 (69.6)	
Thrombus grading				
G0-No	8 (2.6)	2 (1.2)	6 (4.3)	0.003
G1-Possible	14 (4.6)	7 (4.2)	7 (5.1)	
G2-Small	8 (2.6)	1 (0.6)	7 (5.1)	
G3-Moderate	39 (12.8)	14 (8.4)	25 (18.1)	

G4-Large	55 (18)	32 (19.2)	23 (16.7)	
G5-Total	181 (59.3)	111 (66.5)	70 (50.7)	
Intraluminal defect	263 (86.2)	150 (89.8)	113 (81.9)	0.045
Export catheter use	138 (45.2)	62 (37.1)	76 (55.1)	0.002
Needed temporary pacemaker	103 (33.8)	101 (60.5)	2 (1.4)	< 0.001
ER	8 (7.8)	8 (7.9)	0 (0.0)	0.806
Cath lab	85 (82.5)	83 (82.2)	2 (100)	
CCU	10 (9.7)	10 (9.9)	0 (0)	
Needed intubation	134 (43.9)	131 (78.4)	3 (2.2)	< 0.001
ER	30 (22.4)	30 (22.9)	0 (0)	0.397
Cath lab	60 (44.8)	59 (45)	1 (33.3)	
CCU	44 (32.8)	42 (32.1)	2 (66.7)	
Needed inotropic support	129 (42.3)	127 (76)	2 (1.4)	< 0.001
ER	74 (57.4)	74 (58.3)	0 (0.0)	0.065
Cath lab	35 (27.1)	33 (26)	2 (100)	
CCU	20 (15.5)	20 (15.7)	0 (0.0)	
Needed IABP	111 (36.4)	81 (48.5)	30 (21.7)	< 0.001
LV dysfunction	256 (83.9)	152 (91)	104 (75.4)	< 0.001
Ejection fraction (%)	30 (30-40)	30 (30-40)	35 (30-45)	0.014

LV: Left ventricular; LHC: Left heart cath; TIMI: Thrombolysis in Myocardial Infarction; POBA: Plain old balloon angioplasty; IABP: Intra-aortic balloon pump; ER: Emergency room; CCU: Coronary care unit.

Table 3 Clinical predictors of immediate mortality after primary percutaneous coronary intervention of patients with cardiogenic shock

	Univariate		Multivariable	
	OR (95%CI)	P value	OR (95%CI)	P value
Female	1.7 (1.0-2.8)	0.052	1.8 (1.0-3.3)	0.059
Age (years)	1.0 (1.0-1.0)	0.032	1.0 (1.0-1.0)	0.257
Killip class IV	2.0 (1.2-3.1)	0.004	2.0 (1.2-3.4)	0.008
Diabetes mellitus	1.7 (1.1-2.7)	0.022	1.5 (0.9-2.5)	0.126
Hypertension	0.8 (0.5-1.3)	0.337	-	-
Smoker	0.8 (0.5-1.3)	0.320	-	-
Total ischemic time ≥ 4 h	1.0 (0.6-1.7)	0.870	-	-
Multivessel disease	4.4 (2.4-8.3)	< 0.001	3.5 (1.8-6.9)	< 0.001
Bifurcations lesion	2.1 (1.2-3.7)	0.008	1.7 (0.8-3.5)	0.169
Side branch	1.7 (0.9-3.1)	0.090	0.9 (0.4-2.1)	0.839
Thrombus grade ≥ 4	2.9 (1.6-5.0)	< 0.001	2.6 (1.4-4.9)	0.003
Intraluminal defect	2.0 (1.0-3.8)	0.048	1.2 (0.6-2.6)	0.655
Left ventricular dysfunction	3.3 (1.7-6.4)	< 0.001	2.2 (0.8-6.3)	0.146
Ejection fraction (%)	1.0 (0.9-1.0)	0.002	1.0 (1.0-1.0)	0.542

OR: Odds ratio; CI: Confidence interval.

38.7%, and 51.4%, respectively.

Additionally, the identification of clinical predictors of mortality can help guide treatment decisions and improve patient outcomes. Our study identified Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) as independent predictors of immediate mortality. Several clinical predictors of mortality in patients with CS have been identified in the literature, including age: Advanced age is a significant predictor of mortality in patients with CS[21]. Older patients have more comorbidities and are at higher risk of complications. The severity of shock: The degree of hemodynamic compromise, measured by the cardiac index, central venous pressure, and mean arterial pressure, is strongly associated with mortality[21]. AKI: AKI is a common complication in patients with CS and is associated with increased mortality[8]. Delayed revascularization: Delayed revascularization, defined as a time to revascularization of more than 24 h, is associated with increased mortality in patients with CS due to myocardial infarction[22]. Elevated lactate levels: Elevated lactate levels indicate tissue hypoxia and are a marker of poor prognosis in patients with CS[23]. Presence of comorbidities: Patients with preexisting comorbidities such as diabetes, hypertension, and chronic kidney disease have a higher risk of mortality[24]. Use of mechanical circulatory support: Mechanical circulatory support devices such as IABP and ECMO are associated with increased mortality, likely due to the severity of illness in patients requiring these interventions[25].

Further research is necessary to oversee and manage patients with STEMI complicated by CS. To achieve this, some researchers have proposed risk stratification scoring systems that have demonstrated good predictive value for the risk stratification of 30-d mortality[19,26,27]. Along with reperfusion, multidisciplinary management of CS patients is mandatory to improve outcomes. Several studies have reported a significant increase in the incidence of CS complicating STEMI, with one study reporting an incidence of 9% in 2006, which rose to 16% over ten years[13]. Similarly, an analysis of a United States nationwide database found that the incidence of STEMI complicated by CS increased from 6.5% to 10.1% between 2003 and 2010[28]. As a result, targeted research efforts are required to improve outcomes for these high-risk patients. While emergency revascularization of the culprit artery is the only proven effective method thus far, evidence for other supportive and medical therapies is unsatisfactory, and the use of IABP has shown no clinical benefit; however, the use of ECMO and Impella may yield better outcomes[29].

Certain limitations of the study need to be acknowledged. It was a single center-based retrospective study with a relatively small sample; hence, the generalizability of study findings may be limited.

CONCLUSION

In conclusion, immediate mortality rates in patients with CS undergoing primary PCI remain high despite advances in treatment strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality. Such predictors can help guide treatment decisions and risk stratification in patients with CS. These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly those with these high-risk characteristics.

ARTICLE HIGHLIGHTS

Research background

Cardiogenic shock (CS) is a life-threatening complication of acute myocardial infarction with high morbidity and mortality rates.

Research motivation

The management of CS requires a multidisciplinary approach involving cardiology, critical care, and interventional teams. Early identification and diagnosis of CS is crucial, as early interventions have been shown to improve survival rates.

Research objectives

This study aimed to investigate the immediate mortality rates in patients with CS undergoing primary percutaneous coronary intervention (PCI) and identify mortality predictors.

Research methods

We conducted a retrospective analysis of 305 patients with CS who underwent primary PCI and immediate mortality rate was analyzed.

Research results

In a sample of 305 patients, the immediate mortality rate was found to be 54.8% with Killip class IV at presentation, multivessel disease, and high thrombus burden as independent predictors of immediate mortality.

Research conclusions

Immediate mortality rate in patients with CS undergoing primary PCI remains high despite advances in treatment

strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality.

Research perspectives

These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly in those with these high-risk characteristics.

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FOOTNOTES

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the National Institute of Cardiovascular Diseases (NICVD), Karachi.

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.

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Observational Study

Outcomes in patients with COVID-19 and new onset heart blocks: Insight from the National Inpatient Sample database

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a worldwide health crisis since it first appeared. Numerous studies demonstrated the virus's predilection to cardiomyocytes; however, the effects that COVID-19 has on the cardiac conduction system still need to be fully understood.

AIM

To analyze the impact that COVID-19 has on the odds of major cardiovascular complications in patients with new onset heart blocks or bundle branch blocks (BBB).

METHODS

The 2020 National Inpatient Sample (NIS) database was used to identify patients admitted for COVID-19 pneumonia with and without high-degree atrioventricular blocks (HDAVB) and right or left BBB utilizing ICD-10 codes. The patients with pre-existing pacemakers, suggestive of a prior diagnosis of HDAVB or BBB, were excluded from the study. The primary outcome was inpatient mortality. Secondary outcomes included total hospital charges (THC), the length of hospital stay (LOS), and other major cardiac outcomes detailed in the Results section. Univariate and multivariate regression analyses were used to adjust for confounders with Stata version 17.

RESULTS

A total of 1058815 COVID-19 hospitalizations were identified within the 2020 NIS

database, of which 3210 (0.4%) and 17365 (1.6%) patients were newly diagnosed with HDAVB and BBB, respectively. We observed a significantly higher odds of in-hospital mortality, cardiac arrest, cardiogenic shock, sepsis, arrhythmias, and acute kidney injury in the COVID-19 and HDAVB group. There was no statistically significant difference in the odds of cerebral infarction or pulmonary embolism. Encounters with COVID-19 pneumonia and newly diagnosed BBB had a higher odds of arrhythmias, acute kidney injury, sepsis, need for mechanical ventilation, and cardiogenic shock than those without BBB. However, unlike HDAVB, COVID-19 pneumonia and BBB had no significant impact on mortality compared to patients without BBB.

CONCLUSION

In conclusion, there is a significantly higher odds of inpatient mortality, cardiac arrest, cardiogenic shock, sepsis, acute kidney injury, supraventricular tachycardia, ventricular tachycardia, THC, and LOS in patients with COVID-19 pneumonia and HDAVB as compared to patients without HDAVB. Likewise, patients with COVID-19 pneumonia in the BBB group similarly have a higher odds of supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, acute kidney injury, sepsis, need for mechanical ventilation, and cardiogenic shock as compared to those without BBB. Therefore, it is essential for healthcare providers to be aware of the possible worse predicted outcomes that patients with new-onset HDAVB or BBB may experience following SARS-CoV-2 infection.

Key Words: In-patient outcomes; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019, High degree atrioventricular blocks; Bundle branch blocks; Retrospective observational study

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Core Tip: This is the first and largest retrospective observational study based on the 2020 National Inpatient Sample database that illustrates the outcomes of patients with coronavirus disease 2019 (COVID-19) who developed new onset high degree atrioventricular blocks (HDAVB) or bundle branch blocks (BBB). We observed significantly higher rates of inpatient outcomes of interest in patients admitted for COVID-19 pneumonia and the secondary diagnosis of HDAVB or BBB compared to patients who did not. Several reports in the literature described worse outcomes experienced by this patient population. We conclude that elderly patients, whites, and males with common co-morbid conditions, hospitalized for COVID-19 pneumonia and HDAVB, seem to be at a significantly increased risk of developing cardiac complications and have a significantly increased risk of inpatient mortality, necessitating a need for preventative strategies, such as the use of temporary pacemakers or cardiac rhythm monitoring techniques.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has significantly impacted global health and the world's economy[1,2]. The virus primarily targets the respiratory system, but it also elicits a robust systemic immune response, otherwise known as "cytokine storm", leading to multi-organ dysfunction[2,3]. Although much of the focus has been on the acute respiratory distress syndrome caused by the virus, it is crucial for providers to understand the complex interplay between COVID-19 and the cardiovascular system[4,5].

Research has demonstrated that individuals with pre-existing cardiovascular disease are at a significantly higher risk of developing life-threatening SARS-CoV-2 infections and increased case fatality rates. Additionally, COVID-19 has been associated with a myriad of cardiovascular complications, including arrhythmias, acute coronary syndromes, myocarditis, acute heart failure, pericarditis, cardiac tamponade, takotsubo cardiomyopathy, cor-pulmonale, cardiogenic shock, and pulmonary embolism[3,6]. These cardiovascular complications can significantly impact short and long-term mortality associated with COVID-19[7].

Of those hospitalized with COVID-19 pneumonia, 14.1% of patients experience a cardiovascular complication, with arrhythmia incidence rates ranging between 6.9-10.3%[3,8-13]. While tachyarrhythmias are the most commonly cited arrhythmias, bradyarrhythmias still represent 12% of all arrhythmias that can develop in COVID-19 affected patients[13, 14]. Bradyarrhythmias can increase mortality rates, particularly in cases of new onset atrioventricular blocks. However, there is currently a lack of large-scale database analyses regarding hospital outcomes, trends, and demographics of bradyarrhythmias in patients with COVID-19.

To address this gap in knowledge, this review focuses on major cardiovascular complications in COVID-19 patients, with an emphasis on bradyarrhythmias due to high-degree atrioventricular blocks (HDAVB) (of which 1900 patients (59.2%) developed second degree atrioventricular block and 1310 (40.8%) developed complete atrioventricular block) in patients who did not have a prior permanent pacemaker or other implantable cardiac devices such as implantable cardioverter-defibrillator (ICD).

MATERIALS AND METHODS

Study design and data sources

This study is a retrospective cohort analysis of admissions for COVID-19 patients in 2020 using the National Inpatient Sample (NIS) database. The NIS database is the largest publicly available all-payer inpatient healthcare database, maintained by the Agency for Healthcare Research and Quality. It was designed to assess all hospitalizations in non-federal acute care hospitals across the United States, excluding rehabilitation and long-term acute care hospitals, through a weighted probability sampling method. Data was collected from billing records submitted by hospitals to statewide data organizations, representing almost 97% of the United States (US) population. The NIS database then stratifies these hospitalizations according to bed size, teaching status, urban/rural locations, and geographic location. A sample of 20% of all hospitalizations in each stratum is collected, pooled, and weighted to ensure that it accurately represents the entire US population.

The NIS database contains patient and hospital-level information, including primary diagnosis, secondary diagnosis, primary payer type, median household income, hospital teaching status, geographic region, hospital bed size, and urban/rural location. All diagnoses are coded using the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS).

In this database, diagnoses are divided into a single primary diagnosis and secondary diagnoses. The principal diagnosis represents the main reason for hospitalization, while secondary diagnoses include any other ICD-10 codes associated with the hospitalization. The NIS has previously been used to estimate the burden of cardiovascular diseases.

It is worth noting that this study's manuscript is exempt from Institutional Review Board (IRB) approval since it uses de-identified data. The data used in this study is accessible online at <https://www.hcup-us.ahrq.gov>.

Inclusion criteria and study variates

Note to reader: Although High Degree Atrioventricular Block is defined as “≥ 2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles with evidence for some atrioventricular conduction”[15] by the American Heart Association, the term High Degree Atrioventricular Block (HDAVB) throughout the entirety of the manuscript will represent patients with Mobitz I, Mobitz II and Complete heart block only. We chose to use this abbreviation to avoid word redundancy.

This retrospective cohort study focuses on adult patients aged 18 years or older who were hospitalized with COVID-19 pneumonia during the year 2020. We identified the study population by combining multiple ICD-10-CM codes, including U07.1, J12.82, U100, U49, U50, and U85, based on a literature review of similar validated studies on COVID-19, bundle branch blocks and heart blocks which included Mobitz type one, Mobitz type two and complete heart block. We further stratified the population based on the presence or absence of HDAVB without a pacemaker (I44.1, I44.2) or BBB without a pacemaker (I44.7, I45.19, I45.10) using ICD-10 codes.

Patients with prior permanent pacemakers and other intra-cardiac devices were excluded to ensure that analyzed patients had not been previously diagnosed with heart blocks and had no devices placed for this reason.

Demographic characteristics such as age, sex, race, medical insurance status, and mean household income, as well as hospital characteristics such as hospital bed size, location, and teaching status, were included as study variables. Comorbidity burden was assessed using the Charlson comorbidity index, which was adjusted for population-based research.

The study population and the stratification process are outlined in [Figure 1](#).

Clinical outcomes and definitions

The primary outcome of our analysis was to examine the mortality rate in COVID-19 pneumonia patients who had newly diagnosed HDAVB or BBB (without permanent pacemaker). In addition, we also analyzed secondary outcomes such as mean length of stay (LOS), mean total hospital charges (THC), and adjusted odds of inpatient morbidities including but not limited to cardiac arrest, respiratory failure, ventricular and supraventricular arrhythmia, acute kidney injury, and cerebral infarction.

To conduct our statistical analyses, we utilized STATA® (StataCorp, College Station, TX) version 17. The Healthcare Cost and Utilization Project (HCUP) offers year-based discharge weights, which were utilized to quantify weighted nationwide estimates. We used Fisher's exact test or Chi-square test to compare categorical variable proportions and an independent sample *t*-test to compare means of continuous data. We calculated unadjusted odds ratio (OR) using univariate regression analysis for every outcome. With significance of each univariate screen set to *P* value < 0.2, we selected variables to conduct multivariable logistic regression analysis adjusting for possible confounders. Other essential variables, based on literature review, were also included in the model. We used logistic regression analysis for binary or categorical outcomes and linear regression analysis for continuous outcomes. Two-tailed *P* values and a threshold of 0.05 were used to determine statistical significance.

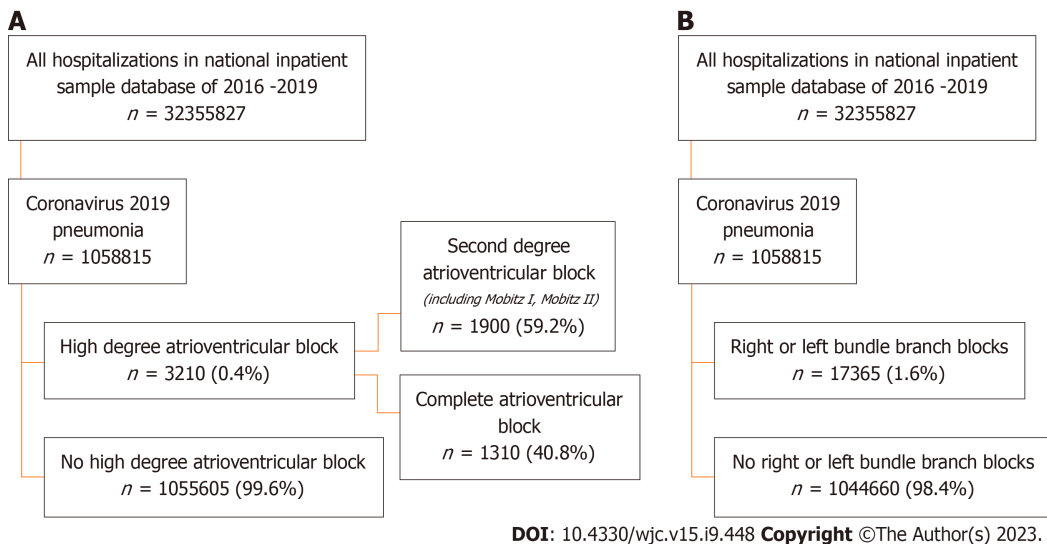


Figure 1 Study population and stratification process. A: Coronavirus disease 2019 (COVID-19) pneumonia hospitalizations stratified by patients with and without high degree atrioventricular blocks; B: COVID-19 pneumonia hospitalizations stratified by patients with and without right and left bundle branch blocks.

Ethical considerations

Our manuscript is exempt from IRB approval, as NIS is a de-identified national administrative database and readily available online at <https://www.hcup-us.ahrq.gov>. Based on that and according to HCUP guidelines, our study did not require Institutional Review Board of Cook County Health's approval.

RESULTS

According to the 2020 NIS database, out of 1058815 COVID-19 pneumonia hospitalizations, 3210 (0.4%) patients had newly diagnosed HDAVB without a pacemaker, while 17365 (1.6%) had newly diagnosed right or left BBB without a pacemaker (Figures 1 and 2). The mean age of COVID-19 patients with and without HDAVB were 72 and 64 years, while COVID-19 patients with and without BBB had a mean age of 72.5 and 64 years, respectively ($P < 0.001$ for both).

Compared to COVID-19 patients without HDAVB or BBB, COVID-19 patients with newly diagnosed HDAVB or BBB were more likely to be white (58% vs 52%, $P = 0.0359$; 62% vs 52%, $P = 0.0359$), be male (66.5% vs 52.7%, $P < 0.001$; 60.6% vs 52.7%, $P < 0.001$), have governmental insurance (82% vs 67%, $P < 0.001$; 79.5% vs 67%, $P < 0.001$), and be treated in large bed size hospitals (50.8% vs 45.4%, $P = 0.0286$; 46.8% vs 45.4%, $P = 0.025$) respectively.

In terms of underlying comorbidities, patients with COVID-19 pneumonia with newly diagnosed HDAVB or BBB were more likely to have complicated diabetes mellitus (55% vs 30%, $P < 0.001$; 43% vs 30.8%, $P < 0.001$), chronic kidney disease (33% vs 19%, $P < 0.001$; 29% vs 19%, $P < 0.001$), congestive heart failure (34% vs 15%, $P < 0.001$; 32% vs 15%, $P < 0.001$), prior myocardial infarction (17% vs 7%, $P < 0.001$; 17.5% vs 7%, $P < 0.001$), history of cerebrovascular accidents (5% vs 4%, $P = 0.0223$; 6% vs 4%, $P < 0.001$), peripheral vascular disease (10% vs 4.5%, $P < 0.001$; 10% vs 4.4%, $P < 0.001$), and a higher number of comorbid conditions in general (Charlson index ≥ 3) compared to COVID-19 patients without HDAVB or BBB.

COVID-19 patients with HDAVB or BBB as compared to COVID-19 patients without were less likely to be female (43.5% vs 47.2%, $P < 0.001$; 39.4% vs 47.3%, $P < 0.001$), to be African-American (18% vs 19%, $P = 0.0359$; 14% vs 19%, $P = 0.0359$), to be Hispanic (17% vs 21%, $P = 0.0359$; 15% vs 21%, $P = 0.0359$), and have private insurance (17% vs 21%, $P = 0.0359$; 15% vs 21%, $P = 0.0359$), and were less likely to have hypertension (32% vs 41%, $P < 0.001$; 37% vs 41%, $P < 0.001$) (Tables 1 and 2).

Multi-variant regression analysis

On multivariate regression analysis of encounters with COVID-19 and newly diagnosed HDAVB without pacemakers as demonstrated in Figure 2A, they were found to have a longer mean LOS of 2.28 d [95% confidence interval (CI): 1.49-3.07, $P < 0.001$], higher mean THC of \$33801 (95%CI: 17314 -50261, $P < 0.001$), higher adjusted odds (aOR) of mortality (aOR: 1.36, 95%CI: 1.1-1.69, $P = 0.005$), cardiac arrest (aOR: 2.04, 95%CI: 1.42-2.92, $P < 0.001$), atrial fibrillation (aOR: 1.36, 95%CI: 1.12-1.68, $P = 0.003$), atrial flutter (aOR: 3.27, 95%CI: 2.33-4.58, $P < 0.001$), ventricular fibrillation (aOR: 4.95, 95%CI: 2.52-9.71, $P < 0.001$), supraventricular tachycardia (aOR: 2.53, 95%CI: 1.68-3.82, $P < 0.001$), ventricular tachycardia (aOR: 3.16, 95%CI: 2.27-4.4, $P < 0.001$), acute kidney injury (aOR: 1.33, 95%CI: 1.11-1.6, $P = 0.002$), sepsis (aOR: 1.59, 95%CI: 1.22-2.06, $P < 0.001$), mechanical ventilation (aOR: 1.41, 95%CI: 1.08-1.84, $P = 0.011$), and cardiogenic shock (aOR: 6.62, 95%CI: 4.14-10.6, $P < 0.001$), compared to those without HDAVB.

Meanwhile, patients with COVID-19 and BBB without pacemakers as demonstrated in Figure 2B had an increased odds of atrial fibrillation (aOR: 1.15, 95%CI: 1.05-1.26, $P = 0.001$), atrial flutter (aOR: 1.68, 95%CI: 1.37-2.06, $P < 0.001$), supraventricular tachycardia (aOR: 1.83, 95%CI: 1.48-2.5, $P < 0.001$), ventricular tachycardia (aOR: 2.35, 95%CI: 1.97-2.8, P

Table 1 Baseline demographics and comorbid condition rate of patients admitted for coronavirus disease 2019 pneumonia with and without high degree atrioventricular block without a pacemaker, *n* (%)

	Study group	Control group	P value
	High degree atrioventricular block (<i>n</i> = 3210/0.4%)	No high degree atrioventricular block (<i>n</i> = 1058815/99.6%)	
Age (year), mean	72	64	< 0.001
Gender			< 0.001
Female	1075 (33.5)	498545 (47.2)	
Male	(66.5)	(52.7)	
Ethnicity			0.0359
White	1862 (58)	550584 (52)	
Black	578 (18)	201175 (19)	
Hispanic	482 (15)	211763 (21)	
Other	225 (7)	84705 (8)	
Chronic kidney disease	1084 (33)	205000 (19)	< 0.001
Hypertension	1030 (32)	437190 (41)	< 0.001
Congestive heart failure	1095 (34)	162930 (15)	< 0.001
Government insured	2555 (82)	673794 (67)	< 0.001
Private insured	480 (15)	292190 (29)	< 0.001
Self-pay	80 (2.6)	35875 (3.6)	0.1828
Poor socioeconomic status	550 (17)	168015 (16)	
Hospital region			0.0144
Northeast	550 (17)	186650 (17.6)	
Midwest	925 (29)	245190 (23.2)	
South	1225 (38)	441800 (42)	
West	510 (16)	181964 (17.2)	
Hospital bed size			0.0286
Small	770 (24)	270620 (25.6)	
Medium	810 (25.2)	304920 (29)	
Large	1630 (50.8)	480065 (45.4)	
Charlson index			< 0.001
0	385 (12)	296468 (28)	
1	642 (20)	296468 (28)	
2	578 (18)	169410 (16)	
3	1605 (50)	296468 (28)	
Median household income			0.0418
First quartile	931 (29)	359997 (34)	
Second quartile	995 (31)	296468 (28)	
Third quartile	738 (23)	232939 (22)	
Fourth quartile	546 (17)	169410 (16)	
Myocardial infarction	570 (17)	77240 (7)	< 0.001
Peripheral vascular disease	320 (10)	47355 (4.5)	< 0.001
Cerebrovascular disease	185 (5)	42075 (4)	0.0223

Dementia	570 (17)	116035 (11)	< 0.001
Chronic obstructive lung disease	875 (27)	247225 (23.4)	0.0244
Rheumatoid arthritis	65 (2)	30120 (3)	0.2037
Peptic ulcer disease	20 (0.6)	4625 (0.4)	0.4797
Mild liver disease	95 (3)	36275 (3.4)	0.5039
Diabetes mellitus	680 (21)	262850 (25)	0.0311
Diabetic complications	1790 (55)	327870 (30)	< 0.001
Hemiplegia or paraplegia	50 (1.5)	16690 (1.5)	0.9732
Renal disease	2220 (70)	421060 (40)	< 0.001
Cancer	260 (8)	57440 (5.4)	0.0371
Moderate/severe liver disease	45 (1.4)	15855 (1.5)	0.9051
Metastatic cancer	210 (6.5)	49170 (4.6)	0.3633
AIDS	60 (1.9)	13980 (1.3)	0.6272

Student's *t*-test and Chi-square test were used to compare the baseline characteristics accordingly, and the resulting *P* values are shown. AIDS: Acquired immunodeficiency syndrome.

< 0.001), acute kidney injury (aOR: 1.12, 95%CI: 1.03-1.21, *P* = 0.004), sepsis (aOR: 1.59, 95%CI: 1.22-2.06, *P* < 0.001), mechanical ventilation (aOR: 1.22, 95%CI: 1.08-1.39, *P* = 0.001), and cardiogenic shock (aOR: 2.11, 95%CI: 1.44-3.08, *P* < 0.001), than those without BBB without pacemaker but with a similar odds of mortality (aOR: 1.05, 95%CI: 0.95-1.16, *P* = 0.326).

Univariate regression analysis

On univariate regression analysis of encounters with COVID-19 and HDAVB as demonstrated in Table 3, they were found to have a longer mean LOS of 3.07 d (95%CI: 2.32-3.84, *P* < 0.001), higher mean THC of \$40692 (95%CI: 24708-56674, *P* < 0.001), increased odds of mortality (aOR: 2.18, 95%CI: 1.8-2.64, *P* < 0.001), cardiac arrest (aOR: 2.78, 95%CI: 2-3.86, *P* < 0.001), atrial fibrillation (aOR: 2.46, 95%CI: 2.1-2.9, *P* < 0.001), atrial flutter (aOR: 5.45, 95%CI: 4-7.42, *P* < 0.001), ventricular fibrillation (aOR: 6.33, 95%CI: 3.27-12.27, *P* < 0.001), supraventricular tachycardia (aOR: 3.39, 95%CI: 2.31-4.96, *P* < 0.001), ventricular tachycardia (aOR: 4.75, 95%CI: 3.05-6.46, *P* < 0.001), acute kidney injury (aOR: 1.73, 95%CI: 1.47-2.03, *P* < 0.001), sepsis (aOR: 1.85, 95%CI: 1.44-2.39, *P* < 0.001), mechanical ventilation (aOR: 1.72, 95%CI: 1.33-2.22, *P* < 0.001), and cardiogenic shock (aOR: 8.75, 95%CI: 5.61-13.63, *P* < 0.001), as compared to those without HDAVB.

Encounters with COVID-19 and with BBB without pacemaker as demonstrated in Table 4 had an increased odds of mortality (aOR: 1.63, 95%CI: 1.42-1.89, *p* < 0.001), atrial fibrillation (aOR: 2.12, 95%CI: 1.88-2.40, *P* < 0.001), atrial flutter (aOR: 2.32, 95%CI: 1.7-3.17, *P* < 0.001), supraventricular tachycardia (aOR: 2.22, 95%CI: 1.64-2.99, *P* < 0.001), ventricular tachycardia (aOR: 4.09, 95%CI: 3.24-5.14, *P* < 0.001), acute kidney injury (aOR: 1.71, 95%CI: 1.53-1.9, *P* < 0.001), sepsis (aOR: 1.81, 95%CI: 1.52-2.26, *P* < 0.001), mechanical ventilation (aOR: 1.67, 95%CI: 1.38-2.23, *P* < 0.001), and cardiogenic shock (aOR: 3.29, 95%CI: 2.04-5.31, *P* < 0.001), than those without BBB without pacemaker.

Absolute values of outcomes such as mortality amongst other outcomes of interest comparing both groups (HDAVB and BBB) can be found in Table 5.

DISCUSSION

This analysis is the most comprehensive and updated study to date that examined newly diagnosed HDAVB and BBB in SARS-CoV-2 positive patients who have not previously received a permanent pacemaker. Several cases in the literature suggesting poor predicted outcomes in this patient population have been described.

Our analysis uncovered several significant findings in patient demographics and major clinical outcomes, summarized in Tables 1 and 2, respectively.

We found that patients with COVID-19 and newly diagnosed HDAVB had a significantly higher odds of inpatient mortality and cardiac arrest. Furthermore, COVID-19 patients with either HDAVB or BBB had a significantly higher odds of cardiac arrest, cardiogenic shock, sepsis, acute kidney injury, and requirement for ventilatory support. Additionally, they had higher total hospital charges and a longer length of stay compared to patients without HDAVB or BBB. Furthermore, we observed a higher burden of atrial flutter, atrial fibrillation, supraventricular tachycardias, and ventricular tachycardias in patients with HDAVB or BBB without pre-existing pacemakers. Patients with COVID-19 and newly diagnosed HDAVB or BBB may have higher mortality rates and adverse clinical outcomes due to a higher burden of co-morbidities, such as chronic kidney disease, diabetes mellitus, and heart failure[7,16]. These conditions may increase the risk of complications and make it difficult for patients to recover from the virus. The increased burden of arrhythmias

Table 2 Baseline demographics and comorbid condition rate of patients admitted for coronavirus disease 2019 pneumonia with and without bundle branch block without a pacemaker, *n* (%)

	Study group	Control group	P value
	All bundle branch blocks without pacemaker (<i>n</i> = 17365/1.6%)	No bundle branch blocks (<i>n</i> = 1044660/98.4%)	
Age (year), mean	72.5	64	< 0.001
Gender			< 0.001
Female	6845 (39.4)	492775 (47.3)	
Male	(60.6)	(52.7)	
Ethnicity			0.0359
White	10766 (62)	543223 (52)	
Black	2431 (14)	198485 (19)	
Hispanic	2952 (17)	219378 (21)	
Other	1216 (7)	83573 (8)	
Chronic kidney disease	5005 (29)	201080 (19)	< 0.001
Hypertension	6390 (37)	431830 (41)	< 0.001
Congestive heart failure	5470 (32)	158555 (15)	< 0.001
Government insured	13360 (79.5)	662990 (67)	< 0.001
Private insured	3065 (18.2)	289605 (29.3)	< 0.001
Self-pay	385 (2.3)	35570 (3.6)	< 0.001
Poor socioeconomic status	3290	165275	
Hospital region			< 0.001
Northeast	3885 (22.4)	183315 (17.6)	
Midwest	4725 (27.2)	241390 (23.2)	
South	6160 (35.4)	436866 (42)	
West	2595 (15)	179880 (17.2)	
Hospital bed size			0.0025
Small	3900 (22.4)	267490 (25.6)	
Medium	5345 (30.8)	300385 (29)	
Large	8120 (46.8)	473575 (45.4)	
Charlson index			< 0.001
0	2952 (17)	292505 (28)	
1	3646 (21)	292505 (28)	
2	3299 (19)	147145 (16)	
3	7466 (43)	292505 (28)	
Median household income			< 0.001
First quartile	5088 (29.3)	355184 (34)	
Second quartile	4705 (27.1)	292505 (28)	
Third quartile	4202 (24.4)	229825 (22)	
Fourth quartile	3334 (19.2)	147145 (16)	
Myocardial infarction	3035 (17.5)	74775 (7)	< 0.001
Peripheral vascular disease	1530 (9)	46145 (4.4)	< 0.001
Cerebrovascular disease	1045 (6)	41215 (4)	< 0.001

Dementia	2835 (16)	113770 (11)	< 0.001
Chronic obstructive lung disease	4300 (25)	243800 (23.4)	0.0592
Rheumatoid arthritis	495 (3)	29690 (3)	0.9993
Peptic ulcer disease	60 (0.4)	4585 (0.4)	0.4011
Mild liver disease	670 (3.8)	35700 (3.4)	0.1675
Diabetes mellitus	4005 (23)	259525 (25)	0.0137
Diabetic complications	7420 (43)	322240 (30.8)	< 0.001
Hemiplegia or paraplegia	320 (1.8)	16420 (1.6)	0.3728
Renal disease	10370 (60)	412910 (39.5)	< 0.001
Cancer	970 (5.6)	56730 (5.4)	0.7950
Moderate/Severe liver disease	240 (1.4)	15660 (1.5)	0.7335
Metastatic cancer	840 (4.8)	48540 (4.6)	0.8478
AIDS	210 (1.2)	13830 (1.3)	0.8074

Student's *t*-test and Chi-square test were used to compare the baseline characteristics accordingly, and the resulting *P* values are shown. AIDS: Acquired immunodeficiency syndrome.

Table 3 A Univariate regression analysis of encounters with coronavirus disease 2019 and with high grade atrioventricular block without pacemakers

High degree atrioventricular block without pacemakers	Adjusted OR	95%CI	<i>P</i> value
Mortality	2.18	1.80-2.64	< 0.001
Cardiac arrest	2.78	2.00-3.86	< 0.001
Atrial fibrillation	2.46	2.10-2.90	< 0.001
Atrial flutter	5.45	4.00-7.42	< 0.001
Ventricular fibrillation	6.33	3.27-12.27	< 0.001
Supraventricular tachycardia	3.39	2.31-4.96	< 0.001
Ventricular tachycardia	4.75	3.05-6.46	< 0.001
Acute kidney injury	1.73	1.47-2.03	< 0.001
Sepsis	1.85	1.44-2.39	< 0.001
Mechanical ventilation	1.72	1.33-2.22	< 0.001
Cardiogenic shock	8.75	5.61-13.63	< 0.001

in patients with HDAVB or BBB could be due to the effect of the virus on the heart's electrophysiology. Previous studies suggested that SARS-CoV-2 can cause myocarditis, which may lead to arrhythmias and other cardiac complications[17, 18].

A retrospective study that included 756 COVID-19 patients demonstrated a 2-fold increase in the risk of death in the presence of atrioventricular block[7]. Multiple underlying mechanisms behind the development of atrioventricular block in COVID-19 patients have been postulated but incompletely understood. Inflammatory mediated injury to the myocardial cells and the intrinsic cardiac conduction system whether at the supra-Hisian or infra-Hisian level and severe hypoxia seem to be the main driving triggers to the development of heart blocks in COVID-19 patients[19]. Other possible underlying mechanisms mostly observed in patients with myocarditis due to COVID-19 are caused by the interruption of the electrical impulse generation or propagation throughout the cardiac conduction system[18]. Other suggested mechanisms in the literature are illustrated in Figure 3. It is also pertinent to mention that the use of hydroxychloroquine and azithromycin in year 2020 and the use of atrioventricular blocking agents such as beta blockers, which can prolong QTc interval and delay conduction at the level of the atrioventricular node, respectively, may have exaggerated the incidence of arrhythmias particularly in COVID-19 patients[20]. Therefore, to prevent the unnecessary over-utility of permanent pacemakers in these patients, it is imperative to re-evaluate this patient population for indications of permanent pacemaker placement after their recovery[21].

Our results suggest that patients with COVID-19 pneumonia who developed new-onset HDAVB or BBB without the presence of prior pacemakers and with concomitant positive SARS-CoV-2 results on admission, regardless of symptom

Table 4 Univariate regression analysis of encounters with coronavirus disease 2019 and with bundle branch block without pacemakers

Right or left bundle branch blocks without pacemaker	Adjusted OR	95%CI	P value
Mortality	1.63	1.42-1.89	< 0.001
Cardiac arrest	1.43	1.04-1.97	0.026
Atrial fibrillation	2.12	1.88-2.40	< 0.001
Atrial flutter	2.32	1.70-3.17	< 0.001
Ventricular fibrillation	2.31	1.11-4.82	0.024
Supraventricular tachycardia	2.22	1.64-2.99	< 0.001
Ventricular tachycardia	4.09	3.24-5.14	< 0.001
Acute kidney injury	1.71	1.53-1.90	< 0.001
Sepsis	1.81	1.52-2.26	< 0.001
Mechanical ventilation	1.67	1.38-2.23	< 0.001
Cardiogenic shock	3.29	2.04-5.31	< 0.001

Table 5 Univariate regression analysis demonstrating absolute value of outcomes of interest in encounters with coronavirus disease 2019 and with high grade atrioventricular block or bundle branch blocks without pacemakers, *n* (%)

In-hospital outcomes Rates	High degree atrioventricular block (<i>n</i> = 3210)	All bundle branch blocks without pacemaker (<i>n</i> = 17365)
Mortality	665 (21.3)	2952 (17.0)
Cardiac arrest	175 (5.6)	504 (2.9)
Atrial fibrillation	172 (5.5)	799 (4.6)
Atrial flutter	209 (6.7)	538 (3.1)
Ventricular fibrillation	44 (1.4)	87 (0.5)
Supraventricular tachycardia	150 (4.8)	555 (3.2)
Ventricular Tachycardia	222 (7.1)	799 (4.6)
Sepsis	365 (11.6)	1233 (7.1)
Mechanical ventilation	324 (10.4)	1528 (8.8)
Cardiogenic shock	103 (3.3)	174 (1.0)
Pulmonary embolism	106 (3.4)	521 (3.0)
Acute kidney injury	1298 (41.6)	5956 (34.3)
Cerebrovascular accidents	50 (1.6)	191 (1.1)

severity, consisted of an older population with a higher comorbidity burden, as evidenced by a higher prevalence of chronic kidney disease, diabetes mellitus, and heart failure. Hypertension, however, was less commonly observed in patients who developed HDAVB. The absence of hypertension in patients who developed HDAVB could be due to the fact that hypertension is a risk factor for other types of heart disease, such as coronary artery disease and heart failure, which may have masked the association with HDAVB in this study. White race and male gender were associated with a higher risk for developing HDAVB compared to other races and female gender. This higher incidence of HDAVB in white and female patients could be related to differences in genetic susceptibility or hormonal factors. However, further research is required to confirm this hypothesis.

Previous studies have shown that older age, male gender, and diabetes mellitus were associated with a higher risk of atrioventricular block. Additionally, a population-based cohort study established a longitudinal increase in the risk of atrioventricular blocks with each 20 mg/dL increase in fasting blood glucose level[22].

We also report a higher odds of tachyarrhythmias in patients with HDAVB as compared to patients without HDAVB. Given the higher burden of co-morbidities and older age in the former, the likelihood of fibrosis in the cardiac conduction system is high, which can lead to the development of HDAVB. Given these findings, it is understandable that higher mortality and major adverse cardiovascular events were more commonly observed in patients with a higher comorbidity burden.

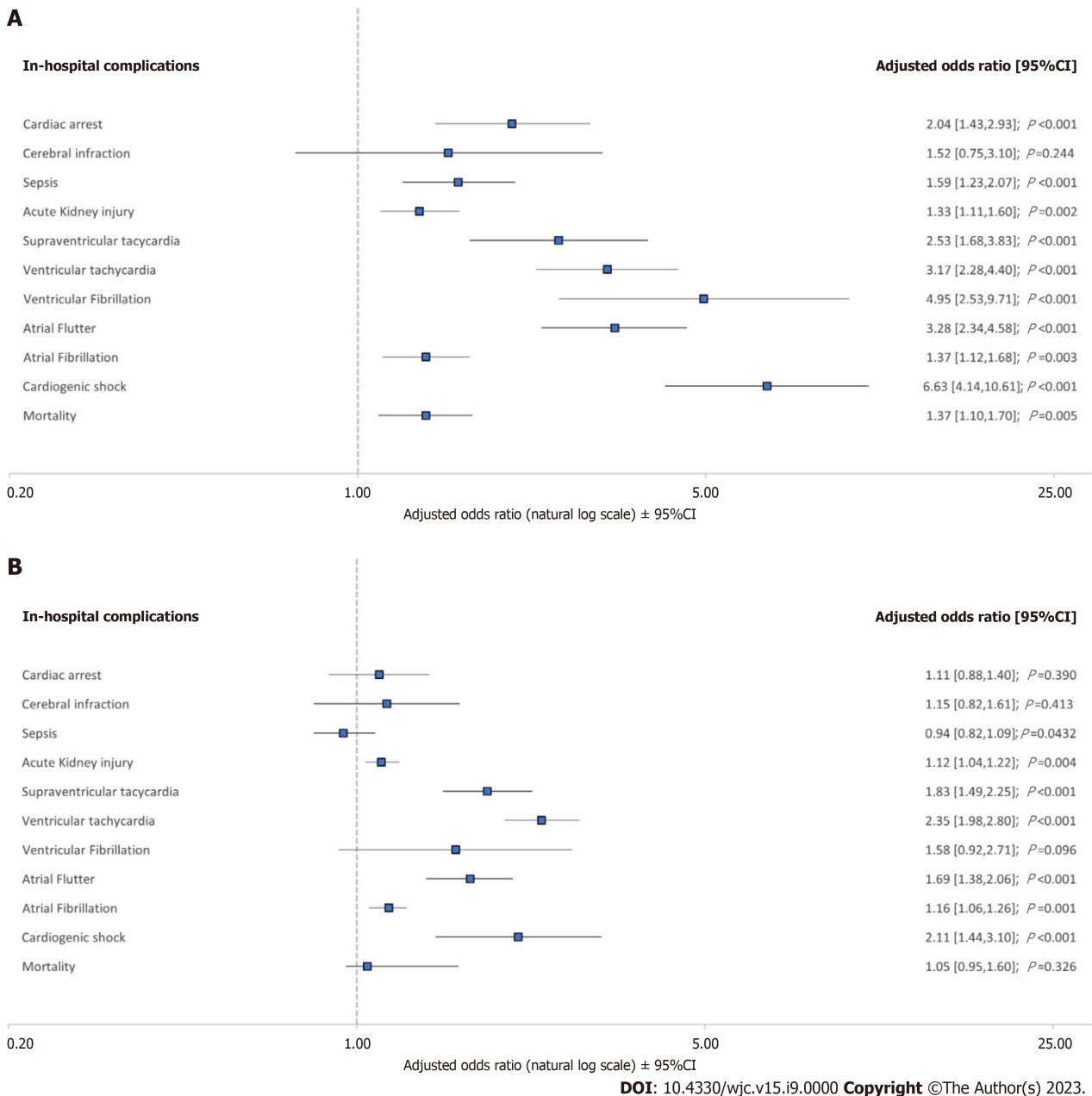


Figure 2 Multivariate regression analysis. A: Outcomes in patients with coronavirus disease 2019 (COVID-19) pneumonia who developed high degree atrioventricular block without permanent pacemaker; B: Outcomes in patients with COVID-19 pneumonia who developed bundle branch block without permanent pacemaker.

Moreover, patients with heart failure are more likely to be on atrioventricular nodal blocking agents precipitating heart blocks as well. HDAVB has been reported with COVID-19 though the incidence is rare and limited to case reports and series. The nature of HDAVB associated with COVID-19 is mostly regarded as transient with spontaneous recovery (incidence and percentages might add reliability) with mere observation[19,23] but has been treated with permanent pacemakers[24-26] and rarely with ablation as well[27].

Several studies have highlighted the association between COVID-19 infection and worse clinical outcomes in patients with new-onset bundle branch blocks. A meta-analysis encompassing 2539 hospitalized COVID-19 patients revealed a higher prevalence of LBBB among those experiencing unfavorable clinical outcomes[28]. Another meta-analysis comprising 1580 patients with COVID-19 infection demonstrated a mortality risk associated with LBBB, indicating its potential as a predictive marker[29]. Similarly, a meta-analysis involving 1904 COVID-19 patients revealed a significantly increased risk of short-term mortality in those with right bundle branch block (RBBB)[30]. Our own study further confirms a high risk of mortality in COVID-19 pneumonia patients with secondary diagnoses of new-onset bundle branch blocks and no prior intracardiac devices. The observed association between COVID-19 infection and new-onset BBB in our study opens up new avenues for understanding potential myocardial injury mechanisms in this context. Acute BBB may signify acute myocardial injury, possibly arising from various etiologies, including COVID-induced ischemic heart disease, inflammation or myocarditis, medication-related side effects, and electrolyte imbalances. Recognizing these potential mechanisms is crucial in guiding appropriate management strategies for these patients, especially those with

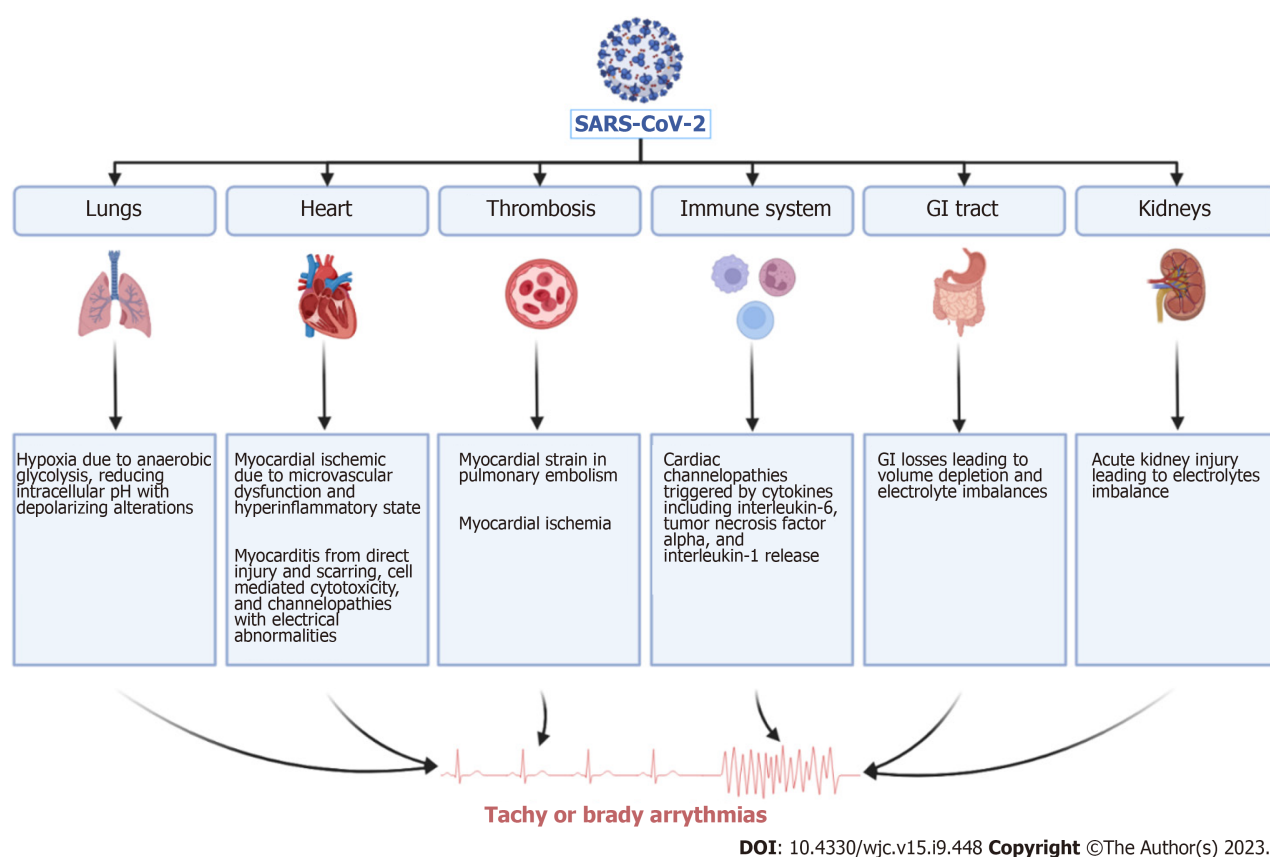


Figure 3 Underlying mechanisms behind the development of atrioventricular block in coronavirus disease 2019 patients. GI: Gastrointestinal; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

significant cardiovascular comorbidities.

Study limitations

Despite several significant findings, our study has several limitations as well. Since its a NIS based study, the limitations of database analysis apply here as well. The diagnosis depends on the ICD-10 coding and may not be representative of the actual real-world figures given the potential for human errors. The NIS database is limited in the use of therapeutic medications that the patients are on and therefore confounders with use of atrioventricular nodal blockers cannot be mitigated. Therefore, due to the unavailability of such data, we were unable to estimate medication effect on the development of HDAVB in our study. Thus, our results may underestimate the contributory effect of those medications on the development of HDAVB. It is pertinent to mention the use of hydroxychloroquine in the year 2020 which can prolong QTc and may have exaggerated the incidence of arrhythmias particularly in COVID-19 patients.

To ensure that all the patients admitted with COVID-19 pneumonia had a secondary diagnosis of new onset HDAVB, we decided to exclude patients with pacemakers or other intracardiac devices which may suggest a prior diagnosis of HDAVB. It is worth noting that due to the possibility that some patients without prior pacemakers may have had undiagnosed asymptomatic atrioventricular heart blocks prior to the diagnosis of COVID-19, those patients cannot be identified nor can be excluded.

CONCLUSION

As SARS-CoV-2 continues to loom with potential for future resurgence, there is a dire need for long term observational studies to better recognize patients at risk of developing fatal arrhythmias such as HDAVB or BBB and to validate management strategies. We conclude that elderly patients, whites, and males with underlying diabetes, chronic kidney disease, congestive heart failure, prior myocardial infarction, history of cerebrovascular accidents, or peripheral artery disease admitted for COVID-19 pneumonia who develop new onset HDAVB are at least six times more likely to develop cardiogenic shock and three times more likely to develop ventricular tachycardia or ventricular fibrillation and have a significantly increased risk of inpatient mortality. Meanwhile, patients who developed new onset BBB had an at least two times increased risk of developing cardiogenic shock and ventricular tachycardia compared to patients who did not develop BBB, albeit without significant increase in inpatient mortality.

Therefore, it is crucial for healthcare providers to recognize the potential for worse outcomes in patients with COVID-19 who develop new HDAVB or right or Left BBB, given their significant co-morbidities and predicted worse outcomes.

By identifying the disease process early in its course, through monitoring techniques and temporary pacemakers, it may be possible to initiate treatment early and prevent the development of adverse outcomes in high-risk patients.

Finally, the management of COVID-19 has evolved over time, including the use of different medications with varying cardiac effects. This evolution may impact the incidence and severity of bradyarrhythmias. Therefore, our dataset from 2020 may not be fully representative of the current situation.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) tremendously impacted patients worldwide. While most research has focused on the virus's effects on the respiratory system, we set to understand the impact that the virus has on the cardiac conductive system. Research has strongly suggested that COVID-19 has a predilection to cardiac tissue. Fewer studies, however, have looked into the effect of the virus on the cardiovascular conductive system. With the availability of pacemakers, cardiac monitoring techniques, and the increasing burden of cardiac arrhythmias triggered by COVID-19, there is a dire need for new studies to establish this association on a larger patient population.

Research motivation

By identifying the gaps in the literature, and with the emergence of case reports and series reported about this topic, we acknowledged the need for large scale studies to draw statistically significant conclusions which could give rise to new interventions that could possibly mitigate life threatening cardiovascular outcomes in high risk patients.

Research objectives

The aim of our study was to analyze the impact that COVID-19 had on the odds of major cardiovascular complications in patients with newly diagnosed heart blocks and bundle branch blocks on a large patient sample. Our analysis was successful in measuring the cardiovascular impact caused by this virus with significance of our results supported by our large sample of patients and patient selection process. We included only patients with new onset high degree atrioventricular blocks or bundle branch blocks, presumed to be triggered by COVID-19 or its treatment. Regardless of causality, which was not the aim of our study, we demonstrated the large burden of serious and life-threatening complications inflicting our patient population. Therefore, our results may suggest that high-risk patients may benefit from early use of temporary pacemakers to mitigate the negative impact coronavirus has on patients with newly diagnosed heart blocks and bundle branch blocks.

Research methods

Using the 2020 National Inpatient Sample database, we selected our patient population of interest, which included all patients hospitalized for COVID-19 pneumonia as the primary diagnosis, utilizing ICD-10 codes. To conduct our statistical analysis, we utilized STATA® (StataCorp, College Station, TX, United States) version 17. We further stratified our sample into patients who had a secondary diagnosis of either high degree atrioventricular blocks or bundle branch blocks. We excluded patients with prior pacemakers using ICD-10 procedure codes. Inpatient mortality was our primary outcome of interest while secondary outcomes included significant cardiac and noncardiac outcomes. Finally, multivariate and univariate regression analyses were conducted on both patient groups.

Research results

Our analysis demonstrated that patients with coronavirus 2019 pneumonia and newly diagnosed high degree atrioventricular blocks had a significantly increased odds of inpatient mortality, cardiac arrest, life-threatening tachyarrhythmias, need for mechanical ventilation, and cardiogenic shock. Patients with COVID-19 pneumonia and newly diagnosed bundle branch blocks experienced no significant increase in mortality on multivariate regression analysis however had similar other outcomes.

Research conclusions

Our study identified high risk groups or patients prone to poor clinical outcomes. Elderly white males with common medical co-morbidities such as diabetes, chronic kidney disease, and peripheral artery disease who were hospitalized for COVID-19 pneumonia and developed high degree atrioventricular block or bundle branch blocks experienced worse clinical outcomes, and thus may benefit from temporary pacemaker placement or long term cardiac monitoring techniques. However, additional research is required to establish clear benefit from the utility of temporary pacemakers or continuous cardiac monitoring techniques on the outcomes experienced in this patient population. Although we identified the increased odds of possibly fatal complications experienced by this patient population, we were unable to measure the contribution of medications used during our patients' hospitalizations due to the limitations of the National Inpatient Sample database. Furthermore, we have no available data to discern the outcomes of these patients following their discharge. This information would be crucial in determining the predicted course of disease in these patients.

Research perspectives

Future research with different methodology should focus on comparing outcomes of patients admitted with COVID-19 pneumonia with newly diagnosed heart blocks secondary to the virus and undergo temporary pacemaker placement to

controls who do not. This will help draw conclusions and establish guidelines that can standardize the approach and utility of temporary pacemakers in high risk patients.

FOOTNOTES

Author contributions: Shoura SJ and Alyousef T contributed to resources and conceptualization; Shoura SJ, Abbasi A, Ali L, Kanitsoraphan C, and Alyousef T contributed to supervision and project administration; Shoura SJ, Atluri R, and Alyousef T contributed to data selection; Shoura SJ, Teaima T, Sana MK, Abbasi A, and Alyousef T contributed to investigation; Shoura SJ, Teaima T, Sana MK, Atluri R, Yilmaz M, Hammo H, Ali L, Kanitsoraphan C, and Alyousef T contributed to validation; Shoura SJ, Abbasi A, Yilmaz M, Hammo H, and Alyousef T contributed to visualization; Shoura SJ, Teaima T, Sana MK, Abbasi A, Yilmaz M, Hammo H, and Alyousef T contributed to writing the original draft; Shoura SJ, Teaima T, and Sana MK contributed to table and figure creation; Shoura SJ, Teaima T, Sana MK, Abbasi A, Atluri R, Yilmaz M, Hammo H, Park DY, Ali L, Kanitsoraphan C, and Alyousef T contributed to manuscript review and editing; Shoura SJ, Teaima T, and Sana MK contributed to literature review; Shoura SJ and Alyousef T contributed to methodology; Atluri R contributed to software and formal analysis; Yilmaz M and Hammo H contributed to writing the second draft and final manuscript polishing; all authors have read and approved the final manuscript.

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Variant of Wellen's syndrome in type 1 diabetic patient: A case report

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Abstract

BACKGROUND

Wellen's syndrome is a form of acute coronary syndrome associated with proximal left anterior descending artery (LAD) stenosis and characteristic electrocardiograph (ECG) patterns in pain free state. The abnormal ECG pattern is classified into type A (biphasic T waves) and type B (deeply inverted T waves), based on the T wave pattern seen in the pericardial chest leads.

CASE SUMMARY

We present the case of a 37-year-old male with history of type 1 diabetes mellitus (T1DM), gastroparesis, mild peripheral artery disease and right toe cellulitis on IV antibiotics who presented to the emergency department with nausea, vomiting and abdominal pain for 3 d and as a result couldn't take his insulin. Noted to have fasting blood sugar 392 mg/dL. Admitted for diabetic gastroparesis. During the hospital course, the patient was asymptomatic and denied any chest pain. On admission, No ECG and troponin draws were performed. On day 2, the patient became hypoxic with oxygen saturation 80% on room air, intermittent mild right-sided chest pain which he attributed to vomiting from his gastroparesis. Initial ECG done was significant for Biphasic T wave changes in leads V2 and V3 and elevated high sensitivity troponin. Patient was transitioned to cardiac intensive care unit and cardiac catheterization performed with result significant for extensive coronary artery disease.

CONCLUSION

This case highlights an exceptional manifestation of Wellen's syndrome, wherein the right coronary artery and circumflex artery display a remarkable 100% constriction, alongside a proximal LAD stenosis of 90%-95%. Notably, this

occurrence transpired in a patient grappling with extensive complications arising from T1DM. Moreover, it underscores the utmost significance of promptly recognizing the presence of Wellen's syndrome and swiftly initiating appropriate medical intervention.

Key Words: Wellen's syndrome; Biphasic T waves; Deeply inverted T waves; Precordial leads; Left anterior descending artery; Pseudo-normalization; Right coronary artery; Left circumflex artery; Case report

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Core Tip: When a patient exhibits atypical symptoms preceding chest pain and displays distinct T wave abnormalities on the electrocardiogram, it is crucial to seek immediate cardiology intervention. This entails conducting emergent cardiac catheterization to evaluate the presence of proximal stenosis in the left anterior descending artery, or in rare instances, the right coronary artery and left circumflex artery. Such stenosis can lead to the development of ischemic cardiomyopathy if left untreated. Acting promptly and carefully monitoring the characteristic T wave patterns, alongside normal or minimally elevated cardiac biomarkers, contributes to improved mortality prognosis.

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INTRODUCTION

Wellen's syndrome is a distinctive condition characterized by distinct alterations in the ST-T waves in the precordial leads, indicating an obstruction in the proximal left anterior descending coronary artery[1]. This syndrome has been observed in individuals experiencing unstable angina, as well as those with atypical presentations devoid of acute chest pain. If left untreated, Wellen's syndrome can cause myocardial infarction and necrosis in the anterior wall of the heart. The hallmark features of Wellen's syndrome are biphasic T waves (type A in 25% of cases) or deeply inverted T waves (type B in 75% of cases) in V2-V3, which can extend to V1-V6 and often involve the proximal anterior left anterior descending artery (LAD). Nevertheless, research has demonstrated that this syndrome is not confined solely to the proximal anterior LAD, as similar changes have been reported in the right coronary artery (RCA) and circumflex artery [2]. The correlation between T wave changes in precordial leads and the heightened risk of developing anterior wall myocardial infarction, despite medical intervention, was first elucidated by de Zwaan *et al*[3] in 1982. The diagnostic criteria for Wellen's syndrome encompass a history of angina, deeply inverted or biphasic T waves in the precordial leads, normal or slightly elevated serum cardiac enzymes, absence of precordial Q waves, minimal or isoelectric ST segment elevation (less than 1 mm), and the presence of the specific electrocardiograph (ECG) pattern during pain-free states[4]. Risk factors associated with Wellen's syndrome include diabetes mellitus, arterial hypertension, metabolic syndrome, hypercholesterolemia, smoking, and a family history of premature heart disease, all of which are present in our patient. This case report, accompanied by a review of the existing literature, emphasizes the critical importance of early recognition of Wellen's syndrome, not only in relation to the proximal LAD, but also its involvement in both the RCA and circumflex artery.

CASE PRESENTATION

Chief complaints

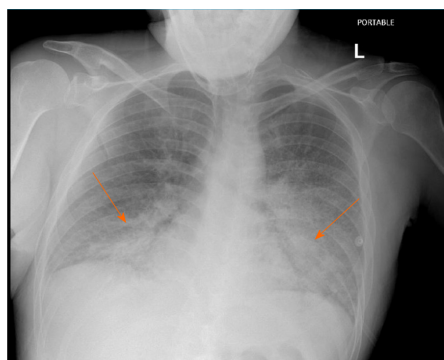
A 37-year-old man with chief complaint of nausea, vomiting, abdominal pain for 3-day duration associated with diarrhea.

History of present illness

The patient arrived at the emergency department with complaints of abdominal pain, characterized as burning, non-radiating and constant, 7/10 in severity, which he attributed to his gastroparesis as he has had multiple admissions with gastroparesis flares. Patient has a past medical history of type 1 diabetes, diabetic gastroparesis, major depression, anxiety, smoking (1 pack per week), 1 g of marijuana consumption and right 4th toe cellulitis recently treated with IV antibiotics. Admits to intermittent depressive episode; during which he stops taking his medication including insulin but denied suicidal ideation and intent.

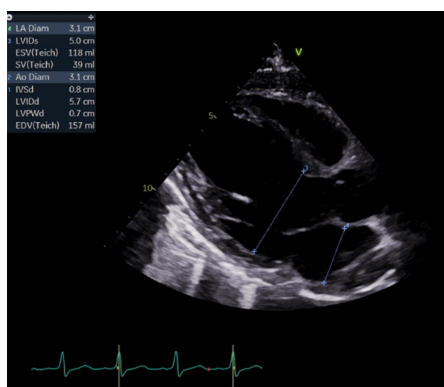
History of past illness

Diabetic gastroparesis, type 1 diabetes mellitus, peripheral artery disease, and right toe cellulitis on antibiotics.



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Figure 1 Chest X Ray consistent with acute pulmonary Edema. Indicating bat wing opacities, interstitial edema, increased cardiothoracic ration and cephalization of pulmonary vesselsl.



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Figure 2 Electrocardiogram indicative of ejection fraction less 20%. Moderately dilated left ventricle and left atrium.

Personal and family history

A noteworthy familial background of cardiovascular disease is documented, encompassing the father, parental uncle, and grandfather, each of whom underwent double bypass surgeries. The father's bypass operation was performed at the relatively young age of 40.

Physical examination

In the physical exam the abdomen was non-distended, tenderness on palpation of the 4 quadrants, positive bowel sounds, no organomegaly appreciated. The blood pressure on admission was 129/99 with heart rate of 124 bpm. Chest symmetry with respiration, no crackles or wheezing noted and normal vesicular breath sounds. Normal S1, S2 and no pathological murmur heard. The patient was euvolemic, and no bilateral lower extremity edema was noted.

Laboratory examinations

Urine toxicology is positive for marijuana. Given the atypical presentation, high sensitivity troponin was not ordered. Uncontrolled diabetes, Hyperlipidemia and hypoxia noted ([Table 1](#)).

Imaging examinations

Patient was admitted for diabetic gastroparesis, bedside point of care ultrasound; was significant for inferior vena cava (IVC) dilation and Kerley B lines. A chest X ray was ordered, which shows acute pulmonary edema ([Figure 1](#)). Given acute and sudden onset of hypoxia, echocardiogram (ECHO) was ordered ([Figure 2](#)), after notable elevation in cardiac enzyme (elevated high sensitivity troponin). The first electrocardiogram (EKG) was then ordered ([Figure 3](#)).

FURTHER DIAGNOSTIC WORK-UP

The patient underwent a treatment regimen that involved the administration of 3 L of normal saline, along with medications such as Benadryl, famotidine, Zofran, and IV fluids at a rate of 125 mL/h. Additionally, the patient received Reglan 10 mg every 8 h and pantoprazole. On the second day at 6:00 pm, the patient experienced a drop in oxygen

Table 1 Consistent with hypoxia from arterial blood gas, elevated troponin and uncontrolled diabetes

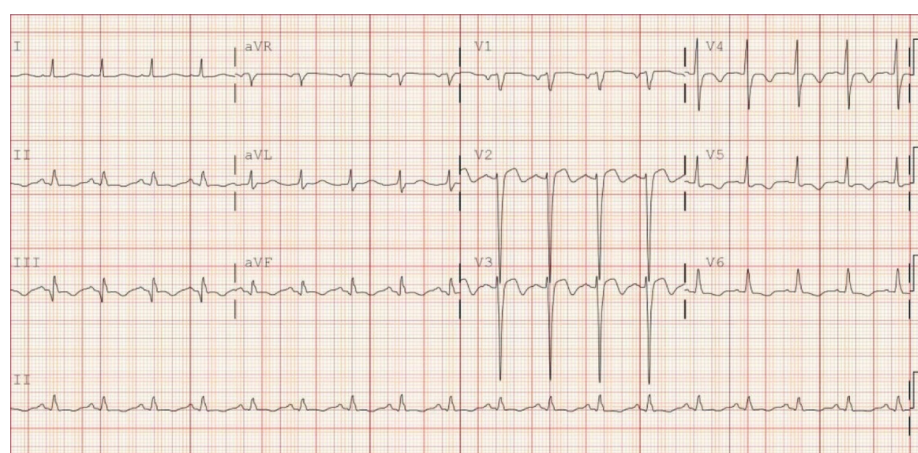
Hematology	Values	Chemistry	Values
WBC	17.00	High sensitivity troponin	12072.1
Hemoglobin	13.7	LDH	472
Hematocrit	40.3	TSH	0.810
MCV	95.1	T4	1.27
MCH	32.3	Hemoglobin A1C	10.9
RDW	12.1	Sodium	138
Platelet count	256	Potassium	4.1
Neutrophil	79.4	Chloride	105
Lymphocytes	13.3	CO ₂ level	23
Monocytes	7.0	Blood urea nitrogen	21
EOS count	0.1	Creatinine	1.05
Basophils	0.2	GRF estimation	> 60
Nucleated RBC	0	LDL	127
RBC	4.2	HDL	44
Procalcitonin	0.07	Total cholesterol	184
		Calcium	
		Arterial blood gas	
		pH	7.40
		pCO ₂	46
		O ₂	64
		HCO ₃	28.5

EOS: Eosinophil; GRF: Ground reaction force; HDL: High density lipoprotein; LDH: Lactate dehydrogenase; LDL: Low density lipoprotein; MCH: Melanin-concentrating hormone; MCV: Mean corpuscular volume; pH: Potential of hydrogen; pCO₂: Partial pressure of CO₂; RBC: Red blood cells; RDW: Red blood cell distribution width; TSH: Thyroid stimulating hormone; WBC: White blood cell count.

saturation, reaching the mid-80s while breathing room air. To address this, the patient was placed on a venti-mask at 50% oxygen concentration. During the examination, the patient acknowledged experiencing mild and intermittent right-sided chest pain, attributing it to vomiting and noting a history of similar pain during gastroparesis flares over the past 5 years. The patient denied any previous history of heart disease. A point-of-care ultrasound at the bedside revealed notable dilation of the IVC and the presence of Kerley B lines. Chest X-ray was ordered, which confirmed the diagnosis of acute pulmonary edema (Figure 1). Given the sudden onset of hypoxia, further investigations were initiated, including laboratory tests and an EKG (Figure 2). The patient received a 40 mg dose of furosemide and was subsequently continued on furosemide 40 mg every 12 h. To alleviate anxiety, the patient was given a STAT dose of alprazolam 0.25 mg orally. Following these measures, an initial EKG was ordered, along with a high sensitivity troponin test (Figure 3). Later that day, a cardiology consultation was sought, and an ECHO was performed. The ECHO revealed a moderately dilated left ventricle with a severely reduced ejection fraction of less than 20%. The left atrium was also found to be moderately dilated (Figure 2). The cardiologist was informed about the clinical findings and the elevated troponin levels. As a result, the acute coronary syndrome (ACS) protocol was initiated. The patient received a heparin drip following a loading dose of aspirin 81mg and a statin 80 mg, both given immediately. The patient was transferred to the cardiac center for coronary angiographic catheterization and right heart catheterization. The results of these procedures indicated the presence of extensive disease in the LAD, with stenosis extending to both the RCA and circumflex artery (Figure 4).

FINAL DIAGNOSIS

Conclusion of the cardiac coronary angiogram report indicated the following: Dominance: Right dominant; left main: Mild luminal irregularities less than 30%; left anterior descending artery: Min lad: 90% stenosis; distal lad: 95% stenosis; diagonal 1: 90% stenosis; circumflex artery: Ostial circ: 100 % stenosis; and RCA: Prox rca: 100% stenosis.



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Figure 3 Electrocardiogram showing Biphasic T wave inversion on V2-V3. T wave inversion in V4-V5.

TREATMENT

Following the placement of an intra-aortic balloon pump in the cardiac laboratory center, the patient was promptly transferred to the intensive care unit. In this setting, the patient's treatment regimen included the immediate initiation of aspirin 81 mg, ticagrelor 180 mg given STAT, followed by 90 mg every 12 h. Additionally, a nitroglycerin drip and 80 mg of atorvastatin were administered. The cardiologist recommended transferring the patient to a tertiary center for urgent coronary artery bypass graft (CABG) surgery given significant coronary artery lesions. On January 23, 2023, the patient underwent quadruple CABG, and a subsequent bedside ECHO revealed no evidence of pericardial effusion. Upon improvement, the patient was discharged with a medication regimen consisting of spironolactone 25 mg, metoprolol succinate 25 mg, aspirin 81 mg, atorvastatin 80 mg, valsartan 40 mg, and dapagliflozin 5 mg once a day.

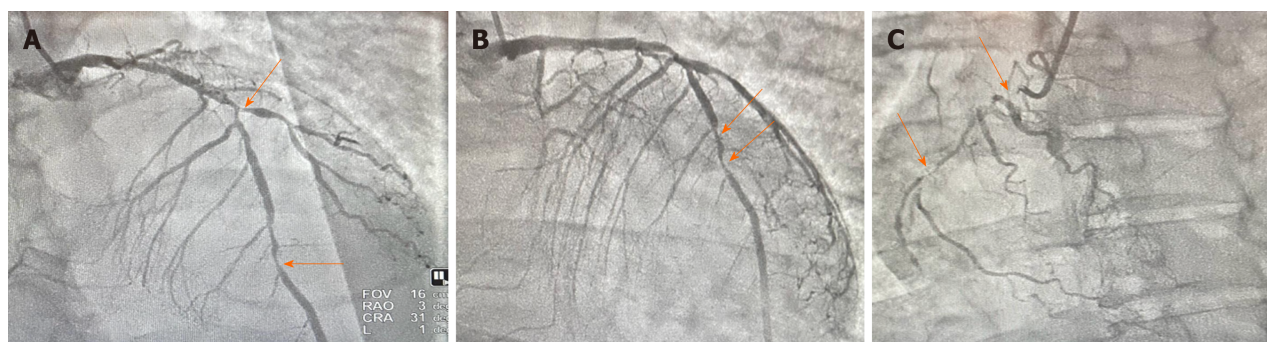
OUTCOME AND FOLLOW-UP

Follow up in Cardiology clinic 1 wk post discharge from the tertiary center after contrary bypass graft. Notable significant improvement of symptoms with improved functional capacity and activities of daily living.

DISCUSSION

Wellen's syndrome was first described in 1982 by de Zwaan *et al*[3] as proximal LAD T-wave syndrome in the process of evaluating subgroup of patients with unstable angina during a stable and pain-free period[5]. Our patient presents with no chest pain, but abdominal pain, which he attributed to his recurrent gastroparesis. Wellen's syndrome was then discovered to be associated with significant critical occlusion of the LAD with a characteristic presentation distinctive to abnormal T wave changes in precordial leads in patients with suspected ACS. The electrocardiographic manifestation of Wellen's syndrome is characterized by 2 patterns; pattern A has biphasic T waves in V2-V3 (25%), and pattern B has symmetric and deeply inverted T waves in precordial chest leads (75%)[5,6]. In this case report, the patient presented on EKG with biphasic T wave in V2-V3 (Figure 2). These T wave changes signifies severe myocardial dysfunction or ischemia, although patients have been known to exhibit this syndrome during a pain free period at the time EKG is taken and have normal or minimally elevated cardiac enzymes, the prognosis of its event represents high risk of extensive anterior wall myocardial infarction within time of presentation[7]. Wellen's syndrome can also be a pre-coronary infarction stage that can lead to detrimental ACS. The concept of occlusion and reperfusion in the EKG sequence of Wellen's syndrome likely involves sudden complete occlusion of the LAD causing transient anterior ST segment elevation myocardia injury, leading to chest pain and diaphoresis stage not captured on EKG. Second stage then involves re-perfusion of the LAD likely secondary to spontaneous clot lysis leading to resolution of the chest pain with improvement in ST elevation and the appearance of biphasic or inverted T wave morphology[8]. Although Wellen's syndrome is known to involve mostly the LAD the syndrome is not limited to the anterior leads. The precordial T wave changes can be seen in the inferior or lateral leads with RCA or circumflex artery occlusion as noted in many studies and events in our case presentation. Diagnostic criteria of Wellen's syndrome includes[9]: Isoelectric or minimally elevated (< 1 mm) ST segment elevation; no precordial Q waves; deeply inverted or biphasic T waves in V2-V3 but may extend to V1-V6; ECG pattern present in pain free state; preserved precordial R wave progression; recent history of angina; and normal or elevated serum cardiac markers.

Wellen's syndrome is often not an acute process as it can develop over days or weeks especially seen in people with risk factors (smoking, hypertension, diabetes and metabolic syndrome *etc.*). Although the syndrome is a temporary



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Figure 4 Coronary angiography report. A to C: Coronary angiogram report consistent with severe triple vessel disease with stenosis in left anterior descending artery (A), left circumflex artery (B) and right coronary artery (C).

obstruction of the culprit coronary artery (pre-infarction state), LAD or artery involved can re-occlude at any time and the first EKG seen is normalization of the T wave called pseudo-normalization after which the T wave becomes upright and prominent; thus sign of hyper acute ST-elevation myocardial infarction during which the patient complains of chest pain that is associated with other symptoms of ACS[10]. Sometimes Wellen's syndrome can manifest in normal coronaries following an episode of vasospasm seen in cases of cocaine abuse, however, it is still appropriate to rule out thrombus formation or coronary thrombosis with angiogram during presentation given the syndromes risk of leading to severe and extensive anterior wall myocardial infarction and possible death. The phenomenon of re-occlusion and re-perfusion was likely experienced by our patient, however given the history of uncontrolled diabetes with complications, his presentation prior to hospital admission maybe masked during occlusion stage given the result of extensive coronary stenosis found on cardiac angiogram (Figure 4).

It is well known fact that uncontrolled diabetes can lead to cardiovascular disease. Its pathophysiology is linked to hyperglycemic state leading to an increase in oxidative stress, which results in micro and macrovascular complications. Persistent elevation in blood sugar can cause an overproduction of superoxide by the mitochondrial electron transport chain leading to complications seen in diabetic patients. The activation of superoxide overproduction pathway leads to increase generation of nitric oxide due to uncoupled state of endothelial nitric oxide synthase (NOS) and inducible NOS. All which leads to deoxyribonucleic acid (DNA) damage due to the formation of the strong oxidant peroxynitrite[11]. DNA damage causes rapid activation of poly (adenosine diphosphate-ribose) polymerase, depleting the intracellular concentration of its substrate nicotinamide adenine dinucleotide, and slowing the rate of glycolysis, electron transport, and adenosine-triphosphate formation and thus causing acute endothelial dysfunction[12]. Hyperglycemic state is an inflammatory state as it induces surge of inflammatory cytokines (such as C reactive protein, interleukin interleukin (IL)-6, IL-8 tumor necrosis factor- α , and endothelin-1) and as result contribute to plaque instability. Accumulation of these inflammatory cytokines leads to endothelial injury and hypercoagulability increasing the risk for cardiovascular event. In clotting cascade, the quantity of clotting factors, including glycation and oxidation is affected during hyperglycemic state increasing the risk of thrombosis[13]. Patients with type 1 diabetes are on insulin regimen for glycemic control. Hyperinsulinemia can lead to an increase in hepatic synthesis on prothrombic factors leading to thrombotic state.

Cardiac autonomic neuropathy (CAN) is the most common complication seen in type I diabetic patients. Poor glycemic control is the risk factor of CAN with prevalence approximately 20%, increases with age and a known predictor of cardiovascular morbidity and mortality in type 1 diabetes[14]. Type 1 diabetes is thought to be caused by an autoimmune reaction that destroys the beta cells of the pancreas. The same immunological factors are seen affecting the sympathetic ganglia leading to cardiac sympathetic dysfunction[15]. All these pathologies can also be seen in patients with type 2 diabetes. In correlation to our patient, who presented with uncontrolled and complicated diabetes as such has increased risk of CAN and atherosclerosis. Our patient presented with Wellen's syndrome, but the diagnosis was late given that patient delayed medical evaluation for cardiac disease, as he believed that all his symptoms of intermittent chest discomfort were due to prolonged vomiting and gastroparesis flares.

CONCLUSION

Wellen's syndrome emphasizes the need for serial EKGs in patients with cardiovascular risk factors, as critical stenosis may be detected and require invasive interventions. This case report highlights the extensive nature of Wellen's syndrome, involving occlusion in the LAD, RCA, and circumflex arteries. It demonstrates that Wellen's syndrome extends beyond proximal LAD disease and presents distinct EKG changes. Clinicians face diagnostic challenges due to atypical presentations, delaying ACS identification. Thus, it is vital for clinicians to identify Wellen's syndrome on EKGs and evaluate high-risk patients regardless of atypical symptoms.

FOOTNOTES

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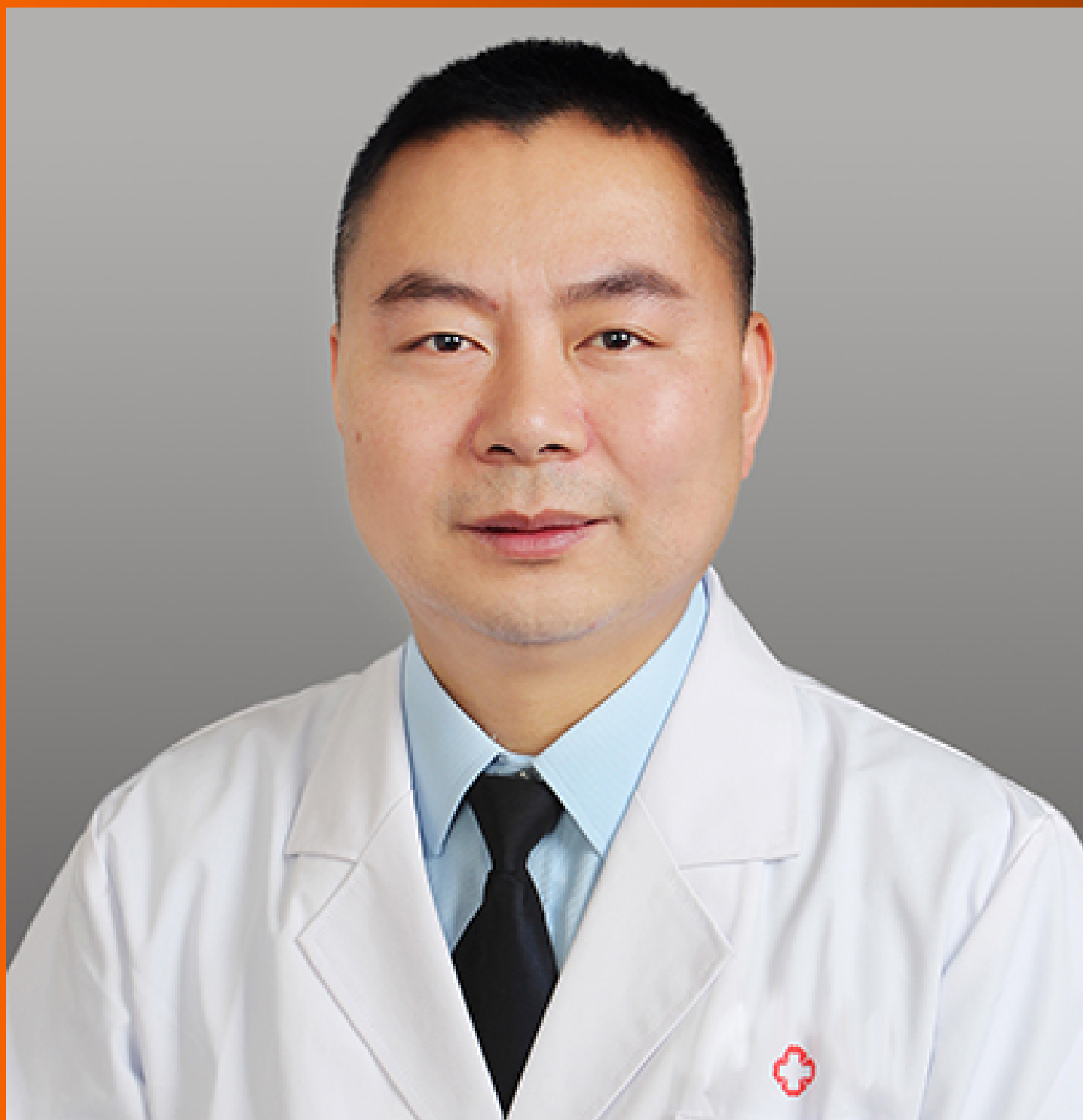
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Candida endocarditis: Update on management considerations

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Abstract

The rise in incidence rates of invasive candidiasis warrants an increase in attention and efforts toward preventing and treating this virulent infection. Cardiac involvement is one of the most feared sequelae and has a poor prognosis. Despite the introduction of several novel antifungal agents over the past quarter century, complications and mortality rates due to *Candida* endocarditis have remained high. Although fungal endocarditis has a mechanism similar to bacterial endocarditis, no specific diagnostic criteria or algorithm exists to help guide its management. Furthermore, recent data has questioned the current guidelines recommending a combined approach of antifungal agents with surgical valve or indwelling prostheses removal. With the emergence of multidrug-resistant *Candida auris*, a focus on improved prophylactic measures and management strategies is necessary.

Key Words: *Candida*; *Candida* endocarditis; Fungal endocarditis; Invasive fungal infection

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Core Tip: The incidence of Candida infective endocarditis has observed a noticeable rise. Despite the progress in medical understanding, Candida endocarditis (CE) continues to be linked with a notable increase in in-hospital mortality. This comprehensive review aims to elucidate the existing diagnostic modalities for identifying CE while emphasizing their inherent limitations. Furthermore, we clarify the prevailing standard treatment protocols, encompassing medical and surgical interventions. Additionally, we highlight the role of screening techniques in identifying high-risk patients and explore the discussion of prophylactic measures tailored to specific patient phenotypes.

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INTRODUCTION

Although our understanding of endocarditis has evolved since its first description by William Osler in the late 19th century, it remains a disease of high morbidity and mortality[1,2]. Candida endocarditis (CE) which accounts for only 1%-2% of all endocarditis cases, is associated with a mortality rate as high as 80%[3-6]. Given that CE is particularly rare, formal studies comparing various management approaches and subsequent outcomes are limited. Current guidelines recommend a treatment regimen of antifungal agents combined with surgical interventions, whether valves or indwelling prostheses removal[7,8]. However, individuals suffering from CE often have multiple comorbidities and are at high risk for reinfection, making conducting invasive interventions challenging.

Furthermore, the uptrend in fungemia incidence rates in recent years has led to an increased number of patients at risk for CE[9]. Nonetheless, CE studies have relatively small sample sizes, which make them insufficiently powered to get robust research evidence into use. Therefore, this review explores the current diagnostic techniques and treatment considerations when evaluating and managing patients with CE.

BACKGROUND AND EPIDEMIOLOGY

Per definition, community-onset candidemia occurs within 48 h of hospitalization, with most cases identified on the day of admission, whereas nosocomial candidiasis occurs after 48 h of hospitalization[10]. The incidence of invasive candidiasis in the community and nosocomial infections has increased. There has been a noticeable increase in the incidence of community-acquired cases since the 1970s due to the intravenous drug (IVD) use epidemic, the use of impure brown heroin, and poor harm reduction practices, which have been associated with *Candida albicans* (CA)[11]. With the implementation of harm reduction strategies in the 1990s, the causative organisms have shifted to non-albicans *Candida* (NAC) species. The increased likelihood of the latter among IVD users has led again to the recognition of IVD use as an important risk factor for candidemia[12].

Different factors were found to increase the incidence of nosocomial candidemia, including increased antibiotics use, prolonged fluconazole prophylaxis in immunocompromised patients, use of total parenteral nutrition, and use of long-term catheters and medical devices[13-16]. Additional risk factors include malignancies of the gastrointestinal tract, genitourinary tracts, and the breast associated with CA infection and hematologic malignancy associated with NAC infection. Lastly, immunosuppressive therapies, including chronic steroid therapy, have been found to increase the incidence of CE and mortality risk[17].

Different *Candida* species can lead to advanced clinical infections, yet the most common agent leading to CE remains CA despite distinct patient characteristics and underlying risk factors[18]. Moreover, *Candida parapsilosis* was linked to infected medical devices such as prosthetic valves and transmitted through direct contact[19-21]. *Candida dubliniensis* and *Candida glabrata* are predominantly found among human immunodeficiency virus/acquired immunodeficiency syndrome patients with oral thrush and patients who are immunosuppressed on broad-spectrum antibiotics, respectively [18,22]. Although CA is primarily sensitive to antifungals, there is an emergence of intrinsic resistance of various *Candida* species to antifungals. Thus, it is essential to conduct antifungal susceptibility to ensure appropriate coverage[23]. *Candida auris* has recently emerged as a pathogen of significant concern worldwide, especially among chronically hospitalized patients. It is intrinsically resistant to multiple currently available antifungal therapies with a high mortality rate, often due to delayed diagnosis and initiation of antifungal therapy[24].

Despite the availability of effective antifungal therapy in most cases, mortality rates related to candidemia remain elevated, ranging from 30%-80%[25]. The latter is likely attributed to patients predisposing factors such as immunocompromised status and malignancies, recent surgery, and prior infective endocarditis (IE). Early diagnosis and administration of appropriate antifungal therapies *via* a multidisciplinary approach may have improved mortality rates over the years[4,23,27-28].

DIAGNOSTIC EVALUATION

Healthcare providers should be vigilant of an underlying CE when managing high-risk febrile patients with predisposing factors such as IVD users, prolonged antibiotic therapy, indwelling central venous catheter, prosthetic heart valve, history of endocarditis, parenteral nutrition, neutropenia, and diabetes mellitus[29]. Although the clinical presentation of CE can sometimes be indistinguishable from those of bacterial endocarditis, the loss of visual acuity, presence of cutaneous nodules, and cerebral embolization should raise concerns for a Candida infection[30,31]. Nevertheless, it remains a challenge to establish the diagnosis and differentiate CE from bacterial endocarditis.

In 1994, Durack *et al*[32] proposed the Duke Criteria, which are used to classify each case as definite, possible, or probable, and has been validated in several subsequent studies. Additionally, further trials emphasized Duke Criteria's high diagnostic sensitivity and specificity[33-35]. Furthermore, in 2000, Li *et al*[36] introduced the modified Duke Criteria, which have become the standard of care. Nevertheless, these criteria were developed to evaluate patients with suspected left-sided native valve IE, as its sensitivity is low in patients with cardiac device infection, prosthetic valves, and right-sided IE[37]. Duke Criteria were primarily implemented in the workup of bacterial endocarditis; however, to date, there are no specific diagnostic criteria for fungal endocarditis.

Fungal culture

Isolation of the causative organism is critical in establishing the microbiologic diagnosis and selecting appropriate therapeutic agents. However, Candida traditionally does not grow well in standard bacterial blood culture media, if at all, requiring a longer time for the organism to grow. The sensitivity of detection of Candida in blood cultures is limited to 50%-75%[38,39]. In one case series from France, 14% of 620 IE cases had negative blood cultures, while another study showed that 31% had negative cultures[40]. Hence, this will delay the diagnosis and treatment, which could lead to drastic outcomes. Therefore, modifications to the original Duke Criteria have been suggested to include additional risk factors, such as CRP/ESR elevation, hematuria, central non-feeding venous lines, and peripheral lines, as part of the criteria. These, in turn, led to increased diagnostic sensitivity[42]. However, when the modified Duke Criteria was tested in blood culture-negative IE, it performed poorly, possibly due to the lack of serological criteria[43].

Immunoassay studies-1, 3- β -D-glucan

In light of earlier addressed issues related to fungal isolation and culture difficulties, which remain the gold standard of diagnostic testing, non-culture-based tests have been developed, and some have found clinical applications. 1, 3- β -D-glucan is a polysaccharide ubiquitous in the fungal cell wall. Its detection in the serum with a cutoff of 60 pg/mL has a sensitivity and specificity of 69.9% and 87.1%, respectively, in a patient with candidemia[31]. It carries several advantages, including improved sensitivity on serial testing, strong specificity, positive likelihood ratio, and most importantly, antifungal agents do not affect 1, 3 β -D-glucan serum levels[44,45]. In a patient with *Candida glabrata* IE, β -D-glucan was found to be a helpful tool in assessing treatment response, whereby after treatment, the assay became negative[46]. Hence, this could be used as a screening tool for CE and to monitor clinical response to therapy.

Mannan antigen and anti-mannan antibody

Mannan is an essential constituent of the Candida cell wall. Both mannan and anti-mannan antibodies have been found in the serum of patients with candidiasis. A meta-analysis by Mikulska *et al*[47] showed that combined testing using immunosorbent assays for detecting mannan antigen and anti-mannan antibodies have a sensitivity of 83% and specificity of 86% in patients with invasive candidiasis. However, its usefulness is limited due to rapid clearance from the bloodstream. Furthermore, immunosuppressed patients may not develop adequate antibody response against the mannan antigen, thus resulting in false negative tests[48].

Polymerase chain reaction

The development of molecular diagnostic techniques has improved the ability to identify the causative pathogen and decreased the required time for microorganism identification from days to hours. Rice *et al*[49] found polymerase chain reaction (PCR) to have a threefold increase in sensitivity in detecting causative agents in the setting of IE compared to traditional bacterial Gram-stain and culture. Multiple cases of successful diagnosis of culture-negative fungal endocarditis utilizing this technique have been reported[50,51]. Multiplex PCR systems, such as BioFire®, are now employed routinely in clinical settings and have been shown to offer a rapid and accurate diagnosis of selected Candida species in fungemic patients. Recent advancements have also led to the development of a novel immuno-based microfluidic device that can rapidly detect CA in under 2 h with a capture efficiency of 77.4% $\pm$ 4.4%[52]. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry is a technique that analyzes large biomolecules, such as DNA, protein, and sugar, as unique molecular fingerprints to allow rapid and accurate identification of microorganisms to decrease wait time for establishing correct diagnosis and initiation of appropriate therapy[53,54].

Limitations

These non-culture-based tests have several disadvantages, which have limited their widespread use. The yield of these tests is time-sensitive, and results might be altered with antifungal administration, which increases the possibility of false negative results. The accuracy of the test and its ability to make an identification depend on the quality of the database from which the test references, which is ever-expanding and improving. Thus, careful interpretation of test results is essential since sometimes the test may detect multiple or unusual organisms, which implies a critical determination of their clinical relevance. The availability of the test remains limited, and the turn-around time is significant, making them

not a first-line diagnostic tool. Finally, these tests are costly, further limiting their widespread use[55,56].

IMAGING MODALITIES

The use of echocardiography in the diagnosis of endocarditis is well established. Transthoracic echocardiogram (TTE) has a sensitivity of approximately 70% in the diagnosis of native-valve endocarditis (NVE) and about 50% for prosthetic-valve endocarditis (PVE). The sensitivity for each will improve to more than 90% when a transesophageal echocardiogram (TEE) is used, suggesting the superiority of TEE. For fungal endocarditis, echocardiography has shown an overall sensitivity of 77%[6]. Indeed, for patients with candidemia, TTE was shown to detect vegetation in 2.9% of patients compared to 11.5% of patients with TEE[57]. Moreover, TTE had a sensitivity of 88.9% with NVE and 76.5% with PVE in the diagnosis of CE compared to TEE, which had an improved sensitivity of 92% with NVE but a worse sensitivity of 61.1% in the case of PVE, which could be related to the small sample of patients with PVE that underwent TEE[4,6].

Other imaging techniques have been developed that have shown promising applications in diagnosing endocarditis [38]. Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography (18F-FDG-PET/CT), which identifies increased uptake of labeled glucose by cells in inflamed tissue, has improved sensitivity and specificity of the modified Duke criteria to 82% and 96%, respectively, even better if the NVE cases were excluded, up to 96% and 94% if only PVE and cardiac-device-related IE are considered. Limitations of this technique include potential myocardial and respiratory artifacts that need to be gated out, difficulty distinguishing between inflammatory from infectious lesions, and limited ability to detect small vegetations along the device leads[58]. 18F-FDG-PET/CT was reported to help diagnose CE and improve accuracy. Hence, it is promising in situations where TTE/TEE might not be diagnostic[59].

Single photon emission tomography with technetium 99m-hexamethyl propylene amine oxime (HMPAO)-labeled autologous leukocytes (^{99m}Tc-HMPAO-labeled SPECT/CT), on the other hand, takes advantage of the natural homing and recruitment of leukocytes to the site of inflammation/ infection to identify potential areas of abnormality. This technique does require additional time to prepare and complete compared to ¹⁸F-FDG-PET/CT. It takes time to obtain, isolate, and prepare autologous leukocytes from the host, and the images are acquired in multiple phases. Other imaging limitations include affection by metallic artifacts, non-specific bowel activity due to hepatic HMPAO excretion, and its limited ability to detect small vegetations[60]. These techniques are technically challenging and require well-trained radiologists who are familiar with the technique. Therefore, they are not widely available and are usually implemented when other evaluation techniques, such as echocardiograms, are inconclusive. The yield of either study may be affected by antibiotic exposure; thus, finding the optimal time to utilize this imaging modality to achieve the maximal result in the course of patient evaluation remains an important question[61,62]. Nevertheless, these techniques have demonstrated very promising results in the diagnosis of PVE and cardiac device-related IE, with one study showing a sensitivity of 80%, specificity of 91%, negative predictive value of 80%, and positive predictive value of 91% using ¹⁸F-FDG PET/CT and 60%, 100%, 100%, and 85% for ^{99m}Tc-HMPAO-SPECT/CT, that the use of nuclear imaging study when appropriate has been included as a consideration in European IE guidelines[61-63].

MANAGEMENT

Medical management

Current Infectious Diseases Society of America (IDSA) guidelines recommend treating native or prosthetic valve CE with either a lipid formulation of amphotericin with or without flucytosine or a high dose echinocandin for initial therapy, with step-down therapy to fluconazole for patients who have susceptible isolates, that have demonstrated clinical improvement, and have cleared Candida from their bloodstream. Step-down therapy to oral voriconazole can be used for susceptible isolates that are not susceptible to fluconazole. Valve replacement is recommended if there is no contraindication, followed by continued antifungal treatment for six weeks after surgery. Finally, long-term therapy with fluconazole is recommended for patients who cannot undergo valve replacement[8]. Despite this seemingly straightforward algorithm, this infection has seen little or no improvement in patient outcomes. While this may indicate an inherent defect in our approach to treatment, one must further analyze this sophisticated pathogen and the hosts most likely to become infected.

As Candida is known to form biofilms that result in decreased cell membrane ergosterol content through reduced expression of ergosterol biosynthetic genes while upregulating the expression of genes involved in amino acid and nucleotide metabolism and efflux pumps[64,65], a combination antifungal regimen would theoretically be more effective in the treatment of fungal infection. However, using an *in vitro* model, Pai *et al* [66] compared the activities of flucytosine, micafungin, and voriconazole as either single agents or in combination against several Candida species and found no difference in the reduction of fungal burden between triple *vs* single agent antifungal therapy. Conversely, a 2011 meta-analysis of 64 cases of CE who received fluconazole alone, concurrently, or in sequence with other antifungals without surgical intervention suggested that multiple-agent therapy is preferable. In this study, Smego and Ahmad[67] reported that combination regimens, including fluconazole cured or improved 86% and 68% of patients with native and prosthetic valve infections, respectively. Furthermore, fluconazole administered alone was associated with a 42% rate of relapse or death. At the same time, the best outcomes were found in patients maintained on chronic suppressive fluconazole therapy following an initial amphotericin or echinocandin regimen for a minimum of six months. Although antifungal

agents tend to have significant side effects and drug-drug interaction profiles, prolonged fluconazole use is relatively benign. In a retrospective study of individuals receiving chronic fluconazole for suppression of artificial implant infection, Penk and Pittrow[68] found no significant adverse events. Of note, this study's maximum duration of treatment was 4.5 years, and the maximum daily dose was 750 mg.

A study compared amphotericin B and echinocandin-based therapy directly. While there was a higher percentage of older patients in the echinocandin group and the majority of infections in the amphotericin B group were community-acquired, the rates of utilization of combination antifungal therapy, suppressive antifungal therapy and adjunctive surgery were statistically equivalent. Mortality rates measured in-hospital, at 42 d and 1 year, did not differ between the two groups. Based on this study, the echinocandin group could be a better choice of initial therapy given similar clinical outcomes and a better side effect profile than amphotericin[69].

Combination antifungal therapy of amphotericin B and flucytosine was shown to have similar clinical outcomes compared to an antifungal followed by adjunctive surgical intervention[70]. Different antifungal combinations have been tried, including azoles plus echinocandins, 5-FC-combination therapies, and polyenes plus azoles[71]. Amphotericin B and flucytosine have been found to work synergistically, albeit with nephrotoxic side effects[67]. Furthermore, the combination of amphotericin B and fluconazole demonstrated antagonism[69]. IDSA guidelines recommend echinocandins with or without fluconazole as first-line therapy, which was found to be non-inferior to amphotericin B in managing endocarditis[8,69]. Additional challenges are encountered with NAC species, such as *Candida lusitanae* and *Candida krusei*, which are intrinsically resistant to polyenes and fluconazole, respectively[72,73].

Significant differences in clinical outcomes have been observed between right and left-sided disease in bacterial and fungal infections[74-6]. In a 2018 retrospective study, Siciliano *et al*[77] found that patients with isolated right-sided CE had a 32% mortality rate *vs* 61% for left-sided disease. Furthermore, individuals with right-sided disease have lower rates of acute heart failure and perivalvular complications. While right-sided CE still portends a poor prognosis, isolated valve involvement should be a characteristic considered when discussing outcomes and treatment options.

Surgical management

Literature on the surgical approach in CE is limited to small prospective studies with conflicting evidence and weak recommendations. For instance, 15 case reports from patients with CE showed that a combination of surgical and medical, when carried out early on admission, had lower mortality than single therapy[27]. A meta-analysis of 879 cases of CE found that patients who underwent adjunctive surgery had lower mortality. However, higher mortality was seen in surgical repairs before 1980, fungal monotherapy, and left-sided endocarditis. Although, this did not meet statistical significance[70]. In contrast, an observational cohort study in 2015 failed to show mortality benefits between those undergoing surgical therapy and those receiving medical treatment alone[69]. The European Society of Clinical Microbiology and Infectious Diseases recommends earlier surgery in the setting of prosthetic valves as opposed to infection involving native valves[38]. The need for surgical intervention may differ among cases caused by different *Candida* species. A recent retrospective study showed that surgery was performed earlier in cases of CE caused by *Candida parapsilosis* compared to CA endocarditis[78]. Rivoisy *et al*[79] demonstrated that in patients with prosthetic valve CE, early surgery was not associated with better survival at six months compared to medical management alone with liposomal amphotericin B induction and long-term suppression with fluconazole.

A newer approach with minimally invasive surgical intervention with angioVac has been used in right-sided IE with vegetation debulking. A meta-analysis of AngioVac-assisted vegetation debulking demonstrated procedural and clinical success of 89.2% and 79.1%, respectively. Also, greater than 50% vegetation removal was achieved in 90% and bacteremia clearance of 82.5% with procedure-related complications of 10.1%. However, documentation of this approach for left-sided endocarditis is not yet available[80]. It has been proposed that debulking in CE can lead to the resolution of fungemia similar to bacteremia in bacterial endocarditis[81].

PROPHYLACTIC MEASURES

Prophylactic measures have been given to selected patients at high risk of complications from candidemia. Several studies have explored high-risk populations, and many were found to have similar underlying genetic alterations leading to candidemia. Some generic modifications include Toll-like receptor signaling influence and certain single nucleotide polymorphisms[82-84]. A meta-analysis by Shorr *et al*[85] showed that prophylactic fluconazole reduced the risk of infection but failed to show improved mortality. The latter was also demonstrated in another randomized controlled trial between 1995-2000 in 26 intensive care units (ICU), where patients with central line catheters were randomized to fluconazole 800 mg *vs* placebo. It also failed to improve primary composite outcomes, including fever resolution, absence of invasive fungal infection, and discontinuation of prophylaxis due to toxicity and the need for additional systemic antifungal medication[86]. On the other hand, prophylaxis might increase the risk of resistance to antifungal drugs, which was described in the SNETRY Antifungal surveillance program that underlined both intrinsic and acquired resistance to fluconazole based on differences in species distribution among the geographic areas, variation in antifungal usage and infection control practice. Other disadvantages include cost and side effects[87]. IDSA guidelines report that prophylaxis with fluconazole (12 mg/kg) loading dose and then 6 mg/kg daily gained weak recommendation when administered to high-risk ICU patients[8]. This points to the need for a new screening modality to identify patients at high risk for severe candidemia and its complications.

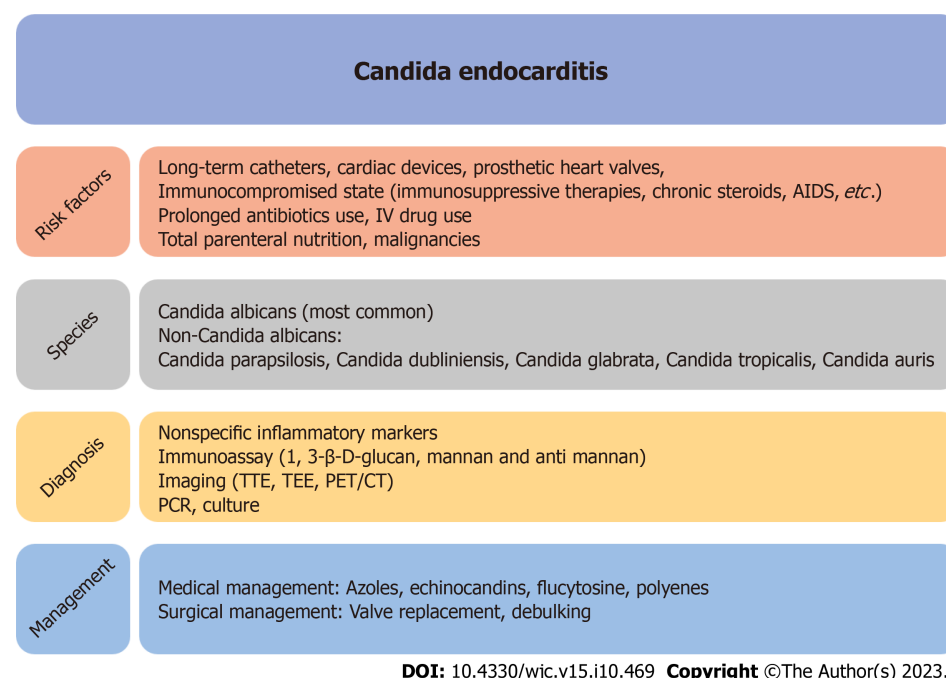


Figure 1 Central Illustration. AIDS: Acquired immunodeficiency syndrome; TEE: Transesophageal echocardiogram; TTE: Transthoracic echocardiography; PCR: Polymerase chain reaction; PET/CT: Positron emission tomography/computed tomography.

CONCLUSION

Despite advances in cardiac surgery and antifungal therapy, overall mortality and morbidity due to CE have not improved significantly. Given the increasing incidence of candidemia and the emergence of multi-drug resistant Candida species, there is an urgent need for further development of fungal-specific diagnostic criteria, including novel diagnostic tests, and management guidelines, both therapeutic and surgical. While the modified Duke criteria have been applied to diagnose fungal endocarditis, one of the major criteria requires positive blood cultures, which can be a source of delay in diagnosing CE. As there are limited data regarding some of the newer diagnostic techniques, criteria specific for fungal endocarditis utilizing fungal antigens and PCR technology would lead to earlier diagnosis and treatment (Figure 1).

New techniques, such as minimally invasive suction thrombectomy, can remove and debulk vegetations[88,89] without the risk and complications associated with conventional surgery and may provide alternative solutions. Current and future innovations in diagnostic tests and medical and surgical management of CE will permit earlier recognition of infection, reduce rates of potential complications, and improve long-term outcomes. The most successful strategy will likely require increased attention to the prophylactic reduction of indwelling foreign devices, antibiotic stewardship, and dedicating resources to the IVD use epidemic.

FOOTNOTES

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Related mechanisms and research progress in straight back syndrome

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Abstract

Despite the high prevalence of straight back syndrome (SBS), there is still limited research on this condition, posing challenges for effective diagnosis and treatment. The disease has been known for a long time, but there have been few related studies, which mostly consist of case reports. These studies have not been systematically summarized, making it difficult to meet the current needs of diagnosis and treatment. This article summarized the existing literature and comprehensively reviewed the diagnosis, pathogenesis, treatment, and research status of mitral valve prolapse related to SBS. We specifically emphasized the mechanisms and prognosis of SBS combined with mitral valve prolapse and discussed the latest research progress in this disease.

Key Words: Straight back syndrome; Mitral valve prolapse; Arrhythmia; Review; Diagnosis; Treatment

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Core Tip: Straight back syndrome (SBS), a benign skeletal abnormality of the thorax, is typically accompanied by mitral valve prolapse. Despite its prevalence, there is limited research on this condition, making effective diagnosis and treatment challenging. Recent studies have revealed controversy on SBS and its related mechanisms. This review focused on the mechanisms and current research progress of SBS associated with mitral valve prolapse.

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INTRODUCTION

Straight back syndrome (SBS), also known as flat chest syndrome, is characterized by the disappearance of the normal kyphotic curvature of the thoracic spine, which results in a decrease in the anterior-posterior diameter of the chest and restriction of the heart (Figure 1). It was first reported by Rawlings[1] in 1960. Due to the presence of heart murmurs during cardiac examinations, patients are often referred to the cardiology department for evaluation[2]. Mitral valve prolapse (MVP) is a valvular heart disease characterized by soft texture of the mitral valve, which can billow upward and back into the left atrium during heart contraction (prolapse). Prolapse of the mitral valve can lead to mitral regurgitation. If the MVP causes significant enlargement of the atria, arrhythmias may occur. Previously, SBS-associated MVP was considered a “pseudo-heart disease,” and patients may have no symptoms or only mild clinical symptoms such as chest tightness and shortness of breath. Even when severe symptoms occur, they are mostly thought to be due to mechanical and structural changes resulting from compression of the large blood vessels in the heart[3]. However, recent studies have found that SBS-associated MVP may be related to the expression of genes, which has attracted wide attention and controversy[2].

In clinical practice, some patients with MVP are often misdiagnosed as having “senile valve disease” or “congenital heart disease” due to the lack of primary disease diagnostic criteria. In the clinic, it is not uncommon for SBS to cause changes in cardiac structure and circulatory function[4]. However, the clinical manifestations can vary widely, often leading to misdiagnosis. Unfortunately, despite being discovered over 60 years ago, research on this subject remains scarce and often centers on case reports. Presently, these studies lack systematic summarization and fail to meet the current diagnostic and treatment reference needs. Therefore, this article comprehensively reviewed the literature on the diagnosis, pathogenesis, treatment, and research status of SBS-related MVP and provided clinical assistance by summarizing the latest and most significant achievements in this field.

DIAGNOSIS AND EPIDEMIOLOGY

SBS is a benign thoracic skeletal malformation that is often misdiagnosed as heart disease as it can cause heart murmurs detectable on physical examination[5]. Patients are usually asymptomatic, and the most common symptoms are chest pain and palpitations. However, there is a lack of large-scale epidemiological investigations into the incidence of SBS in the general population. A previous study by Jiang and Li[6] reported that among 114 SBS patients, the vast majority of cases (108) occurred in individuals under 40 years of age, with approximately 60% (66 cases) occurring in those aged between 20-40 years. The prevalence in females was higher than that in males. The incidence rate significantly decreased, and symptoms were milder in patients over 40 years of age, which may be due to reduced lung tissue and chest wall elasticity with increasing age, leading to natural alleviation of the condition[7]. A study in 2022 found that thoracic vertebrae may undergo degenerative changes with increasing age. In the general population, this change may cause excessive thoracic kyphosis, but in patients with SBS, it may relieve symptoms[8].

In 1956, Deleon *et al*[9] first proposed a diagnostic criterion for SBS, which was a ratio of anterior-posterior to transverse thoracic diameter less than 1/3 measured at the T8 level. In 1980, Davies *et al*[10] revised this criterion and proposed a diagnostic criterion for SBS on lateral chest radiographs, where the distance from the midpoint of the T8 vertebral body to the vertical line connecting the anterior borders of T4 and T12 was less than 1.2 cm (Figure 2). SBS typically occurs in young, lean individuals who lack normal thoracic kyphosis, leading to a decreased sagittal diameter of the thorax[11]. Auscultation may reveal splitting of the second heart sound, and a prominent murmur is generally caused by compression of the right ventricular outflow tract by the sternum, which lessens with deep inspiration. X-ray examination is the most important diagnostic method, especially left lateral images, where the spinal thoracic segments appear straight and the sagittal diameter is narrowed. Twigg *et al*[12] measured the ratio of thoracic anterior-posterior to transverse diameter in 24 patients with SBS and 100 normal individuals, revealing a mean ratio of 37.1%, which is lower than the normal value of 40.0%. Furthermore, X-ray features may include a heart-thorax ratio ≤ 0.5 , protruding pulmonary artery segments, leftward shift of the cardiac silhouette, or signs of a pseudo-enlarged heart. In SBS patients, electrocardiography generally demonstrates normal values. In some patients, due to compression of the heart and positional changes, V1 leads may show a rsR' pattern, avR for the Qr pattern, R/S > 1, or R/S = 1, and some individual patients may exhibit high voltage of the left ventricle, sinus bradycardia, and incomplete right bundle branch block.

In some ultrasonography results of SBS patients, there may be a concomitant finding of MVP. Previous studies have suggested that this may be related to the compression-induced deformation of the mitral valve due to narrowing of the sagittal diameter[13]. However, a study conducted in 2020 indicated that both SBS and MVP may be inherited in an autosomal dominant manner[14]. It is believed that the vertebral malformation occurs during the 8th wk of gestation before ossification of the spine, and the penetrance is incomplete, with a higher expression frequency observed in female subjects. It has been reported in the international literature that 17%-23% of MVP patients have scoliosis, while 54%-67%

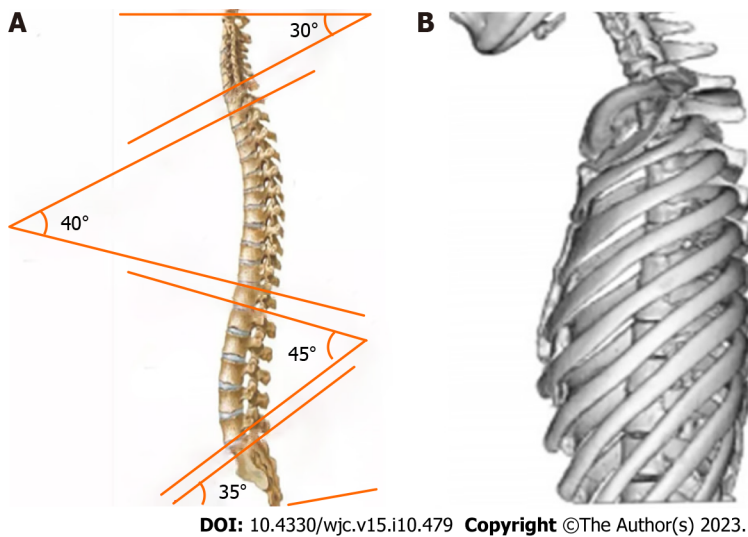


Figure 1 Differentiating between normal individuals and individuals with straight back syndrome with physiological distortion. A: The human spine typically exhibits physiological curvature; B: In individuals diagnosed with straight back syndrome, this curvature is noticeably absent.

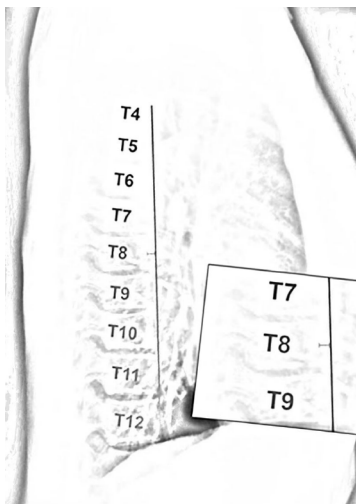


Figure 2 Diagnostic criterion for straight back syndrome on lateral chest radiographs, where the distance from the midpoint of the T8 vertebral body to a vertical line connecting the anterior borders of T4 and T12 is less than 1.2 cm.

of scoliosis patients have concomitant MVP[15]. Based on these studies, it can be inferred that the higher incidence of MVP in SBS is not only a result of physical factors but is also related to genetic factors. National literature has not reported such a high incidence rate, which may be due to inadequate knowledge at the time.

SBS WITH COMORBIDITY MECHANISMS

SBS is often associated with several complications, and the underlying mechanisms are still not fully understood. One theory suggests that compression of the thorax could reduce lung capacity and cause hypoxia, leading to various cardiovascular and respiratory problems. Recent studies have shown that compression may also affect the functioning of the autonomic nervous system, leading to abnormal heart rate variability[16]. Additionally, the reduced sagittal diameter of the chest could lead to mechanical distortion of the heart and major vessels, causing abnormal blood flow[17]. In the study by Grillo *et al*[18], MVP was the most common associated cardiac disease, occurring in approximately 64% of SBS cases. Some studies suggest that the high incidence of MVP and scoliosis in SBS patients may be related to a common genetic background, but further research is needed to clarify this relationship.

Mechanisms underlying the co-occurrence of MVP in SBS

In several previous studies, there was consistent evidence of the co-occurrence of SBS and MVP[19], but it was not until

2017 that Movahed *et al*[20] demonstrated a statistically significant association between these two conditions. In their study, 77% of SBS patients underwent mitral valve repair or replacement due to severe mitral regurgitation caused by MVP. There are two hypotheses regarding the mechanism of SBS co-occurring with MVP. The first hypothesis, proposed by Chen *et al*[3], suggests that scoliosis and MVP are both manifestations of a more common disease, which is inherited in an autosomal dominant manner with incomplete penetrance. Family studies have found a tendency towards clustering of MVP and scoliosis, indicating that these diseases may have a genetic basis.

Additionally, a number of genome-wide association studies have identified several genetic variations associated with SBS, some of which may affect the susceptibility of MVP and scoliosis. For example, one study found that the *LRP2* gene located at 9q22.32 was associated with the susceptibility of scoliosis and MVP[21], whereas another study found a close relationship between the *EFEMP1* gene located at 5q35.3 and both scoliosis and MVP[22]. Furthermore, recent research has suggested that the MVP comorbidity in SBS may be related to the TGF- β signaling pathway, which induces cardiomyocyte apoptosis and promotes fibroblast proliferation[23].

It has also been discovered that SBS and floppy mitral valve disease are both inherited in an autosomal dominant manner with a significant family history, and three possible gene loci (16p12.1-p11.2, 11p15.4, and 13p31.3-p32.1) have been reported[24]. Floppy mitral valve causes enlargement of the mitral valve orifice area, elongation or rupture of the chordae tendineae, and enlargement of the mitral annulus, ultimately leading to MVP. It is believed that these malformations occur during the 8th wk of gestation before ossification of the spine, with incomplete penetrance and higher expression frequency in female subjects[4]. These studies suggest that genetic variations and molecular mechanisms may play important roles in the high incidence of MVP and scoliosis in SBS patients. However, the notion of a “more common disease” proposed by Chen *et al*[3] has yet to be proven.

Another hypothesis suggests that physical compression is a primary factor leading to the co-occurrence of MVP in SBS. The thoracic spine of SBS patients loses its normal posterior convex curvature, resulting in a decreased distance between the sternum and spine. This leads to compression of the heart and torsion of the major vessels, ultimately leading to distorted mitral valve morphology due to pressure[25]. The study by Chen *et al*[3] indirectly supported this view using cardiac magnetic resonance imaging to identify a correlation between the site of cardiac compression in SBS patients and the occurrence of arrhythmia. This evidence indicated that some, if not all, of the cardiac alterations seen in SBS are influenced by physical compression factors.

Mechanisms underlying the cardiac morphological changes and arrhythmia comorbidity in SBS

The causes of cardiac morphological abnormalities in SBS may include: (1) Differing degrees of cardiac pulsation restriction due to varying degrees of front-to-back narrowing of the thoracic cavity caused by flat thoracic vertebrae; (2) Left atrial compression, which increases pulmonary circulation resistance and reduces returning blood volume; and (3) Long-term frequent rapid arrhythmia causing cardiac enlargement and decreased cardiac function. In the study by Chen *et al*[3] among SBS patients with cardiac morphological abnormalities, 54.2% showed a consistent location between arrhythmia origin and the cardiac compression site, suggesting that mechanical compression of the heart may lead to enhanced aberrant electrophysiological activity in the heart through the activation of self-regulatory mechanisms.

Previous understanding of SBS was limited to chest wall deformities, which may cause mild symptoms such as palpitations, chest tightness, and chest pain, while severe cases may have morphological functional changes in the heart chambers, valves, and major vessels. However, recent studies have compared cardiac magnetic resonance imaging, electrocardiogram, and electrophysiological data of 43 SBS patients and found a relationship between the cardiac compression site and arrhythmia occurrence in addition to the morphological and functional changes caused by flat chest walls[3]. This study proposed that arrhythmias are the result of cardiac compression. However, a study conducted in 2013, found that MVP comorbid with various arrhythmias is very common, with ventricular arrhythmias being the most frequent, potentially due to increased sympathetic nervous activity and stimulation of the myocardium by prolonged chordae tendineae[26]. Given that MVP frequently co-occurs with SBS, it may be one of the reasons for the frequent occurrence of arrhythmias in SBS. This view has been partially confirmed by recent research. In the study by Xia *et al*[27], 8.3% of MVP patients were found to have preexcitation syndrome, and follow-up results showed a generally good prognosis for SBS comorbid with MVP.

SBS comorbid with cardiac murmurs

In SBS patients, cardiac murmurs may sometimes be heard on auscultation, but detailed examination often reveals no cardiac abnormalities. There have been reports of SBS being misdiagnosed as cardiac diseases with abnormal heart sounds, such as atrial septal defect, pulmonary valve stenosis, or mitral regurgitation[3]. The mechanism underlying cardiac murmurs in SBS has not been well studied, but a more credible explanation is that the loss of thoracic physiological kyphosis in SBS patients causes displacement of the heart and great vessels. This leads to the right ventricle and pulmonary artery being closer to the posterior sternum, increasing the contact area between the sternum and the posterior heart margin, resulting in a “strengthened” jet effect of blood flow, almost invariably causing grade I-III systolic murmurs in the pulmonary valve auscultation area of each patient[28]. Due to prolonged compression of the heart on the dorsal margin of the sternum, the heart is subjected to long-term overload, causing hypertrophy of cardiomyocytes characterized by increased cell volume, diameter, and length. When hypertrophy reaches the critical limit, it increases the systolic wall tension of the ventricular wall, leading to the parallel proliferation of myocardial fiber cells, followed by thickening of the myocardial fibers. As a result, the thickness of the ventricular wall increases and the cavity does not expand significantly, leading to outflow tract obstruction and the production of murmurs (Figure 3).

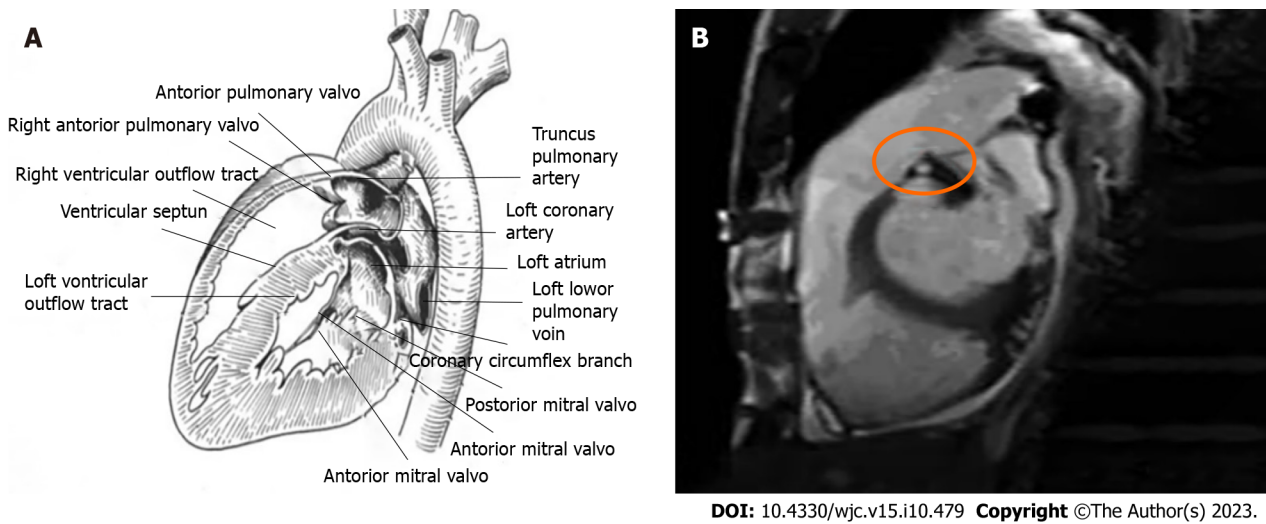


Figure 3 Comparison of right ventricular outflow tract between normal patients and patients with straight back syndrome. A: Right ventricular outflow tract patency in a normal individual; B: Right ventricular hypertrophy and narrowing of the right ventricular outflow tract in a patient with straight back syndrome.

RESEARCH STATUS

It has been over 60 years since SBS was first reported in 1960[1]. Despite the long history, the literature on this topic remains relatively scarce, with case reports dominating the available data (Figure 4). According to recent statistics, the past 10 years have seen the greatest SBS-related research activity, and significant breakthroughs have been made.

Xu *et al*[29] conducted a retrospective analysis of 16 cases of misdiagnosed situs inversus totalis and summarized the clinical features of SBS patients. The authors emphasized the importance of chest X-ray lateral films and concluded that echocardiography is an effective diagnostic tool for SBS. Another study conducted in the same year also highlighted the importance of chest X-ray lateral films as a key diagnostic feature of SBS (Figure 5)[30].

Hou *et al*[31] investigated a method for diagnosing SBS by combining the ratio of the distance from the anterior edge of the T8 vertebral body to the posterior edge of the sternum to the anterior-posterior diameter of the thorax with the ratio of the distance from the anterior edge of the T8 vertebral body to the posterior edge of the sternum to the transverse diameter of the thorax and the curvature arc height from T3 to T12. Recently, studies have also shown that this diagnostic method was more reliable for diagnosing SBS[32-35]. In a recent study of 1569 randomly selected patients who underwent 64-row chest computed tomography (CT) scans, it was found that CT could identify signs that were not visible on X-ray films, leading to a more accurate diagnosis of SBS and a better correlation of clinical symptoms with imaging findings, as has also been reported in studies overseas. Matsumoto *et al*[33] recently used echocardiography and right ventricular angiography to uncover the mechanism underlying the change in heart murmur with respiration, which they found to be due to variation in the diameter of the right ventricular outflow tract during respiration. It was not until 2017 that Marbella *et al*[34] investigated the statistical correlation between SBS and MVP and revealed that 27% of patients with severe mitral valve regurgitation caused by MVP also had SBS.

In terms of treatment, Betz *et al*[35] reported the successful case of a 19-year-old patient with SBS who presented with spinal pain and exertional dyspnea. The patient's symptoms were relieved by a 12-wk course of treatment involving corrective exercises, traction, and posture adjustment. In another study, the use of 3D printing technology to simulate chest wall replacement tissue was reported to alleviate severe compression symptoms in an SBS patient[17]. Another complication of SBS is tracheomalacia caused by chronic compression of the trachea and main bronchi, resulting in decreased mediastinal diameter. In 2021, Schmid *et al*[36] successfully cured a 36-year-old female patient suffering from this condition by proximal aortic, brachial artery, sternoplasty, and anterior tracheal fixation surgery.

SBS is a benign thoracic skeletal abnormality that is usually associated with MVP and a heart murmur often detected during physical examination. Patients are usually asymptomatic, with chest pain and palpitations being the most common symptoms. X-ray examination is the most important diagnostic tool, showing a straightened thoracic spine and a decreased anterior-posterior diameter in the thoracic segment. Recent studies have confirmed the importance of echocardiography and CT in the diagnosis of SBS. The mechanism of SBS with MVP may be due to genetic or physical factors (compression), and the mechanism of heart murmur may also be due to physical factors or indirect causes following MVP.

Although SBS was discovered some time ago, there have been relatively few related studies. Recent studies have explored the importance of diagnostic tools in SBS and reemphasized the clinical features of SBS to avoid misdiagnosis. Some studies have also identified the mechanisms of arrhythmia in patients with SBS and the possible mechanism of heart murmur changing with respiration. Progress has been made in the treatment of SBS in some patients with severe compression symptoms through corrective exercise, traction, 3D printing technology, and surgery.

All these studies have achieved success under the development of new equipment and technologies, which may be one of the reasons for the rapid increase in related research in the past decade. Looking back on the development of medicine

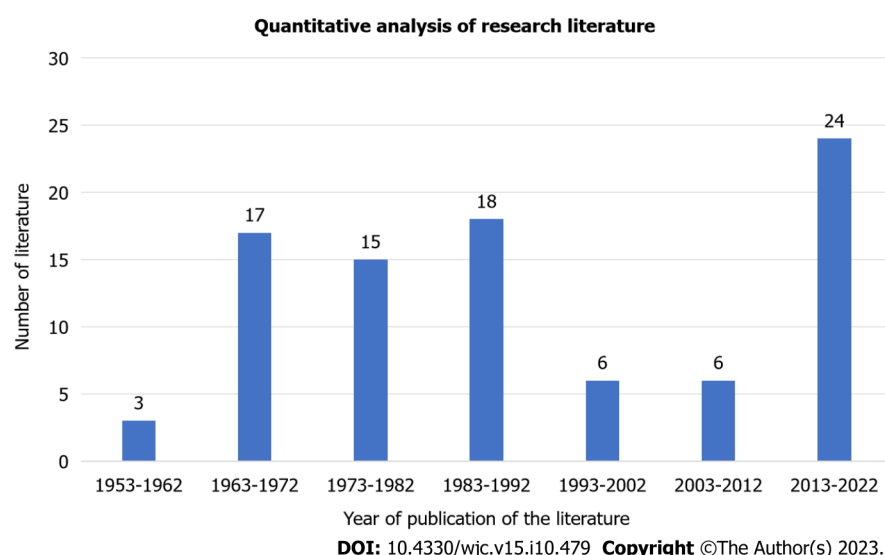


Figure 4 Distribution of straight back syndrome publications from 1953 to 2022.

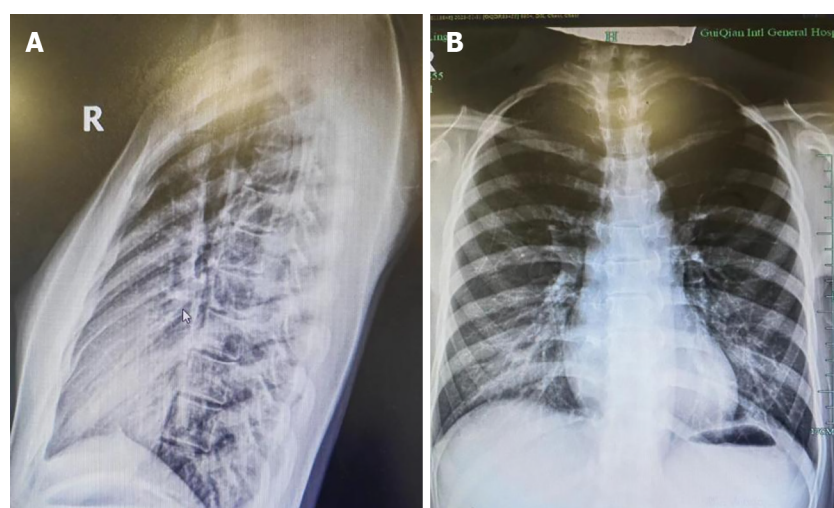


Figure 5 Chest X-ray film of a patient with straight back syndrome. A: Lateral chest X-ray; B: Anteroposterior chest X-ray.

in recent years, adjusting or updating existing diagnostic and treatment methods to improve the quality of life of SBS patients and reduce or eliminate serious complications caused by diseases is the focus of clinical physicians and an important direction of academic research. We hope that this article will serve as a stimulus for future research and provide new ideas.

CONCLUSION

SBS is a thoracic skeletal malformation often accompanied by MVP. Diagnostic criteria include the ratio of anterior-posterior to transverse thoracic diameter and specific X-ray features. The co-occurrence of SBS and MVP may be due to genetic variation and molecular mechanisms or physical compression. Cardiac morphology and arrhythmia in SBS may be caused by restricted cardiac pulsation, left atrial compression, and sympathetic activity. Recent studies have emphasized the importance of chest X-rays, echocardiography, and CT scans for diagnosing SBS. New methods for diagnosing SBS with MVP have been proposed. Treatment options include exercise, traction, posture adjustment, 3D printing, and surgical interventions.

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FOOTNOTES

Author contributions: He GX and Li J provided crucial suggestions and guidance for the writing; Kong MW wrote the manuscript; Pei ZY, Zhang X, Du QJ, and Tang Q reviewed and revised the manuscript; All authors read and approved the final manuscript.

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Value of cardiac magnetic resonance on the risk stratification of cardiomyopathies

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Abstract

Cardiomyopathies represent a diverse group of heart muscle diseases with varying etiologies, presenting a diagnostic challenge due to their heterogeneous manifestations. Regular evaluation using cardiac imaging techniques is imperative as symptoms can evolve over time. These imaging approaches are pivotal for accurate diagnosis, treatment planning, and optimizing prognostic outcomes. Among these, cardiovascular magnetic resonance (CMR) stands out for its ability to provide precise anatomical and functional assessments. This manuscript explores the significant contributions of CMR in the diagnosis and management of patients with cardiomyopathies, with special attention to risk stratification. CMR's high spatial resolution and tissue characterization capabilities enable early detection and differentiation of various cardiomyopathy subtypes. Additionally, it offers valuable insights into myocardial fibrosis, tissue viability, and left ventricular function, crucial parameters for risk stratification and predicting adverse cardiac events. By integrating CMR into clinical practice, clinicians can tailor

patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis. The non-invasive nature of CMR reduces the need for invasive procedures, minimizing patient discomfort. This review highlights the vital role of CMR in monitoring disease progression, guiding treatment decisions, and identifying potential complications in patients with cardiomyopathies. The utilization of CMR has significantly advanced our understanding and management of these complex cardiac conditions, leading to improved patient outcomes and a more personalized approach to care.

Key Words: Cardiac magnetic resonance; Cardiomyopathies; Prognosis; Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy

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Core Tip: Cardiomyopathies encompass a diverse range of diseases affecting the heart muscle, each with varied causes. Symptoms of cardiomyopathies can manifest differently and change over time, necessitating regular evaluation through cardiac imaging techniques. These approaches play a crucial role in diagnosis, treatment guidance, and prognosis optimization. To enhance the precision of anatomical and functional evaluation and obtain valuable prognostic insights, cardiovascular magnetic resonance (CMR) is typically employed. By integrating CMR into clinical practice, clinicians can tailor patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis. This manuscript aims to explore how the CMR contribute to the diagnosis and management of patients with cardiomyopathies specially focus on the risk stratification.

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INTRODUCTION

Cardiomyopathies encompass a diverse range of diseases affecting the heart muscle, each with varied causes. The European Society of Cardiology (ESC) traditionally categorizes them into hypertrophic, dilated, arrhythmogenic, restrictive, or other forms[1]. Moreover, they are further classified as either familial/genetic or non-familial/non-genetic. We must highlight that this classification is highly discussed[2].

Symptoms of cardiomyopathies can manifest differently and change over time, necessitating regular evaluation through cardiac imaging techniques. These approaches play a crucial role in diagnosis, treatment guidance, and prognosis optimization.

Patient evaluation involves gathering medical history, conducting a physical examination, and performing an electrocardiogram (ECG). Transthoracic echocardiography (TTE) can raise suspicions of cardiomyopathy. To enhance the precision of anatomical and functional evaluation and obtain valuable prognostic insights, cardiovascular magnetic resonance (CMR) is typically employed. In some cases, nuclear medicine tests or cardiovascular computed tomography may also be necessary.

This manuscript aims to explore how the CMR contribute to the diagnosis and management of patients with cardiomyopathies.

CARDIOMYOPATHIES WITH DILATED PHENOTYPE

CMR plays a crucial role in the diagnosis and evaluation of dilated cardiomyopathies (DCM). We usually distinguish the DCM on the basis of the etiology between two groups, the non-ischemic DCM (NIDCM) and ischemic DCM (IDCM).

Non-ischemic dilated cardiomyopathy

CMR plays a crucial role in the diagnosis and management of NIDCM. NIDCM is characterized by left ventricular (LV) enlargement, systolic dysfunction, and myocardial fibrosis without significant coronary artery disease[3] and absence of other abnormal loading conditions like hypertension, valvular heart disease or congenital heart disease. CMR provides a noninvasive and accurate assessment of LV morphology, function, and remodeling[3]. It allows for the quantification of myocardial fibrosis, which is useful in assessing viability in ischemic cardiomyopathy[4]. CMR can also provide detailed and clinically useful information about the type and severity of cardiac damage by characterizing tissue changes in the myocardium[5].

One important application of CMR in NIDCM is the identification and characterization of fibrosis microstructure. Late gadolinium enhancement (LGE) imaging, a technique used in CMR, can detect enhancement patterns associated with fibrosis in NIDCM patients[6]. Fibrosis microstructure has been found to modulate reentry in NIDCM, and understanding these variations can improve risk stratification and guide treatment decision[6]. Computational modeling based on CMR images has been used to examine variations in fibrosis microstructure and quantify their effect on reentry inducibility and mechanism[6]. This information can help identify patients at high risk of sudden cardiac death (SCD) and guide the selection of appropriate interventions[6]. CMR is also valuable in differentiating NIDCM from other cardiomyopathies. CMR-derived myocardial parameters, such as total LV myocardial mass index and percentage of non-compacted myocardium, have been found to be discriminators between patients with LV non-compaction cardiomyopathy, other cardiomyopathies, and healthy controls[6]. This differentiation is important for accurate diagnosis and appropriate management of patients with NIDCM[7].

Furthermore, CMR can provide prognostic information in NIDCM. Global longitudinal strain (GLS) of the left ventricle measured by CMR feature tracking (FT) analysis has revealed enhanced prognostic utility when compared to conventional parameters in NIDCM[8]. Moreover, researchers have investigated the prognostic significance of right ventricular (RV) GLS through CMR-FT analysis has been evaluated in a cohort of individuals with NIDCM[8]. These investigations collectively highlight the promising ability of CMR to predict significant cardiac events and events related to heart failure in patients with NIDCM[8].

In relation with sequences like T2-STIR, T1, T2 and Extracellular volume (ECV) mapping there is controversial data some experts state that T1 and ECV have limited value that is explained by the reduced precision in NIDCM due to thinning of the myocardium[9]. Other authors have claimed some potential value of T1 and ECV, elevated ECV and T1 measurements have demonstrated prognostic significance regardless of LV ejection fraction (LVEF) and the presence of LGE[10]. Moreover, an elevated native T2 value suggests the potential existence of myocardial edema, potentially indicating the presence of inflammatory cardiomyopathy[11]. These methods present encouraging novel approaches for risk assessment; nevertheless, additional validation remains necessary.

In summary, CMR is playing a crucial role in the diagnosis, risk stratification, and prognostication of NIDCM. It provides valuable information about LV morphology, function, and remodeling, as well as the presence and characteristics of myocardial fibrosis. CMR can differentiate NIDCM from other cardiomyopathies and help guide treatment decisions. Additionally, CMR-derived parameters, such as GLS, have shown prognostic value in NIDCM. Overall, CMR is a valuable tool in the comprehensive evaluation and management of NIDCM patients.

Ischemic dilated cardiomyopathy

CMR plays a crucial role in the diagnosis and evaluation of IDCM. IDCM is a type of DCM that is caused by ischemic heart disease (IHD)[12]. Approximately 70% of heart failure cases have been attributed to IHD[13]. From the SOLVD study, IHD tended to have a greater impact than NIDCM, with double the risk of hospitalization and quadruple the risk of death[14].

CMR as we shown before this technique can aid in the differentiation of ischemic from non-ischemic cardiomyopathy subtypes. Currently, CMR-derived cardiac imaging is effective for both definition of IHD and for ischemia detection, with important diagnostic and prognostic implications[15].

The “function-perfusion-tissue characterization” triad should be studied in IHD for an adequate evaluation of cardiac viability and ischemic burden. As mentioned, the subendocardial distribution of LGE identifies an ischemic injury as opposed to fibrosis with meso- or subepicardial distribution, typical of non-ischemic alterations[16]. CMR is also effective in defining myocardial viability through discrimination of LGE extension and segmental kinesis[4,17].

From the SPINS registry, extensive ischemic burden was related to a higher risk of major cardiac event, including hospitalization for congestive heart failure (HF), and revascularization was associated with a protective effect only in the extensive ischemia subset[18-21].

CARDIOMYOPATHIES WITH HYPERTROPHIC PHENOTYPE

LV hypertrophy (LVH) is most frequently caused by pressure overload. However, in cardiomyopathies, LVH occurs in the absence of abnormal loading conditions – hypertrophic cardiomyopathy (HCM) accounts for the majority of these cases.

CMR imaging has consolidated its role among the multimodality evaluation of myocardial disease, mostly due to high spatial resolution and unique ability for tissue characterization[22,23]. Non-invasive tissue characterization is crucial for differential diagnosis of LVH, identification of HCM phenocopies and risk stratification. This distinctive feature of CMR has led to a decrease in the use of endomyocardial biopsy (EMB) in cardiomyopathies with LVH, that is now restricted to few indications[24,25]. A recent position statement limited EMB use to patients with LVH in whom non-invasive evaluation produces inconclusive or discordant results, and there is clinical suspicion of phenocopies, particularly infiltrative or storage disease for which target treatment is available[25].

An Integrative CMR approach, Incorporating morphofunctional assessment with tissue characterization, including identification of the presence, location, and pattern of LGE, and combined with parametric mapping findings (particularly, native T1 and ECV), can be of value for differential diagnosis of hypertrophic phenotypes of cardiomyopathy (Table 1).

Table 1 Cardiac magnetic resonance findings in hypertrophic cardiomyopathy and phenocopies

	Morphologic features	Tissue characterization		
		LGE	Mapping	ECV
Athlete's heart	Balanced increase in wall thickness and cavity size	Absent or in RV insertion points	Normal or decreased T1	Normal or decreased
Hypertrophic cardiomyopathy (sarcomeric)	Typically asymmetric LVH, with septal predominance	Mid-mural, patchy, affecting most hypertrophied segments; transmural in advanced stages	Increased native T1, regardless of LGE presence, reflecting interstitial fibrosis	Increased ECV attributed to fibrosis
Amyloidosis	Symmetric or asymmetric LVH	Subendocardial, global, diffuse; transmural in advanced stages. LGE reflects infiltration, not fibrosis; abnormal gadolinium kinetics	Marked increase in native T1 value (AL > ATTR) due to protein accumulation	Markedly increased ECV reflecting protein accumulation
Fabry disease	Concentric LVH, prominent papillary muscles, RV hypertrophy	Mid-mural, basal inferolateral segment	Decreased native T1 values (lipid storage); pseudonormalization in advance stages due to fibrosis. Elevated T2 levels due to inflammation	Normal ECV

ECV: Extracellular volume; LGE: Late gadolinium enhancement; LVH: Left ventricular hypertrophy; RV: Right ventricle.

Athlete's heart

CMR is also useful for distinguishing pathological LVH from physiological adaption to exercise. The “athlete's heart” is characterized by biventricular, symmetrical remodelling, and is associated to a concomitant and proportional increase in cavity size[26,27]. Specific reference values of ventricular size and function for athletes have been reported by D'Ascenzi *et al*[27]. In athletes, the degree of hypertrophy is usually mild, and LV wall thickness rarely exceeds 12 mm[28]. Moreover, reversal of adaptative LVH can be achieved with detraining[29]. When present, in athletes, LGE is usually confined to the RV insertion points (mostly the inferior), and its presence has been correlated with training load and intensity[30]. This pattern of fibrosis does not affect prognosis nor requires further evaluation in otherwise healthy athletes[30]. Mapping data may further differentiate “athlete's heart” from HCM: While the latter is usually associated with increased native T1 and ECV (reflecting interstitial fibrosis)[28,30], these parameters are normal, or even decreased, in athletes. Although echocardiography remains the major imaging tool for athlete pre-participation screening, CMR can be paramount in situations where suspicious of myocardial disease persists based on symptoms, family history, electrocardiographic or echocardiographic data.

HCM

HCM is defined by unexplained LVH in a non-dilated LV with wall thickness ≥ 15 mm or, alternatively, ≥ 13 mm, in the presence of positive family history or a disease-causing gene variant[22]. HCM, the most common genetic cardiovascular disease, with a prevalence of 1:200-1:500, is caused by sarcomeric gene mutations, that are inherited as an autosomal dominant trait[31]. There is marked phenotypic heterogeneity among HCM probands, even among individuals from the same family, that occasionally poses a challenge in terms of diagnosis and risk stratification.

Morphofunctional evaluation: The “classical” HCM phenotype consists of asymmetrical, septal-predominant hypertrophy, that may be associated to dynamic LV tract obstruction (LVOTO)[31]. In hypertrophied hearts, CMR enables precise measurement of maximal wall thickness and an accurate portrayal of LVH pattern, extent and distribution[28]. This is of particular importance in the presence of midventricular or apical variants of HCM, in which echocardiographic evaluation encounters limitations[23].

The presence of apical aneurysms is associated to higher rates of ventricular arrhythmias (VA), SCD, thromboembolic events, and heart failure in patients with HCM[32,33]. CMR has enabled more frequent identification of this high-risk subset of patients, by detecting small aneurysms that may remain unnoticed during non-contrast echocardiographic evaluation[23] but are still relevant for risk stratification. Accordingly, the presence of an apical aneurysm, regardless of size, has been considered a major risk factor by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, assigning it a class IIa (level of evidence B) recommendation for implantable cardioverter-defibrillator (ICD) implantation for primary prevention of SCD[34]. The ESC guidelines on SCD prevention have recently included LV apical aneurysm as an additional factor for consideration of an ICD (class IIb recommendation, level of evidence B)[35], even in patients with a low estimated risk according to the HCM Risk-SCD score[36].

Detection of thrombi within the scarred LV apex also carries meaningful management considerations. In a recent study, Lee *et al*[37] found a linear relationship between aneurysm size and the risk of adverse events, including apical thrombus formation and thromboembolic stroke. Moreover, patients with an aneurysm size ≥ 2 cm showed a significant increase in 5-year SCD risk (9.7% *vs* 2.9%, $P = 0.037$)[37].

Other morphologic abnormalities related to HCM can be further demonstrated by CMR, including mitral subvalvular apparatus abnormalities or myocardial crypts. Maron *et al* reported the presence of myocardial crypts – narrow, deep blood-filled invaginations within LV myocardium – in 61% of genotype positive/phenotype negative (G+P-) patients without overt LV hypertrophy, suggesting this morphologic feature to be part of the phenotypic expression of HCM[38].

Contrastingly, in a large Danish cohort assessed by computed tomography, LV crypts were frequent among the general population, and were not associated with a composite endpoint of death, myocardial infarction, heart failure, or stroke [39]. However, among family members of patients with HCM, the presence of crypts may prompt careful follow-up to monitor progression to an overt phenotype.

Another subclinical marker of HCM observed by CMR has been proposed by the same group – LV apical-basal muscle bundles. LV muscle bundles were suggested as a latent marker in G+/P- individuals, and were related to HCM phenotypic expression, irrespective of LV wall thickness[40].

CMR is useful for depicting papillary muscle (PM) architecture and functional abnormalities. PM hypertrophy (minor axis diameter > 11 mm or combined mass > 7 g/m²) is present in more than half of HCM cases, and may contribute to mid-ventricular obstruction[41,42]. Additional abnormalities that contribute to LVOTO, such as accessory, bifid or displaced PM, can be adequately demonstrated by CMR[41].

Tissue characterization: The presence of LGE in HCM reflects replacement fibrosis, and its prognostic value is well-established[43]. LGE is found in more than half of HCM patients, usually presenting an mid-mural pattern within the most hypertrophied segments[43,44]. In advanced stages of the disease, LGE with transmural extension can be observed and carries a worse prognosis[44].

LGE has been consistently associated increased SCD incidence, and its presence and extent was included as a major risk factor in the ACC/AHA risk stratification algorithm[34] and, more recently, in the 2022 ESC Guidelines for prevention of SCD[35]. In a landmark multicenter study, LGE exceeding 15% of the LV mass was associated with a > 2-fold risk of SCD in patients who were deemed low risk by conventional tools, compared with patients in whom LGE was absent[43]. Therefore, presence of “extensive LGE” (≥ 15% of total LV mass) is regarded as a high-risk parameter, and in HCM patients without a defibrillator, CMR should be repeated every 3-5 years to monitor LGE progression and reconsider SCD prevention strategies[23,34].

T1 mapping and ECV (derived from native and post-contrast T1) allow for identification of diffuse, interstitial fibrosis [23]. Native T1 and ECV may be elevated in segments without LGE, and even in variant carriers without overt LVH[28]. Mapping techniques allow differentiation of HCM from phenocopies (Table 1).

Edema with abnormal T2 findings (T2-Stir) could be observed in HCM patients often indicative of an acute myocardial injury (*i.e.*, ischemic extravascular damage) and associated with electrical instability[45].

Perfusion: Microvascular dysfunction is part of the pathophysiology of HCM and can be evaluated by means of CMR perfusion imaging. In HCM, reduced myocardial blood flow correlates with increased LV wall thickness and mass, presence of LGE, and increased ECV[23,28]. Aguiar Rosa *et al*[46] showed that increased ischemia severity, assessed by CMR, was associated with higher values of native T1 and greater LGE extension. Patients with severe ischemia demonstrated higher incidence of atrial arrhythmias and performed poorer in cardiopulmonary stress testing[46].

HCM phenocopies

CMR has an increasing role in the evaluation of rare forms of myocardial disease that also manifest with LVH, otherwise known as phenocopies of HCM. In such cases, family history, electrocardiographic patterns and extracardiac manifestations may raise diagnostic suspicion, that may be corroborated by imaging findings.

Amyloidosis: Cardiac amyloidosis (CA) produces LV “pseudo-hypertrophy”, resulting from interstitial expansion due to amyloid fibrils deposition, rather than from myocyte proliferation[47]. Transthyretin (ATTR), both hereditary and wild-type, and immunoglobulin-derived light chain amyloidosis are responsible for most cases of amyloid-related myocardial disease[48]. Extracellular expansion in CA is depicted in CMR parametric mapping findings by a marked increase in native T1 Levels and ECV[28]. Patients with CA show global, diffuse subendocardial LGE, that may become transmural in more advanced stages of the disease. This pattern of LGE, in the adequate setting, is very specific for CA[49]. LGE not rarely extends to the RV and the atria, particularly in ATTR[28]. Another characteristic CMR feature in CA is the abnormal gadolinium kinetics, with myocardial nulling preceding with the blood pool, or an equalization of these points [48,49]. More detailed information will be provided in the section entitled cardiomyopathies with restrictive phenotype.

Fabry disease: Fabry disease (FD), an X-linked lysosomal storage disorder, usually leads to concentric LVH, due to both glycosphingolipid accumulation and myocyte hypertrophy[50]. Prominent PM s are a typical feature of FD, as is concomitant RV hypertrophy[28,44].

Parametric mapping is of particular utility for the differential diagnosis of FD. Native T1 decreases with lipid deposition[22]; accordingly, in early stages of FD, native T1 values are low, when compared to normal reference values and other forms of LVH[28,50]. However, as disease progresses and replacement fibrosis becomes evident, pseudo-normalization of native T1 relaxation times occurs[28,50]. ECV remains within normal range in LGE-free areas[50], since FD leads to intracellular storage of glycosphingolipids. T2 values can be elevated due inflammatory response triggered by lipid accumulation.

LGE is present in > 50% of FD patients, and is usually located in the LV basal inferolateral segment, with a mid-mural or subepicardial pattern[22,44,49]. Presence of LGE has been reported in female mutation carriers without LVH[49]. Similar to HCM, presence of LGE in FD is associated to adverse outcomes and poor response to replacement therapy[50].

CARDIOMYOPATHIES WITH RESTRICTIVE PHENOTYPE

Less than 5% of all cardiomyopathy cases are attributed to restrictive cardiomyopathies (RCM), which have a diverse range of causes[51].

RCM is characterized by a significant alteration in myocardial compliance, presenting severe diastolic dysfunction while maintaining preserved systolic function, especially in the early stages. The initial diagnosis typically involves a TTE that reveals normal or increased LV wall thickness, often with a concentric or symmetric distribution, along with a restrictive pattern observed through Doppler analysis. It also shows the absence of LV dilation, preserved LVEF, and significant biatrial enlargement[52]. However, while TTE plays a crucial role in the initial assessment and raising diagnostic suspicions, its utility becomes limited when establishing a differential diagnosis. In such cases, CMR imaging becomes highly relevant.

Two of the most common entities where CMR is essential are the endomyocardial fibrosis (EMF) and CA.

EMF

EMF represents a rare subtype of RCM. It is characterized by an unusual thickening of the endocardium, resulting from the deposition of fibrous tissue[53]. This condition is typically secondary to various factors, including infections (often found in tropical regions), inflammation, exposure to toxic agents, among others. Echocardiographic observations in EMF include apical obliteration due to thickening of the endocardium, a reduction in ventricular cavity size, and a pronounced restrictive diastolic pattern. EMF can primarily affect the left ventricle, both the left and right ventricles (in approximately 50% of cases), or predominantly the right ventricle[54]. The presence of apical thrombus is also a frequently encountered feature.

CMR is the gold standard for EMF evaluation and specifically for localization, characterization, and quantification of fibrous tissue by LGE sequences. LGE strongly correlates with histopathological findings and its extension is associated with increased mortality risk[55]. CMR may also identify apical thrombus or calcifications.

CA

In patients with CA, cine sequences or functional assessment methods provide a means to observe the structural characteristics of the infiltrated myocardium. These characteristics encompass biventricular hypertrophy, thickening of cardiac valves, interatrial septum, pericardial effusion, and biatrial dilation. Additionally, these techniques enable the precise evaluation of both systolic and diastolic function[56]. It is essential to not only focus on the assessment of the LV but also on the other cardiac chambers. Notably, the involvement of RV has been identified as a predictor of mortality in CMR, consistent with findings from TTE[57]. As the disease advances into later stages, there is a notable increase in atrial volume and dysfunction. This phenomenon is attributed to the direct infiltration of amyloid fibrils into the atria and indirectly to elevated filling pressures due to diastolic dysfunction.

The [Table 2](#) summarizes the main cardiac magnetic resonance (CMR) findings in CA with an explanation of the prognostic and diagnostic implications.

To sum up, CMR represents a complementary diagnostic step in the evaluation of patients suspected of having CA. This imaging method is not widely accessible in numerous medical facilities, and its lengthy duration per study restricts the total number of examinations feasible in a day.

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiomyopathy characterized by replacement of myocardium by fatty and fibrous tissue. Historically named Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) because of the RV involvement, the late recognition of left and biventricular forms led to the new term ACM, encompassing both phenotypes. VA through macro-reentry mechanism related to the fibrofatty involvement is one of the main clinical presentations, manifesting in the worst case by SCD. In the advanced stages, the disease is characterized by heart failure [58,59].

Diagnosis criteria established by the International Task Force (ITF) included morphological (dysfunction and structural alteration) and anatomopathological characterization, ECG abnormalities, history of arrhythmias and family history[60]. CMR role was limited to evaluation of regional RV motion wall, RV ejection fraction (RVEF) and RV end-diastolic volume. Critics have been raised about the absence of LV involvement and the limited role of CMR. In 2020, the Padua Criteria was proposed, revisiting the ITF criteria by including tissue characterization provided by CMR. Functional or structural abnormality is enough for the diagnosis[61]. Pathogenic mutations, ECG abnormalities, or VA are no longer sufficient. This highlights the role of CMR, which has become one of the preferred non-invasive imaging techniques, allowing an increase of diagnostic sensitivity for ACM. CMR offers an advanced evaluation of the heart, including ventricular morphology, volume, thickness, ejection fraction, regional motion, myocardial fibrous, adipose content, edema, flow, LGE, as well as new emerging and promising feature as global longitudinal and circumferential strain (assessed by using feature-tracking CMR). Despite its complete evaluation, CMR has some limitations: fatty infiltration is nonspecific and does not preclude the diagnosis.

Prognosis in ACM is mostly related to VA. ICD being the only intervention improving survival[62], risk stratification is vital to identify the high-risk patients benefiting the most from primary prevention ICD implantation. RV dysfunction and syncope history are strong predictor for arrhythmia event and have been both included in the guidelines. CMR is not included in the risk stratification recommendations, neither in the 2019 Heart Rhythm Society guidelines[63], nor the 2022

Table 2 Cardiac magnetic resonance findings in cardiac amyloidosis. Prognostic and diagnostic implications

Parameter	Implications	Ref.
Reduction of the total left atrial emptying fraction in AL-CA patients	+ Related to more advanced stages of the disease and with a worse functional class; + Increase in 2 years-mortality if its value < 16%	Mohty <i>et al</i> [79]
MCF and LAS in AL-CA patients	+ If LAS > -7% and MCF < 52.6% greatest risk of death and heart transplantation	Arenja <i>et al</i> [80]
Anterior aortic plane systolic excursion in AL-CA patients	+ Best predictive value for transplant-free survival	Ochs <i>et al</i> [81]
Strain	+ Correlates well with the level of LGE uptake an alternative to LGE where contrast should not be used; + GLS impaired robust predictor of all-cause mortality in AL-CA patients	Wan <i>et al</i> [82]
Look-Locker sequence (T1 sequence with different inversion times)	+ Increased risk of death if it is impossible to obtain a normal myocardial signal on LGE using this sequence with inversion time over than 300 ms	Mekinian <i>et al</i> [83]
LGE	+ Typical pattern is a diffuse subendocardial uptake and also it was described a transmural pattern enhancement and less frequently a focal patchy one; + Controversy exists regarding the prognostic implication	Maceira <i>et al</i> [84], Fontana <i>et al</i> [85], Raina <i>et al</i> [86]
The difference in the intramyocardial T1 value post-gadolinium between subepi-cardium and subendocardium	+ Worse survival when that difference was lower than 23 ms	Maceira <i>et al</i> [84]
Diffuse subendocardial uptake detected using a modified LGE-CMR protocol with visual T1 assessment	+ High diagnostic precision (PPV 93%, NPV 90%); + Significantly associated with 2 yr mortality	Austin <i>et al</i> [87], White <i>et al</i> [88]
RV gadolinium uptake in AL-CA patients	+ Independent predictor of survival during a period of 6 mo follow up	Wan <i>et al</i> [89]
QALE	+ Score > 9 predicted worse survival, especially useful in patients with a subendo-cardial LGE pattern	Wan <i>et al</i> [90]
Noncontrast T1-mapping	+ A cut-off value of 1020 ms had high sensitivity and specificity (around 90%) for identifying amyloid patients with possible or definite cardiac involvement	Karamitsos <i>et al</i> [91]
T1 mapping with native T1 and extracellular volume	+ Patients with AL-CA and suspected cardiac involvement had increased values; + Only ECV had a significant prognostic implication with greater mortality if its value was > 44%; + Basal ECV had the best prognostic value amongst myocardial T1 mapping parameters	Karamitsos <i>et al</i> [91], Lin <i>et al</i> [92], Wan <i>et al</i> [93]
T2-weighted imaging	+ No gadolinium administration is needed; + A decreased myocardial signal intensity compared with skeletal muscle was associated with shortened survival; + T2 ratio value < 1.36 had a weak sensitivity and specificity (63% and 73% respectively) to predict cardiac involvement	Wassmuth <i>et al</i> [94], Legou <i>et al</i> [95]

AL-CA: Light chain cardiac amyloidosis; CMR: Cardiovascular magnetic resonance; ECV: Extracellular volume; GLS: Global longitudinal strain; LAS: Long axis strain; LGE: Late gadolinium enhancement; MCF: Myocardial contraction fraction; NPV: Negative predictive value; PPV: Positive predictive value; QALE: Query amyloid late enhancement score; RV: Right ventricle.

ESC guidelines for the management of patients with VA and the prevention of SCD[35]. In this context, CMR role is only limited to diagnosis. A 2019 consensus expert developed the ARVC 5-year Risk-VAs calculator: A prediction model for VA risk to guide decision regarding primary prevention ICD (www.arvcrisk.com)[64]. CMR is included only to assess RVEF. CMR parameters of tissue characterization and regional wall motion of both ventricles were not included. The role of CMR in risk stratification remains to be determined. Lack of consistent studies explains the absence of CMR from the risk stratification recommendation, even though some emerging data shows the potential prognosis information provided by CMR.

Different CMR phenotype of ACM are associated with different prognoses. Normal CMR has an excellent negative predictive value for major clinical events[65-67]. Tandri *et al*[68] showed that delayed gadolinium enhancement of RV correlates with inducible VT during electrophysiology testing. Lie *et al*[69] confirm that CMR findings, as low RVEF, RV wall-contraction abnormalities, or RV aneurysms are predictors of life-threatening ventricular arrhythmia. Evaluation of longitudinal strain by feature-tracking CMR could also bring risk stratification information, as reduced strain seems to be associated with sustained VA[70].

Regarding the LV involvement, its association with adverse outcomes is inconsistent[71]. Presence of LV dysfunction is associated with arrhythmic adverse outcomes as reported by a small European registry[72]. Some studies have suggested that CMR imaging features of LV phenotypes, as fat infiltration and LGE, in ACM may be associated with adverse outcomes. Aquaro *et al*[66] highlight that the different CMR presentations of ACM are associated with different prognoses, LV involvement (LV dominant and biventricular) being the worst prognosis. Zhang *et al*[73] confirm the bad prognosis of LV LGE, being associated with an increased risk of ICD therapy and cardiac death, independently of LVEF. LV myocardial assessment by CMR could also predict the HF-related event risk as reported by Chun *et al*[74]. On the contrary LV dysfunction was not a predictor of arrhythmic risk in two meta-analysis[75,76]. Zghaib *et al*[77] showed that LV fibrofatty infiltration in CMR was not associated with arrhythmic outcomes. The role of identification of LV

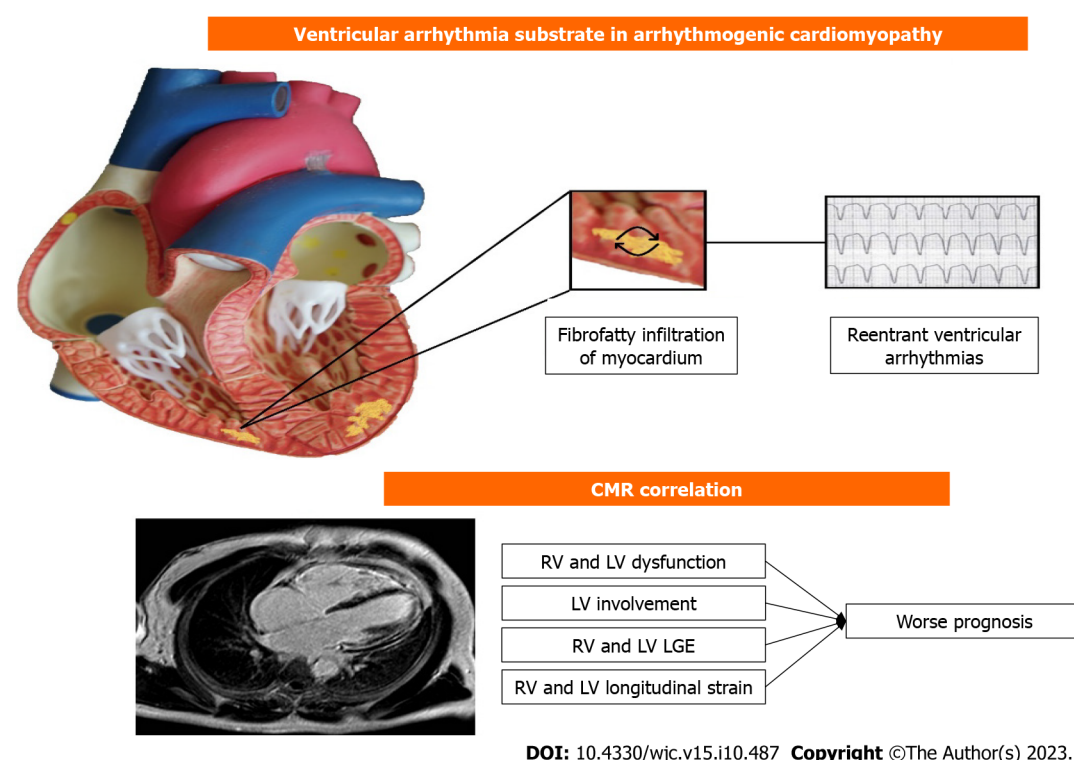


Figure 1 Correlation between cardiac magnetic resonance and ventricular arrhythmia in arrhythmogenic cardiomyopathy. CMR: Cardiac magnetic resonance; RV: Right ventricle; LV: Left ventricle; LGE: Late gadolinium enhancement.

involvement by CMR and its prognosis significance remains to be established.

There is some potential speculation on some cases of ACM that could be explained by an inflammatory activity or hot phase, if the diagnosis it is in a very early-stage sequences like T2-STIR for oedema detection could help[78], this hot phase could be related with arrhythmias during the disease.

To finalise, CMR role in diagnosis is well established (Figure 1). Regarding the risk stratification, only RV function is validated in international guidelines and risk calculator. Lack of consistent data about correlation between CMR characterization and adverse outcomes could explain the absence of CMR role from guidelines, but a few emerging studies show new evidence about CMR imaging, indicating that the presence of structural abnormalities in the RV as observed through CMR plays a crucial role in evaluating the risk of arrhythmias. : RV dilatation, dysfunction and LGE are among the strongest predictors. Regarding the LV involvement, the few data are contradictory, but may trend towards an association with high-risk event. CMR may have a promising role in association with classical clinical feature, but further studies are needed to better define CMR place in risk stratification.

CONCLUSION

Cardiovascular imaging methods play a vital role in investigating cardiomyopathies, furnishing valuable diagnostic and prognostic insights. The inclusion of CMR in the evaluation of all patients is highly recommended, owing to its ability to offer comprehensive anatomical, functional, and tissue-specific data, which holds significant prognostic value. While other imaging techniques might be employed selectively, the integration of multiple modalities of cardiac imaging assumes a crucial role in clinical decision-making, leading to enhanced patient management and care outcomes.

FOOTNOTES

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Retrospective Study

Integrated analysis of comorbidity, pregnant outcomes, and amniotic fluid cytogenetics of fetuses with persistent left superior vena cava

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Abstract

BACKGROUND

Persistent left superior vena cava (PLSVC) is the most common venous system variant. The clinical characteristics and amniotic fluid cytogenetics of fetuses with PLSVC remain to be further explored.

AIM

To develop reliable prenatal diagnostic recommendations through integrated analysis of the clinical characteristics of fetuses with PLSVC.

METHODS

Cases of PLSVC diagnosed using prenatal ultrasonography between September 2019 and November 2022 were retrospectively studied. The clinical characteristics of the pregnant women, ultrasonic imaging information, gestational age at diagnosis, pregnancy outcomes, and amniocentesis results were summarized and analyzed using categorical statistics and the chi-square test or Fisher's exact test.

RESULTS

Of the 97 cases diagnosed by prenatal ultrasound, 49 (50.5%) had isolated PLSVC and 48 (49.5%) had other structural abnormalities. The differences in pregnancy outcomes and amniocentesis conditions between the two groups were statistically significant ($P < 0.05$). No significant differences were identified between the two groups in terms of advanced maternal age and gestational age ($P > 0.05$). According to the results of the classification statistics, the most common intracardiac abnormality was a ventricular septal defect and the most common extracardiac abnormality was a single umbilical artery. In the subgroup analysis, the concurrent combination of intra- and extracardiac structural abnormalities was a risk factor for adverse pregnancy outcomes (odds ratio > 1 , $P < 0.05$). Additionally, all abnormal cytogenetic findings on amniocentesis were observed in the comorbidity group. One case was diagnosed with 21-trisomy and six cases was

diagnosed with chromosome segment duplication.

CONCLUSION

Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Amniotic fluid cytogenetics of fetuses is recommended for PLSVC with other structural abnormalities.

Key Words: Persistent left superior vena cava; Prenatal diagnosis; Amniotic fluid cytogenetics; Pregnancy outcome; Integrated analysis; Comorbidity

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Core Tip: Our study was performed for providing reliable prenatal diagnostic advice through integrated analysis of the clinical characteristics of fetuses with persistent left superior vena cava (PLSVC). We retrospectively studied 97 cases of PLSVC diagnosed using prenatal ultrasonography. Of the 97 cases diagnosed by prenatal ultrasound, 49 (50.5%) had isolated PLSVC and 48 (49.5%) had other structural abnormalities. We found that PLSVC is associated with a certain percentage of other combined structural abnormalities. Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities.

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INTRODUCTION

Persistent left superior vena cava (PLSVC) is the most common venous system variant. The incidence rate of PLSVC in congenital heart disease is approximately 5%-6%, whereas it is only 0.3%-0.5% in the normal population[1,2]. Previous research has shown that the probability of adverse pregnancy outcomes in isolated PLSVC is lower, and the risk of adverse pregnancy outcomes is significantly increased when combined with other malformations[3]. With improvements in genetic examination technology, some studies have reported that the proportion of fetal chromosomal abnormalities among PLSVC fetuses has significantly increased, which is different from the classic opinion of this disease[4,5].

Since fetal ultrasound examinations are unaffected by pulmonary gases, the prenatal period is the best time to perform vascular examinations[6,7]. Previous studies on PLSVC have focused on a few aspects, some only on the types of comorbidities and others only on pregnancy outcomes. There is a lack of comprehensive studies that provide reliable conclusions for patients and clinicians.

Our study retrospectively collected the clinical data, including the age of the pregnant women, ultrasonic imaging information, pregnancy outcomes, and amniocentesis results, from 97 cases of fetal PLSVC. We integrated clinical information, imaging features, and molecular-level results to provide reliable advice to patients and clinicians in multiple dimensions. Fetal PLSVC cannot be viewed as a purely vascular anatomical variant, and this disease is associated with a certain percentage of other combined structural abnormalities. Therefore, examination for other structural abnormalities should be performed when PLSVC is diagnosed.

MATERIALS AND METHODS

Study population

Ninety-seven patients with PLSVC diagnosed using prenatal ultrasonography at Tongji Hospital between September 2019 and November 2022 were retrospectively studied. Clinical characteristics included maternal age, gestational weeks, prenatal ultrasound images, specific types of combined intra- and extracardiac abnormalities, pregnancy outcomes, amniocentesis conditions, and results. The range of maternal age was 22 to 39 years, with a mean age of 30.36 ± 3.94 years. The weeks of gestation at which PLSVC was diagnosed in our hospital was 18 to 34 wk, and the average weeks of gestation was 24.72 ± 3.99 wk. There were 87 single pregnancies (89.7%) and 10 twin pregnancies (10.3%), including two double chorionic villi and double amniotic sac twin fetuses (20.0%) and eight cases of single chorionic villi and double amniotic sac twin fetuses (80%). This study was approved by the Ethics Committee of Tongji Hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Pregnancy at 12 to 34 wk of gestation; (2) complete clinical data; and (3) standard and clear cardiac ultrasound images.

The exclusion criteria were as follows: (1) Pregnancy with three or more fetuses; (2) frequent fetal movement leading to poor-quality echocardiography; and (3) incomplete clinical data.

Ultrasound instruments and examinations

Using the color Doppler ultrasound instruments GE VOLUSON E8 and VOLUSON E10 (GE, Milwaukee, WI, United States) with a probe frequency of 2 to 5 MHz, after determining the fetal orientation and the relationship between the viscera and heart position, the fetal heart examination conditions were selected. The fetal heart segmental analysis method was used to determine the heart, blood vessel structure, and connection relationship. The focus was on four-chamber heart, three-vessel, and three-vessel trachea sections, combined with color Doppler observation of the blood flow direction and vascular morphology[8,9]. According to prenatal screening guidelines, a comprehensive ultrasound examination was performed on fetuses diagnosed with PLSVC to determine whether there are any concomitant intracardiac or extracardiac abnormalities[10,11].

Statistical analysis

Statistical software (SPSS 26.0, IBM Corp., Armonk, NY, United States) was used for the data analysis. The measurement data conforming to a normal distribution are expressed as the mean $\pm$ SD. The independent samples *t*-test was used for comparison between groups, and the paired sample *t*-test was used for comparison within groups. Count data are expressed as cases (%), and the χ^2 test or Fisher's exact probability method was used for comparison between groups. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of clinical characteristics between the group with isolated PLSVC and the group with additional malformations

Ninety-seven cases diagnosed using prenatal ultrasound were included in our study, including 49 cases (50.5%) with isolated PLSVC and 48 (49.5%) with other structural abnormalities. The mean age in the isolated PLSVC group was 30.39 ± 4.04 years, and the mean age of those having PLSVC with other malformations was 30.46 ± 3.89 years. There was no statistically significant difference in gestational age between the two groups. The clinical characteristics of the patients are shown in Table 1. We summarized the maternal age, number of fetuses, gestational weeks at first diagnosis, pregnancy outcomes, and amniocentesis conditions. After statistical analysis, we found significant differences in pregnancy outcomes and amniocentesis conditions between the two groups ($P < 0.05$). No statistical differences were found between the two groups in terms of maternal age, number of fetuses, and gestational weeks at first diagnosis. These observations demonstrate that PLSVC with other structural abnormalities may be associated with more adverse pregnancy outcomes. Pregnant women were more likely to be recommended for amniocentesis diagnosis.

Types of intracardiac structural abnormalities in PLSVC fetuses

After summarizing the clinical features, we found that a considerable proportion of PLSVC cases had other structural abnormalities. We summarized the specific types of abnormalities observed with PLSVC to provide a reference for improving the accuracy of ultrasound screening.

Among the included cases, 22 presented with cardiovascular system abnormalities, including 11 with both intracardiac and extracardiac abnormalities. The specific types and number of cases are listed in Table 2. Among these, interventricular septum defects were the most common, followed by aortic coarctation. These results indicate that when a PLSVC is found, scanning of the interventricular septum and aortic arch should be performed.

Types of extracardiac structural abnormalities in PLSVC fetuses

In addition to the cardiovascular system, the types of combined abnormalities of other systems in PLSVC were relatively complex, with 37 cases of abnormalities in extracardiac structures, including 11 combined with both intracardiac and extracardiac abnormalities. The specific types and numbers of cases are listed in Table 3. Among them, a single umbilical artery was observed in the largest number of cases, followed by persistent right umbilical vein and urinary system abnormalities. These results indicate that when PLSVC is found, scanning of the umbilical vascular structure and urinary system should be performed.

Subgroup analysis of combined intra- and extracardiac abnormalities

Based on the above observations, we found that the number of patients with PLSVC combined with intra- and extracardiac abnormalities was not consistent. Therefore, we further investigated how intra- and extracardiac structural abnormalities affect pregnancy outcomes through subgroup analysis. In our case series, 13 (13.4%) patients with PLSVC terminated their pregnancy, and 84 (86.6%) continued their pregnancy. Among the 13 terminated pregnancy cases, 12 (92.3%) had other structural abnormalities and seven (53.8%) had both intracardiac and extracardiac structural abnormalities. We found that patients with PLSVC with extracardiac abnormalities had the highest sustained pregnancy

Table 1 Clinical characteristics in the isolated persistent left superior vena cava group and the persistent left superior vena cava with other malformations group, *n* (%)

	Isolated PLSVC (<i>n</i> = 49)	PLSVC with other malformations (<i>n</i> = 48)	χ^2	<i>P</i> value
Age				
< 35 years old	42 (85.7)	39 (81.3)	0.35	0.55
≥ 35 years old	7 (14.3)	9 (18.7)		
Number of fetuses				
Singleton	43 (87.8)	44 (91.7)	0.40	0.53
Twins	6 (12.2)	4 (8.3)		
Gestational age at initial diagnosis				
Before 28 wk	46 (93.9)	45 (93.8)	0.001	0.97
After 28 wk	3 (6.1)	3 (6.2)		
Pregnancy outcome				
Persistent pregnancy	48 (98.0)	36 (75.0)	11.01	0.001
Terminated pregnancy	1 (2.0)	12 (25.0)		
Amniocentesis status				
No apparent abnormalities	5 (10.2)	14 (29.2)	15.33	< 0.001
Abnormal results	0 (0.0)	7 (14.6)		
No amniocentesis performed	44 (89.8)	27 (56.2)		

PLSVC: Persistent left superior vena cava.

Table 2 Specific types of intracardiac structural abnormalities in 97 cases of persistent left superior vena cava, *n* (%)

Type of intracardiac structural abnormalities	<i>n</i> (%)
Ventricular septal defect	7 (31.8)
Aortic coarctation	5 (22.7)
Tetralogy of Fallot	3 (13.6)
Right-sided aortic arch	3 (13.6)
Left pulmonary artery originating from the right pulmonary artery	1 (4.5)
Single atrium with complete endocardial cushion defect	1 (4.5)
Midline heart with ventricular wall hypertrophy	1 (4.5)
Absence of right superior vena cava	1 (4.5)
Total	22 (100)

rates. Using statistical methods, we compared the other subgroups with this group to identify risk factors. In terms of sustained pregnancy rate, the presence of simultaneous abnormal cardiac and extracardiac structures was a risk factor affecting sustained pregnancy rate (odds ratio > 1, *P* < 0.05). Specific data are presented in [Table 4](#).

Amniotic fluid cytogenetics of fetuses with PLSVC

Amniotic fluid cytogenetics enables further investigation of cases with imaging abnormalities and plays an irreplaceable role in clarifying the etiology. In our case series, 26 pregnant women chose amniocentesis, including five isolated PLSVC cases and 21 PLSVC cases with other abnormalities. No obvious abnormalities were observed in the amniocentesis results of the isolated PLSVC group. However, amniocentesis results in the group with combined intracardiac and extracardiac abnormalities displayed a certain proportion of anomalies, including one case with 21-trisomy and six cases with abnormal copy number variations (CNVs). Despite the limited research data on CNVs in PLSVC cases, specific types of analysis can still provide effective information for clinical practice. Six cases of abnormal CNVs were identified as repetitions of chromosomal regions, including two cases classified as potentially benign, three cases classified as variants of uncertain significance, and one as potentially pathogenic. The results are presented in [Table 5](#). These observations

Table 3 Specific types of extracardiac structural abnormalities in 97 cases of persistent left superior vena cava, *n* (%)

Type of extracardiac structural abnormalities	<i>n</i> (%)
Single umbilical artery	9 (24.3)
Persistent right umbilical vein	6 (16.2)
urinary system abnormalities	6 (16.2)
Neurological system abnormalities	3 (8.1)
Pleural effusion	2 (5.4)
Pulmonary cystadenoma	2 (5.4)
Absence of nasal bone	2 (5.4)
Gallbladder abnormalities	2 (5.4)
Situs inversus	1 (2.7)
Scoliosis	1 (2.7)
Multiple malformations	3 (8.1)
Total	37 (100)

Table 4 Analysis of pregnancy outcomes in persistent left superior vena cava with intracardiac and extracardiac abnormalities

Type	Persistent pregnancy, <i>n</i> (%)	OR	95%CI	<i>P</i> value
PLSVC only with extracardiac abnormalities	24 (92.3)			
PLSVC only with intracardiac abnormalities	8 (72.7)	4.5	0.63-31.95	0.12
PLSVC with intracardiac and extracardiac abnormalities	4 (36.3)	21.0	3.16-139.67	0.001

PLSVC: Persistent left superior vena cava.

Table 5 Six cases with abnormal copy number variation sequencing results in persistent left superior vena cava

	Chromosomal location	Variation type	Fragment size	Clinical significance
1	Chromosome 15	Repetition	0.4 Mb	Potentially benign
2	Chromosome 2	Repetition	0.5 Mb	Potentially benign
3	Chromosome 11	Repetition	3.9 Mb	VUS
4	Chromosome 19	Repetition	187.4 Kb	VUS
5	Chromosome 1	Repetition	2.3 Mb	VUS
6	Chromosome 1	Repetition	> 10 Mb	Potential pathogenicity

VUS: Variants of uncertain significance.

imply that CNVs may be associated with PLSVC combined with other abnormalities. When PLSVC cases with other abnormalities are detected, amniocentesis may contribute to the prenatal diagnosis and clinical decision-making.

DISCUSSION

PLSVC is the most common venous system variant. However, the risk of adverse pregnancy outcomes is significantly increased when PLSVC is combined with other malformations. Our study was performed to provide reliable prenatal diagnostic recommendations through integrated analysis of the clinical characteristics of fetuses with PLSVC.

Fetal ultrasound examination is not affected by pulmonary gases; therefore, ultrasound can comprehensively observe the superior vena cava, and prenatal screening is the best time for PLSVC[7]. Several case reports have demonstrated difficulties in the diagnosis of PLSVC in adults, and certain patients require special examination methods[12,13]. PLSVC has typical sonographic features, with a cross-sectional view of the PLSVC visible on the left side of the pulmonary artery

in a three-vessel tracheal section[14]. In cases of PLSVC, approximately 90% enter the right atrium through the coronary sinus and approximately 10% directly enter the left atrium. In patients presenting with the left superior vena cava entering the right atrium through the coronary sinus, a dilated coronary sinus is observed on a four-chamber view[15,16]. Some cases in this study were not detected in the mid-trimester systematic screening, and most missed cases were twins. The limitations associated with scanning due to mutual fetal occlusion may be the main reason for missed diagnoses. This study integrates clinical factors, imaging information, and amniotic fluid cytogenetic information. As such, it is innovative compared to previous studies, showing that PLSVC is not just a simple anatomical variant, but is also associated with a higher rate of other structural abnormalities. In cases of PLSVC combined with other structural abnormalities, there are differences in pregnancy outcomes and amniocentesis.

This study classified and summarized the types and proportions of intra- and extracardiac abnormalities associated with PLSVC. These types of intracardiac and extracardiac abnormalities are consistent with previous research findings, both domestic and international[17-20]. A previous case report indicated that PLSVC can occur with anorectal malformation, an abnormality that we did not observe[21]. However, in this study, the proportion of patients with concurrent intracardiac and extracardiac abnormalities ($n = 11$) was slightly higher than that in similar studies from China[22]. Our results indicate that when a PLSVC is detected, scanning of the interventricular septum, aortic arch, umbilical vascular structure, and urinary system should be performed. These findings may help clinicians reduce the incidence of missed diagnoses.

Pregnancy is a dynamic process, and the composition of fetal peripheral blood also varies with gestational age[23,24]. Amniotic fluid cytogenetics maintains a relatively stable state and greatly improves the accuracy of prenatal diagnoses, especially in cases with imaging abnormalities. Chromosome karyotype analysis is the gold standard for diagnosing chromosomal-related diseases; however, traditional chromosome karyotype analysis cannot detect chromosomal microdeletions or microduplications below 5-10 Mb.

Genomic copy number variant sequencing (CNV-seq) is a second-generation sequencing-based test that can be used to identify CNVs as an aid to prenatal diagnosis when a pregnant woman has an indication for interventional prenatal diagnosis and provides informed consent. Studies have found that the proportion of PLSVC fetuses with chromosomal-related abnormalities is 12.5%, and in isolated PLSVC cases, the proportion of chromosomal-related abnormalities can reach 7%[4]. Du *et al*[5] also demonstrated that in PLSVC cases, especially in cases of combined intracardiac and extracardiac abnormalities, the proportion of chromosomal abnormalities significantly increases. Most previous studies in China focused on chromosomal abnormalities, such as permanent left superior vena cava combined with trisomy 21 and trisomy 18, lacked a summary of the classification of abnormal results of PLSVC combined with CNVs[22,25].

In this study, a total of 26 pregnant women chose amniocentesis for diagnosis, including one case with 21-trisomy and six cases with abnormal CNVs results, all of which showed duplication of chromosomal regions, of which five cases were microduplications of less than 10 Mb.

This study had some limitations. Because the PLSVC incidence rate is only 0.3%-0.5% in the normal population[26], the number of included cases was small, which means that the credibility of the study needs to be further improved. In addition, no significant pathogenic abnormalities were found in the isolated PLSVC group, and in seven cases, abnormalities were found in the amniocentesis results of the group with other abnormalities. The risks of abnormal karyotypes and CNVs may increase in the presence of comorbidities. However, because amniocentesis is an invasive test with some risks[27], the comorbidity group chose to undergo amniocentesis more often, leading to confounding factors in the analysis. However, this study innovatively integrated and analyzed data at clinical, imaging, and genetic molecular levels, which can provide reliable prenatal diagnostic recommendations.

CONCLUSION

In conclusion, examination for other structural abnormalities should be performed when PLSVC is diagnosed. Poor pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Amniotic fluid cytogenetics of fetuses is recommended for PLSVC with other structural abnormalities.

ARTICLE HIGHLIGHTS

Research background

Persistent left superior vena cava (PLSVC) is the most common venous system variant. Previous research has shown that the probability of adverse pregnancy outcomes in isolated PLSVC is lower, and the risk of adverse pregnancy outcomes is significantly increased when combined with other malformations. In recent years, some studies have reported that the proportion of fetal chromosomal abnormalities among PLSVC fetuses has significantly increased, which is different from the classic opinion on this disease. There is a lack of comprehensive studies that provide reliable conclusions for patients and clinicians.

Research motivation

In recent years, the advancement of prenatal diagnostic technology has overturned traditional concepts of some diseases.

Research objectives

We integrated clinical information, imaging features, and molecular-level results to provide reliable advice to patients and clinicians in multiple dimensions.

Research methods

We retrospectively collected cases of PLSVC diagnosed using prenatal ultrasonography between September 2019 and November 2022. The clinical characteristics of the pregnant women, ultrasonic imaging information, gestational age at diagnosis, pregnancy outcomes, and amniocentesis results were summarized and analyzed.

Research results

The differences in pregnancy outcomes and amniocentesis conditions between the two groups were statistically significant ($P < 0.05$). According to the results of the classification statistics, the most common intracardiac abnormality was a ventricular septal defect and the most common extracardiac abnormality was a single umbilical artery. Additionally, all abnormal cytogenetic findings on amniocentesis were observed in the comorbidity group.

Research conclusions

PLSVC is associated with a certain percentage of other combined structural abnormalities. Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Integrated analysis of multiple levels could provide more information.

Research perspectives

In future studies, researchers should collect more amniotic fluid cytological data and follow-up prognosis of related fetuses.

FOOTNOTES

Author contributions: Yang X and Su XH performed the conception and design; Zeng Z and Guo LL performed the development of methodology; Fan Y and Wu Y contributed to the analysis and interpretation of data; Yang X and Su XH contributed to the writing and review of the manuscript; Xu XY performed the study supervision; Yang X and Su XH contributed equally to this work; all authors had final approval of the submitted versions.

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Retrospective Study

Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest

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Abstract**BACKGROUND**

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide.

AIM

To explore factors influencing prehospital return of spontaneous circulation (P-ROSC) in patients with OHCA and develop a nomogram prediction model.

METHODS

Clinical data of patients with OHCA in Shenzhen, China, from January 2012 to December 2019 were retrospectively analyzed. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression were applied to select the optimal factors predicting P-ROSC in patients with OHCA. A nomogram prediction model was established based on these influencing factors. Discrimination and calibration were assessed using receiver operating characteristic (ROC) and calibration curves. Decision curve analysis (DCA) was used to evaluate the model's clinical utility.

RESULTS

Among the included 2685 patients with OHCA, the P-ROSC incidence was 5.8%. LASSO and multivariate logistic regression analyses showed that age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and pathogenesis were independent factors influencing P-ROSC in these patients. The area under the ROC was 0.963. The calibration plot demonstrated

that the predicted P-ROSC model was concordant with the actual P-ROSC. The good clinical usability of the prediction model was confirmed using DCA.

CONCLUSION

The nomogram prediction model could effectively predict the probability of P-ROSC in patients with OHCA.

Key Words: Cardiac arrest; Cardiopulmonary resuscitation; Recovery spontaneous circulation; Logistic regression analysis; Predictive model

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Core Tip: A large gap in the rate of prehospital return of spontaneous circulation remains between China and other countries and that the relative contributions of aid measures of the factors to prehospital return of spontaneous circulation vary across countries. There is still not such model, including pre-emergency medical service intervention factors and Prehospital emergency measures, developing for prehospital return of spontaneous circulation in China. Compared to similar models from other countries, the model proposed in the present study is interpretable, convenient to implement, easy to comprehend in busy prehospital processing, and comprehensive, including prehospital drug administration. Therefore, it could serve as a potentially assistive tool for clinical aid decision-making.

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA), a leading cause of death worldwide, has an average incidence of (30.0-97.1) cases per 100000 person-years[1], with a survival rate of only 8.8% at hospital discharge[2]. In China, 550000 people develop OHCA annually[2] with a survival rate of only 1.3% after discharge, making OHCA a major public health issue. The survival rate from hospital discharge of patients with OHCA who have achieved a return of spontaneous circulation (ROSC) to hospital handover is still approximately 10%[3]. Moreover, patients with prehospital ROSC (P-ROSC) have better neurological outcomes compared with those who do not. Some areas regions have reported high ROSC rates during hospital handovers, such as 25% in England[4] and 29.1% in Tasmania, Australia[5]. In China, however, the P-ROSC rate was only 6.26% in a recent survey in Beijing[6], demonstrating that a large gap still exists between countries.

Investigations have reported a range of pre-emergency medical service (EMS) intervention factors for patients with OHCA that are associated with P-ROSC, including age, prehospital drug administration, witnessed status, first rhythm, and response time[7]. The relative contribution of each of these factors to P-ROSC varies across countries. However, no model including pre-EMS intervention factors and prehospital emergency measures has been developed for ROSC during hospital handovers in China. Therefore, the development of an effective prediction model is required for ROSC during hospital handovers based on pre-EMS intervention factors and prehospital emergency measures.

This study aimed to identify independent factors associated with P-ROSC and develop and evaluate a nomogram model in China to predict whether ROSC can be achieved during the prehospital period in OHCA.

MATERIALS AND METHODS

Study design and setting

A multicenter retrospective study was conducted at the Shenzhen Center for Prehospital Care, which covered all hospitals in Shenzhen; that is, approximately 150 hospitals, from January 2012 to December 2019. All first-aid measures were performed according to the American Heart Association (AHA) Guidelines for cardiopulmonary resuscitation (CPR).

Participants

We retrospectively collected data from emergency medical technicians (EMTs). The inclusion criteria were patients with OHCA aged ≥ 18 years, The exclusion criteria were incomplete cases, dead patients (*i.e.*, rigor mortis, lividity, decomposition, or decapitation) without CPR by the EMTs, and patients whose family members forwent all treatments.

Data collection

Data were gathered from two sources: The Registration System of Pre-hospital First Aid Information and Statistics and the Patient Care Report Form. The extracted data included clinical features such as sex, age, time of arrest (*i.e.*, 0-8, 8-16, or 16-24 min), season of arrest, bystander CPR, initial rhythm, CPR duration, ventilation mode, defibrillation, epinephrine dose, use of other drugs (atropine, lidocaine, and amiodarone), and outcomes (P-ROSC).

According to the 2015 AHA guidelines, ROSC was defined as the clinical indication of the presence of vital signs, including palpable pulses or blood pressure.

Statistical analysis

IBM SPSS Statistics for Windows, version 26.0, and R 3.1.2 were used to perform all analyses. The *t*-test and Mann-Whitney U test were used for numerical variables, while the chi-square test was applied to categorical variables. A model was established using least absolute shrinkage and selection operator (LASSO) regression and multivariable backward regression. For the LASSO regression, lambda.min (a minimum mean squared error) and lambda.1se (lambda.min with one standard error) were identified as the goodness penalty lambda based on the lambda-choosing path[8]. To screen for potential predictive factors, LASSO regression models with a lambda.1 se penalty were constructed. The variables selected *via* LASSO were included in a multivariate backward regression analysis to identify the independent influencing features of patients with OHCA. A nomogram prediction model was then constructed based on the variables with statistical significance. The discrimination and calibration of the model were assessed using receiver operating characteristic (ROC) and calibration curves, as well as the Hosmer-Lemeshow test. Internal verification was performed by strengthening the bootstrap method for 1000 repetitions, as shown in the calibration curves. The clinical practicability of the model was evaluated using decision curve analysis (DCA) according to the net benefit with different threshold probabilities.

RESULTS

A total of 2685 cases of patients with OHCA satisfied the inclusion and exclusion criteria. Table 1 presents the characteristics of all OHCA incidents in which first-aid treatment was implemented.

Feature selection and model development

We applied LASSO regression to identify potential predictors and then employed multivariate backward logistic regression to establish the model. As shown in Figure 1, the LASSO regression identified seven features through the lambda.1se penalty: Age, bystander CPR, initial rhythm, CPR duration, ventilation mode, use of amiodarone and lidocaine, and etiology. A model was then formed based on the factors evaluated using multivariate logistic regression (Table 2, Figure 3), during which amiodarone was eliminated.

Validation of the predictive model

The area under the receiver operating characteristic curve (AUC) of the P-ROSC prediction model was 0.9627 (95%: 0.9485-0.9769), which demonstrated the good discrimination ability of the model (Figure 3). A strengthened bootstrap self-sampling method was used to verify the model internally. Furthermore, the calibration plots fitted well with the ideal curves (Figure 4), indicating that the predicted probability was consistent with the actual probability, as suggested by the results of the Hosmer-Lemeshow test ($\chi^2 = 8.421$, $df = 8$, $P = 0.3935$). DCA to evaluate the clinical utility showed a net benefit for the "treat-all" or "treat-none" strategy (Figure 5), which suggested that the model was clinically useful.

DISCUSSION

The survival to hospital discharge in patients with OHCA worldwide is only 4.5%[9]. P-ROSC is a short-term survival event. However, recent studies have shown that patients who achieve P-ROSC have better neurological outcomes than those who do not[10,11]. Therefore, pre-EMS intervention factors and prehospital emergency measures have been analyzed to evaluate whether EMS intervention measures, including drug treatments, are necessary to inform EMT decisions to terminate the rescue following an appropriate determination to terminate resuscitation.

Age is an influencing factor in OHCA outcomes[12], age is considered as an influencing factor of OHCA outcomes. Consistent with the results of previous studies[13], age was significantly associated with ROSC in the adjusted model (OR: 0.98, $P < 0.001$) in the present study. In terms of etiology, cardiovascular system diseases accounted for the largest proportion of patients with OHCA (53.3%) in this study, while OHCA caused by central nervous system diseases had the highest rate of P-ROSC failure, followed by patients with traumas.

In some regions, the number of CPR bystanders has reached 50%, particularly in advanced countries[14]. However, although it is increasing annually, the bystander CPR rate remained poor in the current study. Rajan *et al*[15] suggested that sustained bystander CPR could increase by more than two-fold. In our study, CPR by bystanders increased the chances of ROSC by 2.6-fold ($P = 0.004$) compared with no bystander CPR.

The initial rhythm is another critical factor because timely defibrillation can increase the ROSC rate when a shockable rhythm occurs[16]. In the present study, the initial rhythm was also an essential variable of P-ROSC after adjusting for other variables ($P < 0.001$). Moreover, patients with agonal electrocardiography (Ag ECG) characteristics, such as slow

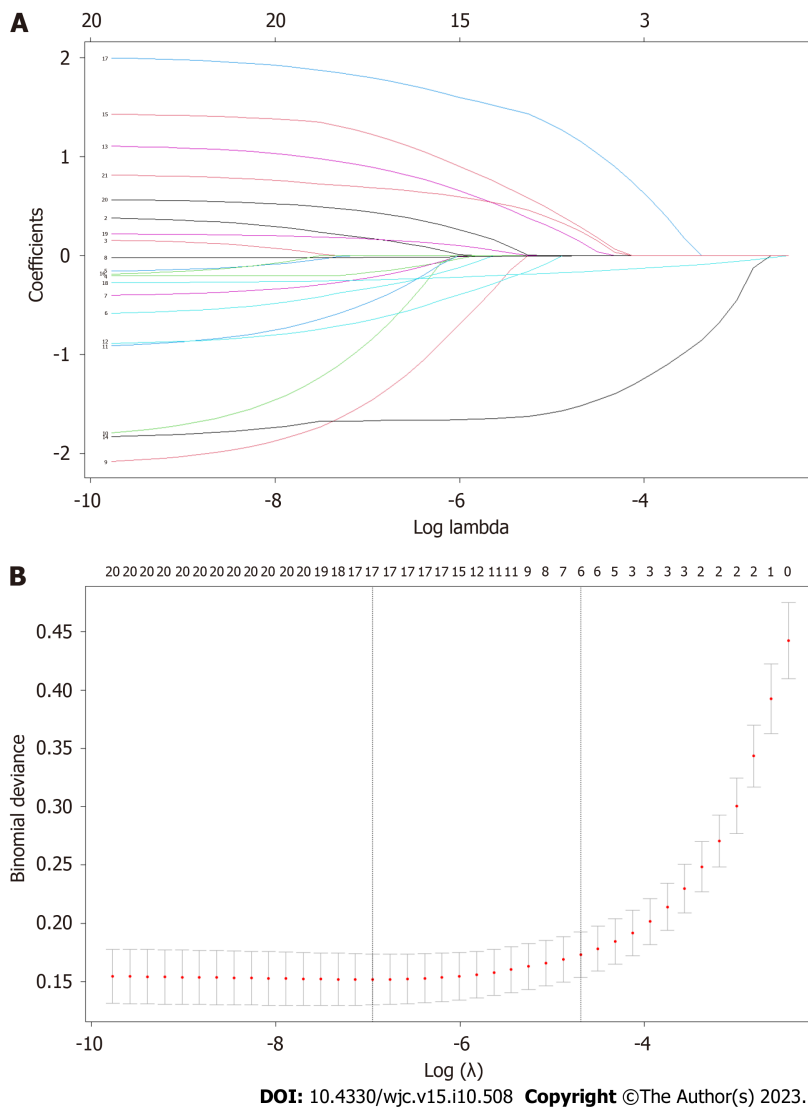


Figure 1 Factor selection of prehospital return of spontaneous circulation via least absolute shrinkage and selection operator regression.

A: Least absolute shrinkage and selection operator coefficient profiles of the 17 features. A coefficient profile plot was conducted against the log (lambda, λ) sequence; B: Through 10-fold cross-validation, and the optimal parameter (lambda, λ) selection via the minimum criteria. A partial likelihood deviance (binomial deviance) curve was plotted versus log λ . The dotted vertical line on the right was drawn at lambda.1se and four features were selected.

ventricular escape and bradycardia, who progressed to OHCA during treatment, had a higher P-ROSC rate, implying that a shorter time of no reflow time could improve prognosis.

Furthermore, CPR duration is a vital factor in predicting OHCA outcomes. Despite advances in CPR, no comprehensive agreement has been reached regarding the duration of CPR and the time for its termination in patients with OHCA. Funada *et al*[17] reported that CPR sustained in patients with OHCA > 26 min commonly caused ROSC failure. In the present study, the optimal cut-off time was 27.5 min and each additional minute of CPR was related to a 22% decrease in the probability of P-ROSC (OR: 0.78, $P < 0.001$) after adjustment for variable. Moreover, some studies suggested no possibility of ROSC in CPR lasting > 30 min, usually accompanied by irreversible damage to the brain[18]. Hence, uncertainties in the proper termination rules for CPR in basic and advanced life support care could increase pressure on ambulance transport, competition for medical resources, and risk of exposure to public accidents owing to high-speed transport[19]. However, the appropriate resuscitation termination for patients with OHCA remains controversial. Based on the model performance, we found that patients with OHCA and organ function as well as family abandonment of rescue do not require resuscitation times > 30 min. Conversely, in terms of OHCA of young adults (such as sudden cardiac deaths and sudden deaths of unknown causes), ECG manifestations of ventricular fibrillation or bradycardia, or a slow ventricular escape, the intensity of continuous resuscitation should be strengthened until the family approves that resuscitation can be terminated, even beyond 30 min of sustained CPR.

Finally, regarding prehospital advanced airway management (AAM) in patients with OHCA[20,21], some studies have shown that endotracheal intubation (ETI) can improve the probability of sustained ROSC, survival to hospital discharge, and neurologic outcomes[22]. In the present study, ETI was significantly associated with P-ROSC (OR: 8.28, $P < 0.001$). Moreover, Benoit *et al*[23] suggested that a delay in ETI was related to worse ROSC outcomes. In addition, Izawa *et al*[24] confirmed that AAM resulted in better survival in patients with non-shockable rhythms than in those with shockable

Table 1 Characteristics of the patients with out-of-hospital cardiac arrest

Features	Patients			P value
	Total (n = 2685)	ROSC failure (n = 2529)	ROSC (n = 156)	
Gender				0.730
Female	668 (24.9)	631 (25.0)	37 (23.7)	
Male	2017 (75.1)	1898 (75.0)	119 (76.3)	
Age	56.18 ± 17.98	56.63 ± 17.96	49.01 ± 16.82	< 0.001
Season				0.570
Spring	636 (23.7)	599 (23.7)	37 (23.7)	
Summer	625 (23.3)	582 (23.0)	43 (27.6)	
Autumn	666 (24.8)	632 (25.0)	34 (21.8)	
Winter	758 (28.2)	716 (28.3)	42 (26.9)	
Time (min)				0.029
08-16	953 (35.5)	888 (35.1)	65 (41.7)	
16-24	1049 (39.1)	984 (38.9)	65 (41.7)	
00-08	683 (25.4)	657 (26.0)	26 (16.7)	
Bystander CPR				< 0.001
No	2246 (83.6)	2135 (84.4)	111 (71.2)	
Yes	439 (16.4)	394 (15.6)	45 (28.8)	
Initial rhythm				< 0.001
VF/VT	293 (10.9)	232 (9.2)	61 (39.1)	
Asystole/PEA	2358 (87.8)	2278 (90.1)	80 (51.3)	
Ag ECG (slow ventricular escape, bradycardia)	34 (1.3)	19 (0.8)	15 (9.6)	
Duration of CPR	35 (15.0)	38 (18.0)	10 (16.0)	< 0.001
ETI				< 0.001
No	2194 (81.7)	2104 (83.2)	90 (57.7)	
Yes	491 (18.3)	425 (16.8)	66 (42.3)	
DF				< 0.001
No	2000 (74.5)	1914 (75.7)	86 (55.1)	
Yes	685 (25.5)	615 (24.3)	70 (44.9)	
Epinephrine dose	3 (3.0)	3 (3.0)	3 (2.0)	< 0.001
Atropine				0.243
No	2081 (77.5)	1966 (77.7)	130 (83.3)	
Yes	604 (22.5)	563 (22.3)	26 (16.7)	
Lidocaine or amiodarone				< 0.001
No	2556 (95.2)	2426 (95.9)	135 (86.5)	
Yes	129 (4.8)	103 (4.1)	21 (13.5)	
Etiology				0.019
Cardiac	1430 (53.3)	1327 (52.5)	103 (66.0)	
Trauma	122 (4.5)	116 (4.6)	6 (3.8)	
Toxicosis or asphyxia	45 (1.7)	44 (1.7)	1 (0.6)	
Brain and nervous	64 (2.4)	60 (2.4)	4 (2.6)	

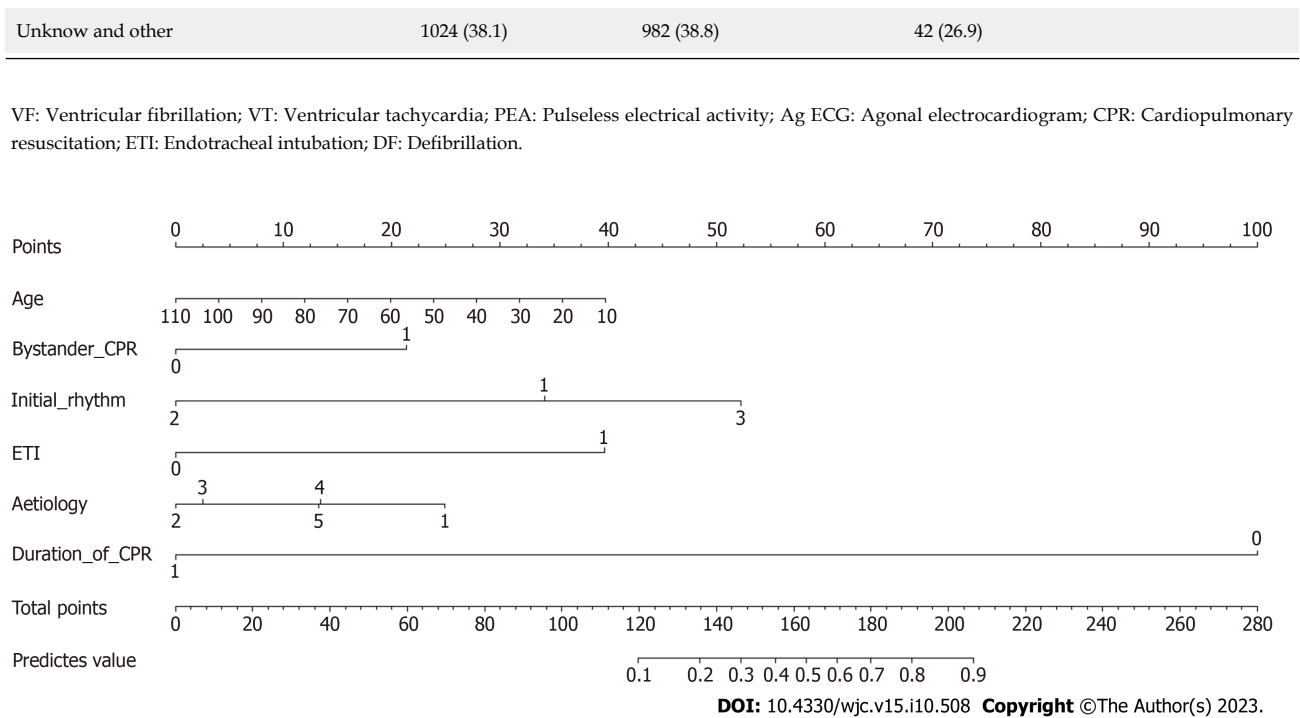


Figure 2 Nomogram prediction model of prehospital return of spontaneous circulation. Six predictors were included: Age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and etiology. Each variable was assigned a score on a point-scale axis. The total score was easily calculated by adding each single score. The probability of prehospital return of spontaneous circulation is estimated by projecting the total score to the lower total-point scale.

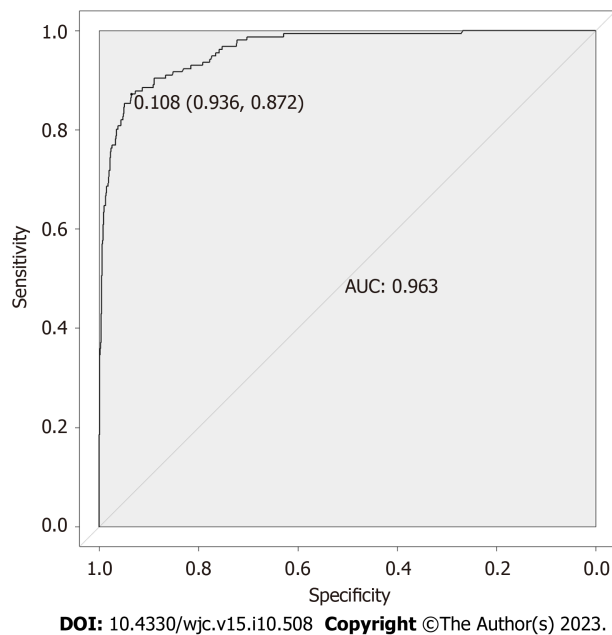


Figure 3 Receiver operating characteristic curves of prehospital return of spontaneous circulation model. The area under the receiver operating characteristic curve of the prehospital return of spontaneous circulation prediction model was 0.9627 (95%: 0.9485-0.9769).

rhythms, which might indicate the impact of shockable rhythms on the role of ETI in OHCA. Therefore, the effects of ETI in such situations warrant further investigation.

Ji *et al*[4], Morgan *et al*[5], and Navab *et al*[13] and others have established models in the United Kingdom, Australia, and Iran, respectively, to describe the influencing factors of clinical features and prehospital emergency measures on the ROSC rate as well as the survival rate of patients with OHCA. However, these researchers did not collect data on prehospital drug administration, including the use and dosage of epinephrine or other drugs. We developed a simple model applied to OHCA of all etiologies that covered pre-EMS intervention factors and prehospital emergency measures, including drugs and their dosage, although prehospital drug administration was not included in the model. Liu *et al*[7]

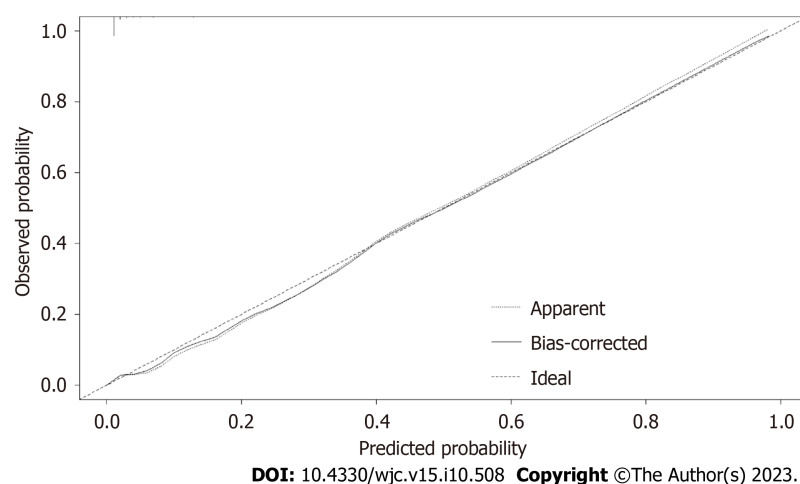


Figure 4 Calibration curves of the prehospital return of spontaneous circulation model. The dotted line represents the apparent model, while the solid line is bias-corrected by strengthening bootstrapping.

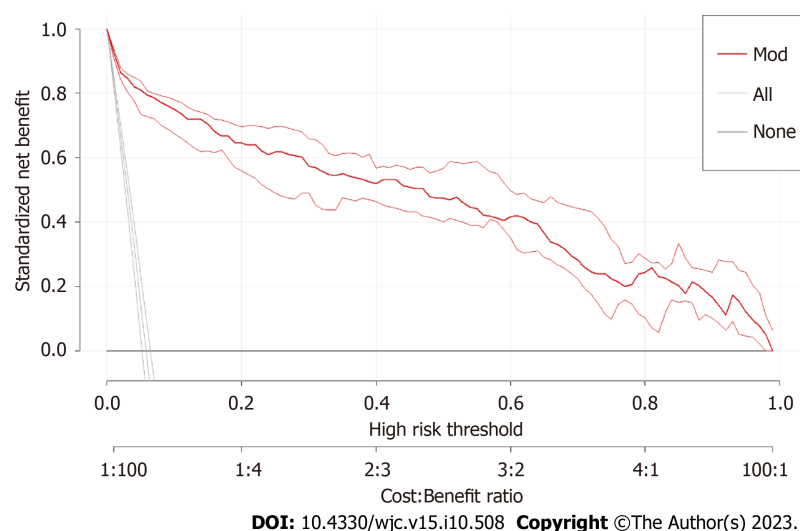


Figure 5 Decision curve analysis of the prehospital return of spontaneous circulation model. The X- and Y-axes show the threshold probabilities and net benefits, respectively. The solid red line indicates the prehospital return of spontaneous circulation model. The "All" and "None" lines represent interventions for all or none of the patients, respectively.

developed a P-ROSC score for patients with OHCA that also collected prehospital drug administration data. However, the model was not appropriate for trauma-induced OHCA, which limited its wide application. Another prospective study that included individuals between 1998 and 2008 generated the RACA score, which is a widely applicable score for ROSC in OHCA. However, it is not a contemporary cohort[25].

Limitations

Due to the retrospective design, the accuracy of data collection and potential confounders could not be assessed, and the identification of specific causalities was limited. Furthermore, incomplete data restricted the research. In addition, we did not collect no-reflow time data because the number of patients with OHCA witnessed by bystanders at the scene was too small.

CONCLUSION

We developed a simple and accessible model to predict the probability of achieving P-ROSC in China. The P-ROSC, with just six factors, is interpretable, convenient to implement, and comprehensive in busy prehospital processing; thus, it could serve as a possible assistive tool for clinical-aid decision-making.

Table 2 Multivariable logistic regression analysis of prehospital return of spontaneous circulation

Features	Multivariable analysis			Selected factors for model		
	OR	95%CI	P value	OR	95%CI	P value
Age	0.98	0.964-0.997	0.018	0.98	0.964-0.996	0.017
Bystander CPR			0.004			0.001
No	1			1		
Yes	2.621	1.36-5.051		2.854	1.504-5.414	
Initial rhythm			< 0.001			< 0.001
VF/VT	1			1		
Asystole/PEA	0.174	0.087-0.349	< 0.001	0.16	0.081-0.318	< 0.001
Ag ECG (slow ventricular escape, bradycardia)	4.539	0.89-23.15	0.069	4.103	0.806-20.895	0.089
CPR duration	0.778	0.75-0.807	< 0.001	0.776	0.749-0.805	< 0.001
ETI			< 0.001			< 0.001
No	1			1		
Yes	8.227	4.384-15.439		8.288	4.441-15.465	
Lidocaine or amiodarone			0.113			
No	1					
Yes	2.271	0.823-6.271				
Etiology			0.008			0.007
Cardiac	1			1		
Trauma	0.156	0.037-0.65	0.011	0.145	0.035-0.601	0.008
Toxicosis or asphyxia	0.171	0.007-4.026	0.275	0.163	0.007-3.907	0.263
Brain and nervous	0.393	0.079-1.95	0.253	0.371	0.075-1.844	0.226
Unknow and other	0.384	0.205-0.721	0.003	0.389	0.208-0.728	0.003

OR: Odds ratio; CI: Confidence interval; VF: Ventricular fibrillation; VT: Ventricular tachycardia; ETI: Endotracheal intubation; PEA: Pulseless electrical activity; Ag ECG: Agonal electrocardiography; CPR: Cardiopulmonary resuscitation.

ARTICLE HIGHLIGHTS

Research background

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide. In China, 550000 people develop OHCA annually with a survival rate of only 1.3% after discharge, making OHCA a major public health issue.

Research motivation

A large gap of prehospital return of spontaneous circulation (P-ROSC) rate remains between China and other countries and that the relative contributions of aid measures for each of these factors to P-ROSC vary across countries. There are still not such model, including pre-EMS intervention factors and Prehospital emergency measures, have currently been developed for P-ROSC in China.

Research objectives

To develop a nomogram prediction model which is interpretable, convenient to implement, easy to comprehend in busy prehospital processing, and comprehensive, including prehospital drug administration. Therefore, it could serve as a potentially assistive tool for clinical aid decision-making.

Research methods

Clinical data of patients with OHCA were retrospectively analyzed A nomogram prediction model for P-ROSC in patients with OHCA was developed and validate.

Research results

Among the included 2685 patients with OHCA, the P-ROSC incidence was 5.8%. LASSO and multivariate logistic regression analyses showed that age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and pathogenesis were independent factors influencing P-ROSC in these patients. The area under the ROC was 0.963. The calibration plot demonstrated that the predicted P-ROSC model was concordant with the actual P-ROSC. The good clinical usability of the prediction model was confirmed using decision curve analysis.

Research conclusions

We developed a simple and accessible model to predict the probability of achieving P-ROSC in China. The P-ROSC, with just six factors, is interpretable, convenient to implement, and comprehensive in busy prehospital processing; thus, it could serve as a possible assistive tool for clinical-aid decision-making.

Research perspectives

If we go one step further, we start to conduct prospective studies to identify the specific causalities and to improve the accuracy of data collection.

FOOTNOTES

Co-first authors: Jing-Jing Wang and Qiang Zhou.

Author contributions: Wang JJ, Zhou Q contributed equally to this work and share first authorship; Deng Z, Wang JJ, and Zhou Q designed the research study; Wang JJ and Zhou Q analyzed the data and wrote the manuscript; Deng Z were responsible for revising the manuscript for important intellectual content; Wang JJ, Zhou Q, Huang ZH, Han Y, Qin CZ, Qin CZ, and Xiao XY performed the primary literature and data extraction; All authors read and approved the final version.

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Cardiovascular complications following medical termination of pregnancy: An updated review

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Abstract

BACKGROUND

Around 1 million cases of medical termination of pregnancy (MTP) take place yearly in the United States of America with around 2 percent of this population developing complications. The cardiovascular (CVD) complications occurring post MTP or after stillbirth is not very well described.

AIM

To help the reader better understand, prepare, and manage these complications by reviewing various cardiac comorbidities seen after MTP.

METHODS

We performed a literature search in PubMed, Medline, RCA, and google scholar, using the search terms "abortions" or "medical/legal termination of pregnancy" and "cardiac complications" or "cardiovascular complications".

RESULTS

The most common complications described in the literature following MTP were infective endocarditis (IE) ($n = 16$), takotsubo cardiomyopathy (TTC) ($n = 7$), arrhythmias ($n = 5$), and sudden coronary artery dissection (SCAD) ($n = 4$). The most common valve involved in IE was the tricuspid valve in 69% ($n = 10$). The most observed causative organism was group B Streptococcus in 81% ($n = 12$). The most common type of TTC was apical type in 57% ($n = 4$). Out of five patients de-

veloping arrhythmia, bradycardia was the most common and was seen in 60% (3/5) of the patients. All four cases of SCAD-P type presented as acute coronary syndrome 10-14 d post termination of pregnancy with predominant involvement of the right coronary artery. Mortality was only reported following IE in 6.25%. Clinical recovery was reported consistently after optimal medical management following all these complications.

CONCLUSION

In conclusion, the occurrence of CVD complications following pregnancy termination is infrequently documented in the existing literature. In this review, the most common CVD complication following MTP was noted to be IE and TTC.

Key Words: Cardiovascular complications; Termination of pregnancy; Infective Endocarditis; Stress cardiomyopathy; Outcome

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Core Tip: The most common cardiovascular complications following the medical termination of pregnancy (MTP) are infective endocarditis (IE) and takotsubo cardiomyopathy (TTC). The most common organism identified in IE is group B Streptococcus and the tricuspid valve is the most common valve involved. TTC occurs most commonly in the first trimester after MTP. Spontaneous coronary artery dissection mostly presents with chest pain and the right coronary artery is the most common vessel to be involved. Bradyarrhythmia is the most common arrhythmia noted. These patients improve with appropriate medical management and mortality tends to be low.

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INTRODUCTION

The legality of abortion and the various restrictions imposed on the procedure vary significantly among various states of the United States and are ever-changing. The initial law, *Roe vs Wade*, which was made in 1973, streamlined the decision-making process. Over the last 50 years, there has been a paradigm change in the perspective of patients regarding the termination of pregnancy in the United States. Centers for Disease Control (CDC) reports an abortion rate of 11.4 for the year 2020 with around 1 million abortions taking place annually in the United States. Around 2% of this population have been reported to develop complications[1].

Due to the recent identification of female-specific factors associated with a greater cardiovascular (CVD) risk, it provides the potential to implement effective and targeted preventative measures to decrease disease burden at an individual and population level[2]. Therefore, having an understanding of the female specific risk stratification and prevention is important. Recent CVD risk guidelines have included miscarriage and stillbirth as risk factors for women[3]. Because of the changing times and laws, we must highlight various CVD complications which are associated with the termination of pregnancy[4]. In this article, we review the various cardiac comorbidities reported after the medical termination of pregnancy (MTP). We also describe their clinical profile, management, and outcomes observed in these patients. Various systemic reviews discuss the complications associated with the termination of pregnancy. However, none describes cardiac complications following the same. Therefore, this article can contribute towards a better understanding, and facilitate preparedness and management of the cardiac complications following termination of pregnancy.

MATERIALS AND METHODS

In this review, we aimed to describe the demographic details, clinical presentation, diagnosis, and management of the various CVD complications following MTP. We used the meta-analysis guidelines for the material and methodology of our study.

Search strategy

We performed a systemic search in various bibliographic databases including PubMed, Medline, RCA, and google scholar databases, using the search terms “abortions” or “medical/legal termination of pregnancy” and “cardiac complications” or “cardiovascular complications”. The reference citation analysis tool was also used to find more articles. We screened references of the initial articles for identifying other relevant articles. Search strategies were tailored to each database for identifying relevant articles. All search outputs were exported to Microsoft Excel version 2022. For those articles where the main text was missing, we reached out to the authors. We acknowledge their support in sharing their work with us.

Study selection

All articles reported in English including adult patients (age > 18 years) published before August 2022, were eligible to be included in this review. Articles lacking clinical details, including comments, opinions, and letters, were excluded. The inclusion and exclusion criteria for the patients were established in advance before the initiation of the study. To be included in this review, articles had to provide clinical details of the pregnancy and the reported cardiac complication. For those articles where the main text was missing, we directly contacted the authors. We acknowledge their support in sharing their work with us. We added complete information on the studies included in this study. Two reviewers independently screened the abstracts. Cardiac complications had to fulfill the diagnostic definitions as described below.

Definitions

Infective endocarditis: Cases of infectious endocarditis (IE) had to fulfill the Modified Duke's criteria, which include the presence of either a blood culture of the organism consistent with IE or an echocardiogram showing positive evidence of IE, abscess, new partial dehiscence of a prosthetic valve, or new regurgitation (major criteria). Minor criteria include a previous heart condition or history of intravenous drug use, fever, presence of microorganisms not typically seen with IE, immunological phenomena such as glomerulonephritis, Roth spots, or vascular phenomena such as major arterial emboli or Janeway lesions. The presence of two major criteria, one major and three minors, or five minor criteria is diagnostic for definitive IE[5].

Takotsubo cardiomyopathy: Cases of takotsubo cardiomyopathy (TTC) had to fulfill the Mayo Clinic diagnostic criteria, which include: (1) Transient left ventricular systolic dysfunction with regional wall motion abnormalities extending beyond a single epicardial coronary distribution; (2) Absence of obstructive coronary disease or any angiographic evidence of acute plaque rupture; (3) Presence of new electrocardiogram (EKG) changes as either sinus tachycardia (ST)-segment elevation and/or T wave inversion or elevation in cardiac troponin levels; and (4) Documentation of absence of pheochromocytoma or myocarditis[1].

Spontaneous coronary artery dissection: Cases of spontaneous coronary artery dissection (SCAD) had to provide details of coronary angiography, which used an iodinated contrast agent to fill the lumen of coronary arteries and X-rays to image the lumen. Alternatively, if an alternate imaging modality such as optical coherence tomography or intravascular ultrasound was used to delineate the cause of narrowing and showed a tear or blood accumulation in the arterial wall, it would also be eligible for inclusion[6].

Cardiac arrhythmia: To be included in this review, reported arrhythmias had to have details of an investigation showing the pattern of the arrhythmia[7].

Risk and bias assessment: Two reviewers (Singh T and Vojjala N) independently screened for risk of error and bias in the articles. Disagreements were resolved through final verification and consensus of the third reviewer (Mishra AK)[8].

Data extraction: Extracted data include information on the publication year, authors, study type, and methodology. We also extracted data on study participants, including recent age, gender, clinical presentation, CVD, imaging, and laboratory parameters and management. Finally, we studied the outcomes, including CVD complications and mortality[9,10].

Data synthesis and analysis: Continuous variables are expressed as the mean or percentages. Given the small sample size under each subgroup, we were not able to identify any odds or associations.

RESULTS

The initial screening identified 300 cases that were published between 1990 and 2022, of which 34 fulfilled the inclusion criteria, as shown in the PRISMA diagram (Figure 1). These included 16 cases of IE, seven cases of TTC, six cases of arrhythmia, and five cases of SCAD. The clinical profile, management, and outcomes of these events are described in Tables 1-4[11-41].

Of the 16 cases of IE following abortion, 15 occurred following elective surgical abortion and one was a case of clandestine induced abortion. Only two patients had an underlying risk factor for IE, including a history of aortic valve replacement (AVR)/mitral valve replacement (MVR) for IE and rheumatic heart disease. The median age of these patients was 24 years[15-37]. Following termination of pregnancy, the initial clinical presentation occurred as early as one week after the abortion to as late as several weeks, with the most delayed presentation seen 60 d after the abortion. Data on prior antibiotic prophylaxis was available for 11 patients, four of whom received prophylaxis, including doxycycline in two cases, ampicillin and gentamicin in one, and a combination of ciprofloxacin and doxycycline in one. The tricuspid valve was the most commonly involved, as seen in 11 patients (69%), with multivalvular involvement in two patients and rare pulmonary valve involvement in one patient (6%). Group B Streptococcus (GBS) was the most common organism detected in these patients ($n = 13$, 81%), with culture being negative in one patient. *Escherichia coli* and methicillin sensitive *Staphylococcus aureus* were positive in one patient each. Most patients had IE related complications at the time of presentation, with the most common complication being septic emboli as seen in 69% ($n = 11$) followed by heart failure in 19% ($n = 3$). All patients were treated with intravenous antibiotics and 56% ($n = 9$) required surgical intervention, including MVR in two patients, tricuspid valve replacement in four, AVR in two, and pulmonary valve replacement in one. An embolectomy was performed on one patient, along with medical management. The prognosis for this subset of patients was good, with a mortality rate of 6% ($n = 1$) in Table 1[10-25].

Table 1 Patients with infective endocarditis following medical termination of pregnancy

No.	Age/details	Time interval	Antibiotic prophylaxis	Microbiological diagnosis	Valves involved	Other complications	Management	Final outcome	Ref.
1	17 yr/ clandestine abortion	28 d	No	Neg	TV	None	Mx	Survived	[10]
2	30 yr/post ciprofloxacin and doxycycline	10 d	No	GBS	MV	S Ar, R Ar	Mx, MVR	Survived	[11]
3	31 yr/post-surgical abortion	48 d	No	GBS	TV	STE	Mx, TVR	Survived	[12]
4	37 yr/post-surgical abortion, past history of AVR/MVR for IE	60 d	Yes (ampicillin and gentamycin)	GBS	AV	SE	Mx	Survived	[13]
5	18 yr/elective abortion	Several weeks	No	GBS	TV	SE	Mx	Survived	[14]
6	30 yr/elective abortion	28 d	No	GBS	TV	SE, 1 st HB	Mx, TVR	Survived	[15]
7	33 yr/elective abortion	28 d	No	GBS	TV	SE, VRA	Mx, TVR	Survived	[16]
8	24 yr/elective abortion	28 d	No	GBS	TV	SE, RHF	Mx	Survived	[17]
9	15 yr/elective abortion	7 d	Doxycycline	GBS	PV	SE, PAA	Mx, PVR	Survived	[18]
10	15 yr/elective abortion	11 d	Ciprofloxacin + doxycycline	GBS	AV	HF, AR	Mx, AVR	Survived	[19]
11	18 yr/elective abortion	14 d	Doxycycline	GBS	TV	SE	Mx, Emb	Survived	[20]
12	22 yr/elective abortion	7 d	-	GBS	TV	SE, PAA, TR	Mx	Lost to follow-up	[21]
13	Young female	-	-	-	Mu	-	Mx, AVR, TVR	Death	[22]
14	37 yr	11 d	-	GBS	TV	SE, SI	Mx	Survived	[23]
15	25 yr/rheumatic heart disease	14 d	-	MSSA	Mu	SE	Mx	Survived	[24]
16	21 yr	21 d	-	E coli	MV	HF	Mx, MVR	Survived	[25]

GBS: Group B streptococcus; MSSA: Methicillin sensitive staphylococcus aureus; MV: Mitral valve; TV: Tricuspid valve; AV: Aortic valve; PV: Pulmonary valve; Mu: Multiple valves involved; S Ar: Septic arthritis; R Ar: Reactive arthritis; STE: Septic thromboembolism; SE: Septic embolism; 1st HB: First degree heart block; VRA: Valve ring abscess; RHF: Right heart failure; PAA: Pulmonary artery aneurysm; HF: Heart failure; TR: Tricuspid regurgitation; AR: Aortic regurgitation; SI: Sacroiliitis; Mx: Medical management; MVR: Mitral valve replacement; PVR: Pulmonary valve replacement; AVR: Aortic valve replacement; Emb: Embolectomy; TVR: Tricuspid valve replacement.

TTC was reported in seven cases in the literature as a post-abortion CVD complication. The mean age at presentation was 34.4 years, with a range of 22 to 43 years. Of the four patients (57%) for whom gestational age was available, all had undergone an abortion or miscarriage in the first trimester (within less than 12 wk). Three (43%) patients had experienced miscarriages, two (29%) had undergone surgical termination of pregnancy, and one had undergone an elective abortion. One patient had a history of myoma removal surgery during the 14th wk of pregnancy, which resulted in fetal death four weeks later and led to five recurrent episodes of TTC that improved with follow-up care. The most common presentation in the emergency department was chest pain, which was reported by three (43%) patients, with one patient experiencing right-sided pain radiating to the neck and the other two experiencing severe left-sided, non-radiating acute pain. Other common presentations included hypotension ($n = 1$), abdominal pain, and vaginal bleeding ($n = 1$). Abnormal EKG finding was reported in three (43%) patients only. EKG findings in most patients were normal sinus rhythm ($n = 2$) or T wave inversion ($n = 2$) in the inferior and anteroseptal walls. Other EKG findings included up-sloping ST depression ($n = 1$) and sinus tachycardia ($n = 1$). Troponin levels were available and elevated in six (86%) patients. Coronary angiography was performed on six (86%) patients who did not show any evidence of obstructive coronary artery disease. Echocardiograms in all seven (100%) patients reported a reduced ejection fraction (EF) of less than 40%, with the most common wall involvement being the apex in 57% ($n = 4$) and basal wall in 29% ($n = 2$). Only 43% were started on guideline-directed medical therapy ($n = 3$). Treatment for these patients commonly included beta-blockers (BB) and angiotensin-converting-enzyme inhibitors (ACEi) in 43% ($n = 3$), and diuretics in 29% ($n = 2$). Other pharmacological agents used for treatments

Table 2 Patients with takotsubo cardiomyopathy following medical termination of pregnancy

No.	Age, gestation	Clinical feature	TTC criteria: EKG and Trop; echo; coronary angiography negative; pheochromocytoma	Possible pathophysiology	Treatment given	Outcome: Mortality and EF repeat	Ref.
1	36 yr, 12 wk gestation	Misc; hypovolemia	EKG: ST and Trop T elevated; eCHO: TTE (35%) EF, hypok LV apex; coronary angiography: Negative	Catecholamine surge: (1) Direct toxicity; (2) Coronary vasoconstriction; and (3) Microvascular spasm	IV furosemide	5 th d repeat echo: LV to EF: 60%. F/u: 11 mo, no relapse	[26]
2	22 yr, gestation: NA	Post Sx TOP with evacuation of retained POC; hypovolemia	EKG: Normal and Trop T elevated; 2D echo: DCM; coronary angiography: Negative	Catecholamine release post procedure	Diuretics. Bisoprolol and lisinopril	Echo: Repeat day 2 had EF 56%. Follow-up, full recovery	[27]
3	37 yr, Misc	Chest pain, radiating to the neck	EKG: ST depression, Trop T elevated; 2D echo: EF < 40%; coronary angiography: Negative	NA	NA	F/u echo EF normal. F/u Trop T normal	[28]
4	43 yr, gestation: NA	Chest pain	EKG: Normal and Trop T elevated; echo: LV hypokinesia, apical, diaphragmal, posterior-basal segments; coronary angiography: Negative	Stress factors: (1) H/o fetal death at 18 wk gestation; and (2) Domestic stress	Beta-blockers, ACE inhibitors, aspirin	5 d later, 2D echo EF 72%, normal wall movements. F/u: Developed 4 episodes of TTC, 6 mo, 9 mo, 10 mo, and 19 mo later. With eventual normalization of EF	[29]
5	43 yr, 9 wk gestation	Post Sx TOP. Shock, hypoxia, cardiac arrest requiring CPR	EKG: T wave inv, Trop T elevated; echo: LV EF 33%, LV apex hypo/akinesia; angiography: NA	h/o autoimmune diseases; post-op stress; cervical infiltration of epinephrine	Infusion of levosimendan	Echo: 3 mo later showed return of the LV function to normal	[30]
6	28 yr, 12 wk gestation	Chest pain	EKG: T wave inv, Trop T elevated; echo: EF (30%-35%); hypokinesia mid ventricular and hyperkinesia apical and basal wall; coronary angiography: Negative	Post abortion depression; suicidal ideation	Carvedilol. Lisinopril spironolactone	F/u echo: NA. Hemodynamically stable on follow-up	[31]
7	32 yr, 10 + 1 wk gestation; Misc	Abdominal pain, vaginal bleeding. Later underwent POC evacuation	EKG: Intermittent VT and QRS broadening. Trop T: NA; TTE: EF: 32%, global LV hypokinesia and akinesia of inferior and inferio-septal wall; coronary angiography: Negative	Septic miscarriage with blood C/S: Group C Streptococcus; amphetamine usage	IV antibiotics	Full recovery in 6 wk. 2D echo: Normal on repeat	[32]

Misc: Miscarriage; POC: Product of conception; Sx TOP: Surgical termination of pregnancy; CPR: Cardiopulmonary resuscitation; ST: Sinus tachycardia; DCM: Dilated cardiomyopathy; VT: Ventricular tachycardia; Post-op: Post-operation; EF: Ejection fraction; LV: Left ventricle; TTC: Takotsubo cardiomyopathy; TTE: Transthoracic echocardiography; NA: Not available; EKG: Electrocardiogram; C/S: Culture and susceptibility; F/u: Follow-up.

included aspirin, antibiotics, spironolactone, and levosimendan ($n = 1$ each). Six (87%) patients with available follow-up information had echocardiograms showing restoration of EF. Following the initial episode, one patient had five distinct episodes of TTC recurrence following an altercation with her partner. No recurrences were reported for the remaining patients, and there were no reported mortalities[26-32].

In four reported cases of SCAD following abortion or stillbirth, individual patient data was available for three patients. The median age of these patients was 36 years, with a range of 33 to 41 years. All three patients presented within 14 d of undergoing abortion or stillbirth. The most common clinical presentation was chest pain, which was reported by two patients (50%). EKG changes in these patients included ST elevation, with the most common leads involved being the inferior leads (50% of patients), mimicking acute myocardial infarction. Cardiac biomarkers were normal in all cases. Echocardiography was performed on two patients, with one showing normal findings and the other showing decreased left ventricle contractility with an EF of 30%. Coronary angiography showed dissection in the right coronary artery in two patients (one with proximal involvement and one with distal involvement) and the left anterior descending artery in one. Management included percutaneous coronary intervention besides medical management for two of the three patients. All three patients survived the event. One patient had no similar episode after eight months of follow-up, while the other patient had a remnant anoxic brain injury[33-36].

Out of five patients developing arrhythmia, the most common type reported was bradycardia which was seen in 60% ($n = 3$) of patients. Other two patients developed an arrhythmia post administration of prostaglandin F2 alpha drugs. The two patients who developed bradycardia did so after the passage of the product of conception (POC) and the application of pressure to their cervix. The mechanism which was speculated to cause this was the triggering of the vagus nerve during this process, resulting in the development of bradycardia. In all these patients, bradycardia improved after forceps assisted removal of the POC. There was also a patient who developed supraventricular tachycardia (SVT) after the administration of the misoprostol injection[37-41].

Table 3 Patients with spontaneous coronary artery dissection following medical termination of pregnancy

No.	Age	C/F and EKG	Labs and imaging	Angiography	Management and prognosis	Ref.
1	36 yr	Chest pain 2 wk post abortion. ECG: STE in V2-V4, STD in inferior leads	Cardiac biomarkers: Normal. Echo: Normal	Angiography: Type C dissection in LAD	Management: PCI with stenting to LAD. Survived, no similar episodes at follow-up after 8 mo	[33]
2	41 yr	2 wk post still birth, became unresponsive, cardiac arrest post CPR, ROSC. ECG: STE in leads 2, 3, avF	Cardiac biomarkers: Normal. Echo: Decreased LV contractility, EF: 30%	Angiography: Type 2 SCAD involving distal RCA	Management: Medical management. Survived post cardiac arrest, anoxic brain injury	[34]
3	33 yr	Chest pain 10 d post abortion. EKG: STE in inferior leads	Cardiac biomarkers: Increased	Angiography: Dissection involving RCA	Management: PCI. Survived	[35]
4	N/A	2 cases had SCAD a/w stillbirth and miscarriage	N/A	N/A	N/A	[36]

C/F: Clinical features; EKG: Electrocardiogram; N/A: Not applicable; STE: Sinus tachycardia elevation; STD: Sinus tachycardia depression; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; SCAD: Spontaneous coronary artery dissection; LV: Left ventricle; EF: Ejection fraction; LAD: Left anterior descending artery; RCA: Right coronary artery; PCI: Percutaneous coronary intervention.

Table 4 Patients with arrhythmia following medical termination of pregnancy

No.	Age	Clinical details	Arrhythmia observed	Possible mechanism for arrhythmia	Treatment given	Outcome	Ref.
1	NA, 2 nd trimester	Induced by PGF2a	Bradycardia	Drug induced hypokalemia	NA	NA	[37]
2	32 yr, 20 th wk gestation	Induced by PGF2a	Bradycardia and hypotension	PG acting on ventricular receptor	IV RL, 0.5 mg atropine no response	F/u 1 mo EKG and echo normal	[38]
3	37 yr, 10 wk gestation	In miscarriage	Bradyarrhythmia	POC through cervix trigger vagal stimulation	POC removed	EKG normal on F/u	[39]
4	42 yr, 12 wk gestation	Miscarriage, with lower abdominal pain	Bradyarrhythmia with hypotension. USG TVS: POC in UC	POC through cervix, triggering vagus	POC removed	BP and HR improved	[40]
5	Age: NA, 2 nd trimester	Induced by PGF2a and IV oxytocin	Bradycardia, hypothermia and hypotension	Rupture of the cervix	NA	NA	[41]

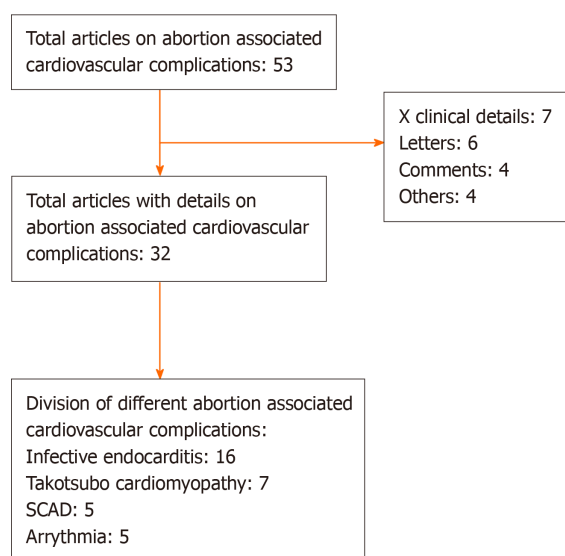
PGF2a: Prostaglandin F2 alpha; NA: Not available; USG: Ultrasound; TVS: Transvaginal ultrasound; POC: Product of conception; UC: Uterine cavity; RL: Ringer lactate; F/u: Follow-up; EKG: Electrocardiogram; BP: Blood pressure; HR: Heart rate.

DISCUSSION

In the year 2020, the CDC reported rate of abortion was 11.2 abortions per 1000 women of age 15-44 years in the United States[1]. The type of abortion can also be classified as either being safe (performed in a safe, clean environment with experienced providers and no legal restrictions) or unsafe (performed with hazardous materials and techniques, by a person without the needed skills, or in an environment where minimal medical standards are not met)[42]. Abortion related complications and deaths occur predominantly in unsafe abortions and in settings where it is illegal[43]. Complications following an abortion can be diverse. The maternal mortality rate following safe, legal induced abortion for 2013-2019 was reported to be 0.43 deaths per 100000 reported legal abortions[1]. Pregnancy is a state of altered neuro-humoral balance and continuous inflammation with significant effects on the physiology of the CVD system[44-47]. It is probable that even abortion or stillbirth can also result in altered neuro-humoral balance and chronic inflammatory changes affecting the functioning of the CVD system[4,42]. In this descriptive review, we highlight the various CVD complications following MTP reported in the medical literature. We identified four distinct CVD complications following MTP, which have been defined as above (Figure 2).

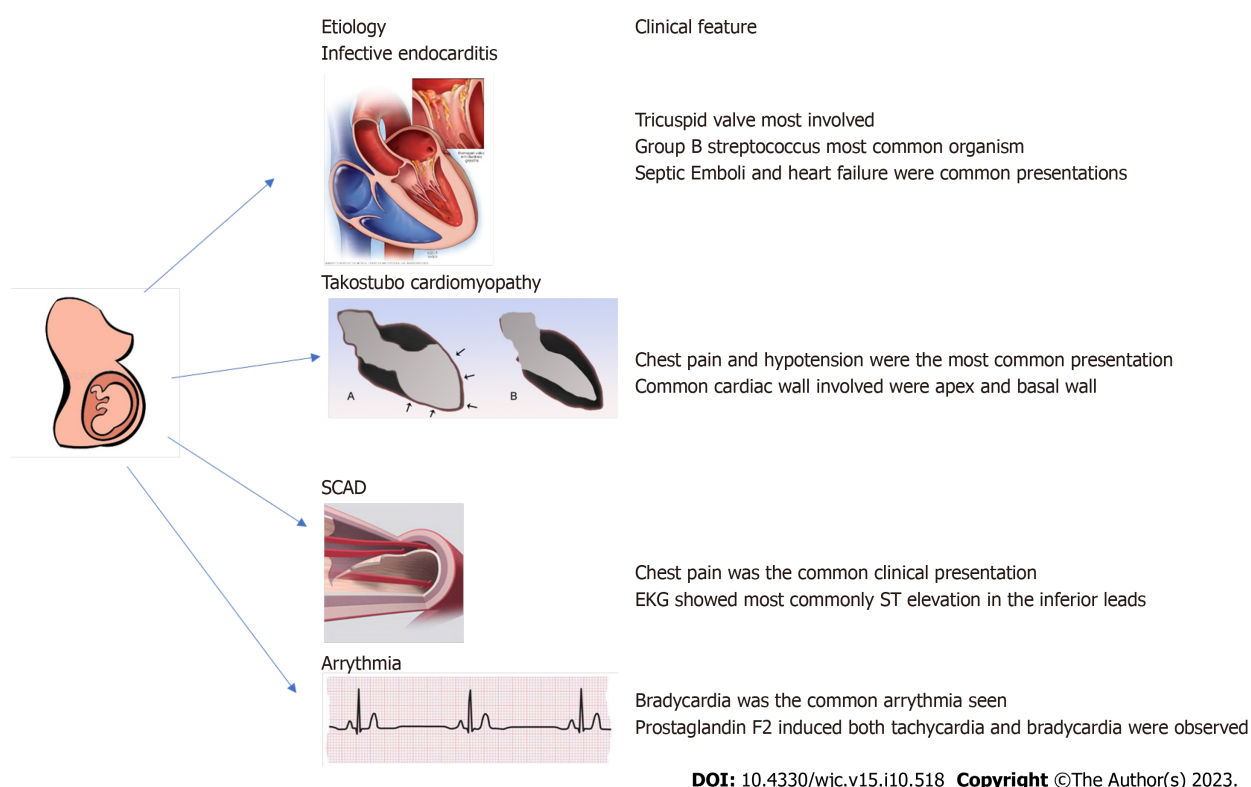
IE

In this review, IE was the most common CVD complication observed following MTP. While multiple organisms are reported to cause IE, in these patients the most common organism causing IE was GBS, which is a common colonizer of the genital tract and lower gastrointestinal tract[48,49]. The reported risk factors that predispose to GBS IE are diabetes mellitus, malignant disease, advanced liver disease, human immunodeficiency virus, alcohol use disorders, and injection drug use[50]. Surgical abortion has been reported to be an independent risk factor for IE in patients with GBS, irrespective



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Figure 1 Flow diagram of study participant inclusion. SCAD: Sudden coronary artery dissection.



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Figure 2 Cardiovascular complications following medical terminations of pregnancy. SCAD: Sudden coronary artery dissection; EKG: Electrocardiographic.

of the presence or absence of underlying structural heart disease or antibiotic prophylaxis before the procedure[12,13]. The Society of Obstetricians and Gynaecologists of Canada recommends antimicrobial prophylaxis for patients who are undergoing surgical abortion to reduce the incidence of post-abortion infections[51]. This recommendation is based on a meta-analysis of 12 randomized controlled trials conducted in pregnant women at less than 16 wk gestation. Patients who received antibiotics during the abortion procedure had a 0.58 (0.47-0.71) relative risk of developing upper genital tract infection, compared to those who did not receive the antibiotics[52]. A single appropriate antibiotic regimen was not recommended in the study. Though antibiotic therapy has been shown to prevent genitourinary infections, antibiotics were not uniformly administered in the above subsets of patients. Clinicians providing MTP should be aware of this rare complication in patients with risk factors as mentioned above. So far there are no studies to guide antibiotic prophylaxis in patients undergoing MTP, however, patients with risk factors for developing GBS IE might benefit from pre-procedure

prophylaxis. In a study done in Sweden on women undergoing an induced abortion, the administration of antibiotics reduced the post-abortion complications in patients with positive bacterial screening to the level with those having negative bacterial screening[53]. Despite the above study, given the rarity of this complication, prolonged prophylactic anti-biotic courses are not feasible or evidence-based.

The most common valve involved was the tricuspid valve, but multivalvular involvement was also seen[15,17,21,54]. Pelvic infections occurring after a septic abortion can provide a portal of entry for bacteria through pelvic veins into the venous system. This can subsequently spread to the right-sided circulation, eventually causing tricuspid endocarditis. Most of these patients presented with constitutional symptoms like chills, anorexia, and weight loss. Complications including septic pulmonary emboli are common among patients with right-sided IE, occurring in up to 75% of patients with tricuspid involvement. Clinical manifestations of such emboli include cough, pleuritic chest pain, hemoptysis, and dyspnoea[42,55,56]. In our study, the common complications seen were septic emboli and heart failure. All patients were treated with appropriate antibiotics based on culture and sensitivity results[57-61]. Patients with septic emboli, para-valvular abscess, conduction blocks, and the presence of large vegetations required surgical management as shown in Table 1. Overall, the prognosis was good with a mortality of 6.25%.

TTC

TTC, also called transient apical ballooning syndrome, was initially described in Japan in 1990[62,63]. Improved access to coronary angiography has led to increased recognition of TTC in patients presenting with symptoms of acute coronary syndrome, with studies reporting a 20-fold increase in incidence from 2006 to 2012[64-66]. Mayo Clinic Criteria and International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) are two of the most commonly used tools to establish the diagnosis[64,67]. In our study, Mayo Clinic Criteria was used. TTC has been reported to be precipitated in 70% of patients by several acute triggers including emotional, natural disaster, illness, envenomation, infection, *etc.*[68-70]. In this paper we discuss TTC precipitated following MTP. Patients who developed TTC post MTP presented with symptoms and signs of ACS including chest pain, ST-T wave changes in EKG, and elevated troponin as seen in patients with other precipitators of TTC[71]. In this review apical wall involvement was the most common echocardiographic abnormality, as reported by Templin *et al*[64] in 81.7% of their patient population ($n = 1750$)[72]. Multiple mechanisms have been proposed to precipitate TTC[72]. The various mechanisms postulated to precipitate TTC in this review were catecholamine surge following physical and emotional distress (depression, posttraumatic stress disorder, and suicidal ideation) and exogenous epinephrine[26,31,32]. It has been hypothesized that direct myocardial damage from catecholamines may cause TTC and the regional wall motion abnormalities occur due to the regional distribution of adrenergic receptors. At presentation all these patients had low left ventricular EF, however, less than half of the patients were treated with guideline directed medical therapy with ACEi and BB. Interestingly, no mortality was reported and at follow-up all these patients were found to have normal left ventricular ejection fraction.

SCAD

SCAD is a rare condition, with an estimated prevalence of 0.2% to 1.1%[49,73]. The prevalence of SCAD post pregnancy, stillbirth, and abortion remains unknown. There are several proposed mechanisms for the development of SCAD in these situations, including structural changes to the vascular system due to excess progesterone during pregnancy leading to the loss of normal corrugation of elastic fibers, increasing the fragmentation of reticular fibres, and decreasing the amounts of mucopolysaccharides reducing the strength of vessel wall, increased mechanical stress on the coronary artery during labor, prolonged coronary artery spasm, and the use of uterotonic drugs[36,74-77]. Maternal risk factors, such as multiple pregnancies, advanced age, and anxiety, may also increase the risk of SCAD due to repeated exposure to high levels of progesterone and altered neuro-hormonal balance[74,75,77]. In this review, SCAD was reported within 2 wk of MTP presenting as an ACS. Although the risk of SCAD post pregnancy and stillbirth may differ, early intervention with high clinical suspicion can result in good outcomes, as reported in various studies[44,73,78].

Arrhythmia

Bradycardia was the most common arrhythmia observed in our review[35-37,47]. The common cause of bradycardia is vagal stimulation during the passage of the fetus or POC through the cervix, a phenomenon known as cervical vasovagal shock[39,40]. This is typically observed with retained POC, and management often involves dilatation and curettage to remove the POC. In a study conducted in Cambridge, Kyejo *et al*[40] suggest that for patients with symptomatic bradycardia secondary to cervical shock, it is important to stop cervical manipulation and remove all instruments, keep the patient in the supine position with legs elevated to improve venous return, and, if necessary, administer 500-600 microgram of IV atropine followed by a saline flush. In this review, removal of the POC with forceps improved shock and bradycardia. Other causes of arrhythmia observed in our patients include prostaglandin F₂ and E (misoprostol), which have been linked to tachycardia and SVT. A study in mice suggests that these medications may cause tachyarrhythmias due to their direct effect of inflammatory mediators on the heart[79]. Stopping the medications resulted in the improvement of arrhythmias in these patients.

This review has several limitations. It included all the patients with MTP and reported CVD complications from various case reports over the years, which had varied uniformity in reporting. These patients were young and lacked baseline echocardiography or electrocardiography. All the reports of SCAD and TTC consistently did not report cardiac catheterization results[80]. Reports did not mention functional status at discharge, recurrence, and long-term follow-up details[81-84]. However, the strengths of this study are: (1) Having a strict inclusion criterion for each clinical entity; and (2) Evidence-based detailing on the clinical profile and the outcome of each described complication. As per the authors' knowledge, there are previous studies done including Kyriacou *et al*[3] who have reported that women with previous

pregnancy loss, following a miscarriage, stillbirth, and induced abortion, are at higher risk of coronary heart disease and stroke. However, this is the first review detailing the clinical profile, imaging details, complications, and outcomes of the various CVD complications following MTP.

CONCLUSION

In conclusion, CVD complications are uncommon following MTP. The most frequently reported complications are IE and TTC. IE can occur in these subgroups of patients without risk factors for IE. Perioperative antibiotics prophylaxis was not uniformly administered. IE can occur within 1 wk of MTP, and the most common organism identified is GBS. The most commonly involved valve reported is the tricuspid valve, and the most common complication reported is septic emboli. More than half of the IE patients required surgical intervention owing to worsening heart failure, valvular regurgitation, para valvular abscess, conduction block, and embolic phenomenon. TTC most commonly occurred after MTP in the first trimester. Most patients presented with acute chest pain, troponin elevation, and nonspecific ST-T changes. The most common pattern of TTC as identified by echocardiography was apical. All these patients had low EF at presentation and at follow-up most had normal EF even though only half of them were treated with ACEi and BB. SCAD occurred within 2 wk of MTP. Most patients presented with chest pain and EKG abnormalities. The most common vessel involved in dissection was the right coronary artery. Bradycardia was the most common pattern of arrhythmia noted and occurred during the time of MTP and was self-limiting. All patients with the above complications improved with appropriate medical management. Overall, mortality was low in this population.

ARTICLE HIGHLIGHTS

Research background

Millions of medical terminations of pregnancy (MTP) take place yearly in the United States of America with a smaller percentage of this population developing complications. There is a lack of structured reporting of the cardiovascular (CVD) complications in this subset of patients.

Research motivation

The CVD complications occurring post MTP or after stillbirth are not very well described. The literature on the various CVD comorbidity following MTP is scanty.

Research objectives

In this review we aimed to study the various cardiac comorbidities seen after MTP, which will help the reader better understand, prepare, and manage these complications.

Research methods

A literature search in multiple databases including PubMed, Medline, RCA and google scholar, using the search terms “abortions” or “medical/Legal termination of pregnancy” and “cardiac complications” or “cardiovascular complications” were conducted. All research studies, clinical studies, case series, and case reports with relevant clinical details were included.

Research results

The most common complications described in the literature following MTP were infective endocarditis (IE), takotsubo cardiomyopathy (TTC), arrhythmia, and sudden coronary artery dissection (SCAD). The most common valve involved in IE was the tricuspid valve. The most observed causative organism of endocarditis was group B Streptococcus. The most common type of TTC was apical. Bradycardia was the most common arrhythmia. All four cases of SCAD-P type presented as acute coronary syndrome with predominant involvement of the right coronary artery. Mortality was only reported following IE in 6.25%. Clinical recovery occurred after optimal medical management following all these complications.

Research conclusions

The most common CVD complications following the MTP are IE, TTC, bradycardia, and SCAD. Most of these complications are adequately treated with appropriate medical management.

Research perspectives

As per the authors' knowledge, this is the first review detailing on the clinical profile, imaging details, complications, and outcomes of the various CVD complications following MTP.

FOOTNOTES

Author contributions: Mishra AK and Hadley M planned and formulated the study; Singh T and Vojjala N collected and analysed the data; Singh T, Mishra AK, John KJ, George AA, and Jha A completed the manuscript; Singh T and Mishra AK revised the manuscript; Mishra AK and Hadley M reviewed the manuscript; and Hadley M approved the manuscript.

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Do cardiopulmonary resuscitation real-time audiovisual feedback devices improve patient outcomes? A systematic review and meta-analysis

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Abstract

BACKGROUND

Cardiac arrest is a leading cause of mortality in America and has increased in the incidence of cases over the last several years. Cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest; however, healthcare workers often do not perform CPR within recommended guidelines. Real-time audiovisual feedback (RTAVF) devices improve the quality of CPR performed. This systematic review and meta-analysis aims to compare the effect of RTAVF-assisted CPR with conventional CPR and to evaluate whether the use of these devices improved outcomes in both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) patients.

AIM

To identify the effect of RTAVF-assisted CPR on patient outcomes and CPR quality with in- and OHCA.

METHODS

We searched PubMed, SCOPUS, the Cochrane Library, and EMBASE from inception to July 27, 2020, for studies comparing patient outcomes and/or CPR quality metrics between RTAVF-assisted CPR and conventional CPR in cases of IHCA or OHCA. The primary outcomes of interest were return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD), with secondary outcomes of chest compression rate and chest compression depth. The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale and Cochrane Collaboration's "risk of bias" tool. Data was analyzed using R

statistical software 4.2.0. results were statistically significant if $P < 0.05$.

RESULTS

Thirteen studies ($n = 17600$) were included. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. Overall pooled ROSC in patients in this study was 37% (95% confidence interval = 23%-54%). RTAVF-assisted CPR significantly improved ROSC, both overall [risk ratio (RR) 1.17 (1.001-1.362); $P = 0.048$] and in cases of IHCA [RR 1.36 (1.06-1.80); $P = 0.002$]. There was no significant improvement in ROSC for OHCA (RR 1.04; 0.91-1.19; $P = 0.47$). No significant effect was seen in SHD [RR 1.04 (0.91-1.19); $P = 0.47$] or chest compression rate [standardized mean difference (SMD) -2.1; (-4.6-0.5); $P = 0.09$]. A significant improvement was seen in chest compression depth [SMD 1.6; (0.02-3.1); $P = 0.047$].

CONCLUSION

RTAVF-assisted CPR increases ROSC in cases of IHCA and chest compression depth but has no significant effect on ROSC in cases of OHCA, SHD, or chest compression rate.

Key Words: Real-time audiovisual feedback; Cardiopulmonary resuscitation; Cardiac arrest; Return of spontaneous circulation; Survival to hospital discharge; Cardiopulmonary resuscitation quality

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Core Tip: Real-time audiovisual feedback (RTAVF) devices have been shown to significantly improve cardiopulmonary resuscitation (CPR) quality in manikin/simulation studies. Despite this improvement, previous reviews have not seen a translation into improvement in patient outcomes. This systematic review and meta-analysis is the largest one to-date conducted on this topic, including 13 studies and 17600 patients. We found that the use of RTAVF devices significantly improves CPR quality metrics of chest compression rate and depth. Contrary to prior literature, we found that usage significantly increases return of spontaneous circulation in cases of in-hospital cardiac arrest but does not improve survival to hospital discharge.

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INTRODUCTION

Nearly 356000 out-of-hospital cardiac arrest (OHCA) cases and 292200 in-hospital cardiac arrest (IHCA) cases occur annually in the United States, making cardiac arrest one of the leading causes of natural death in America[1-3]. In addition, the incidence of cardiac arrest cases has increased over the last twenty years, but little progress has been made in improving survival to hospital discharge (SHD) and functional status including neurological and cardiovascular outcomes[2,4]. Consequently, cardiac arrest places a significant burden on public health and society and remains important to research and manage effectively[5,6].

High quality cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest[7-14]. The International Liaison Committee on Resuscitation guidelines specifically emphasize the quality of manual chest compression, including proper hand position, hands off time, compression rate, and compression depth[15]. However, the quality of CPR performed by healthcare workers (HCWs) often does not meet recommended guidelines, with the average rate of chest compressions and compression depth being lower than recommended[16-25].

Real-time audiovisual feedback (RTAVF) devices have enabled improvement in consistency and quality of CPR both inside and outside the hospital[26,27]. The American Heart Association (AHA) and the International Liaison Committee on Resuscitation have recommended the use of RTAVF devices for CPR training[28-30]. Previous systematic reviews and meta-analyses examining the effect of RTAVF devices during cardiac arrest cases concluded that RTAVF-assisted CPR resulted in closer adherence to CPR guidelines but not improved patient outcomes[31,32]. However, these studies focused on simulation manikin studies, including only three human trials. This systematic review and meta-analysis aims to compare the effect of RTAVF-assisted CPR with conventional CPR and to evaluate whether the use of these devices improved outcomes in both in-hospital and OHCA patients.

MATERIALS AND METHODS

Search Strategy

Database searches were performed by two independent authors in PubMed, SCOPUS, the Cochrane Library, and EMBASE with individualized search strategies developed for each database ([Supplementary Table 1](#)). The search included all studies from the establishment of the database to July 27, 2020 without language, methodology, or document filters. References cited in relevant reviews and included studies were also examined. The current systematic review and meta-analysis was constructed in accordance with the PRISMA 2009 guidelines.

Study Eligibility

Studies were included if HCWs were performing CPR using RTAVF devices, where HCWs were defined as anyone with medical training including physicians, nurses, paramedics, emergency medical services, physician assistants, and medical residents. Studies must compare RTAVF-assisted CPR with CPR performed without any device or disabled audiovisual feedback features on cardiac arrest patients, and complete data must be available with a minimum of two metrics reported with measures of central tendency and variability. Language was restricted to English. Simulation studies, animal studies, case reports, conference abstracts, reviews, trial protocols, and studies with incomplete or missing data were excluded.

Review Process and Data Collection

Abstracts of studies were reviewed for relevance by two independent authors. Abstracts with common agreement between reviewers were identified for further review of the full manuscript. Disagreements regarding the inclusion or exclusion of any studies were independently resolved by a third author. Data was extracted from articles selected for inclusion in the present study. Primary outcomes of interest were patient outcomes: return of spontaneous circulation (ROSC) and SHD. Secondary outcomes of interest were CPR quality metrics: chest compression rate and chest compression depth. Mean values and standard deviations were extracted from studies. Methodological quality was reviewed utilizing the Newcastle-Ottawa Quality Assessment scale for cohort studies and using the Cochrane Collaboration's "risk of bias" tool for randomized controlled trials (RCT)[[33,34](#)]. Methodological quality was assessed by two independent authors with disagreements resolved by a third author.

Statistical Analysis

Data was analyzed using R statistical software 4.2.0. Random-effects models were used[[35,36](#)]. When values were presented as interquartile range or range or median, they were converted into mean and standard deviation for analysis using the methodology presented in Wan *et al*[[37](#)] 2014. Pooled risk ratio (RR) or standardized mean difference (SMD) was calculated for binary and continuous metrics respectively[[38-40](#)]. Heterogeneity was assessed using I^2 [[41,42](#)]. Publication bias was assessed using funnel plots and Egger's tests. Results were statistically significant if $P < 0.05$.

RESULTS

Study Selection

A PRISMA flow diagram is shown in [Figure 1](#). The systematic search of articles identified 9422 results. 102 full-text articles were identified as potentially relevant after title and abstract screening. Thirteen studies were included after full-text review ([Figure 1](#))[[8,26,27,43-52](#)]. Thirteen studies reported data on ROSC and ten reported data on SHD. Important characteristics for each study are summarized in [Table 1](#).

Study Characteristics

A total number of 17600 participants from 13 studies were included for analysis. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. All studies were published between the years 2006 and 2020. Six studied the influence of RTAVF devices in OHCA, while six studied their influence in IHCA. One examined both OHCA and IHCA ([Table 1](#))[[44](#)]. All studies examined adult populations, with Park *et al*[[49](#)] 2018 examining patients greater than 15 years old.

Risk of Bias

Risk of bias was assessed in all 13 studies. Of the studies included, four were RCTs[[45,46,51,52](#)]. Using Cochrane's Risk of Bias tool, the risk of bias was assessed to be low risk in three RCTs and medium risk in one RCT ([Supplementary Table 2](#)). Using the Newcastle-Ottawa Scale, the risk of bias was assessed to be low in eight studies and medium in one study ([Supplementary Table 3](#)). Egger's test found no evidence of publication bias in any outcomes of interest ([Supplementary Figure 1](#)).

Outcomes

Pooled ROSC was 37% (95% confidence interval (CI) = 23%-54%) ([Supplementary Figure 2A](#)). Park *et al*[[49](#)] 2018 was identified as a potential outlier using leave-one-out sensitivity analysis with the lowest survival rate of 9%. Visual inspection of the associated funnel plot found no clear asymmetry ([Supplementary Figure 2B](#)).

Table 1 Characteristics of included studies

Ref.	Region	Enrollment year	n	Female	ROSC	Setting	Study type
Abella <i>et al</i> [26], 2007	United States	2002-2005	156	71	43%	IHCA, adult patients	Prospective cohort
Goharani <i>et al</i> [45], 2019	Iran	2015	900	546	55%	IHCA, adult patients	RCT
Hostler <i>et al</i> [46], 2011	United States, Canada	2007-2009	1587	1000	45%	OHCA, adult (> 20 yr)	RCT
Kramer-Johansen J <i>et al</i> [27], 2006	London, Norway, Sweden	2002-2003	284	106	19%	OHCA, adult	Non-randomized controlled trial
Lakomek <i>et al</i> [47], 2020	Germany	2016	196	112	54%	OHCA, adult	Non-randomized controlled trial
Vahedian-Azimi <i>et al</i> [52], 2020	Iran	2013-2014	22	10	27%	IHCA, adult	RCT
Vahedian-Azimi <i>et al</i> [51], 2016	Iran	2014	80	49	54%	IHCA, adult (≥ 18 yr)	RCT
Couper <i>et al</i> [43], 2015	England	2009-2013	400	182	40%	IHCA, adult (≥ 18 yr)	Prospective cohort
BoBrow <i>et al</i> [8], 2013	Arizona	2008-2011	484	162	23%	OHCA, adult (≥ 18 years)	Prospective cohort
Crowe <i>et al</i> [44], 2015	Arizona	2010-2013	101	27	42%	OHCA/IHCA, adult	Prospective before-after
Sutton <i>et al</i> [50], 2014	Pennsylvania	2011-2013	8	2	50%	IHCA, children (1-8 yr)	Prospective cohort
Lukas <i>et al</i> [48], 2012	Germany	2007-2011	638	184	50%	OHCA, adults (> 18 yr)	Retrospective Matched-pair analysis
Park <i>et al</i> [49], 2018	South Korea	2013-2016	12670	4571	9%	OHCA, > 15 yr	Before-after

ROSC: Return of spontaneous circulation; IHCA: In-hospital cardiac arrest; RCT: Randomized controlled trials; OHCA: Out-of-hospital cardiac arrest.

ROSC

Thirteen trials reported ROSC as an outcome of interest ($n = 17600$). ROSC occurred in 1693 patients (21.0%) in the RTAVF-assisted CPR group and 1602 patients (16.8%) in the conventional CPR group. All studies included data on ROSC in both the RTAVF-assisted CPR group and the conventional CPR group. Using a random-effects model, patients in the RTAVF group were significantly more likely to achieve ROSC than the conventional CPR group (RR 1.17; 95%CI = 1.001-1.362; $P = 0.048$) (Figure 2).

Subgroup analysis revealed that the location of cardiac arrest was significantly correlated with patient outcomes (P value for interaction = 0.02) (Supplementary Figure 3). ROSC in the setting of IHCA was significantly improved in the RTAVF group (RR 1.36; 1.06-1.80; $P = 0.002$). However, ROSC in the setting of OHCA was not significantly different between the two groups (RR 1.04; 0.91-1.19; $P = 0.47$).

Potential causes of heterogeneity in ROSC were explored, with subgroup analysis on study type comparing RCTs with non-RCTs, and region comparing studies within Europe, Middle East/Asia, and North America (Supplementary Figure 4). Heterogeneity remained significant within at least one subgroup in both analyses.

SHD

Ten trials reported SHD as an outcome of interest ($n = 16684$). SHD was reported in 994 patients (13.1%) in the RTAVF-assisted CPR group and in 1028 patients (11.2%) in the conventional CPR group. No significant difference was found in SHD between the two groups (RR 1.23; 0.94-1.60; $P = 0.12$) (Figure 3). Subgroup analysis found no significant correlation between SHD and the location of cardiac arrest (P value for interaction = 0.26) (Supplementary Figure 5).

Secondary Outcomes

Eight studies reported compression rate as an outcome of interest ($n = 2804$). The average compression rate was 107.3 ± 9.4 in the RTAVF-assisted CPR group and 117.5 ± 13.8 in the conventional CPR group, with a nationally recommended rate of 100-120 compressions per minute[53]. A non-significant difference was seen between the two, with patients in the intervention group receiving a lower compression rate [SMD -2.1; (-4.6-0.5); $P = 0.09$] (Supplementary Figure 6). While both groups had an average compression rate within the nationally recommended guidelines, the proportion of compressions that fell between 100-120 compressions per minute was likely higher in the intervention group than in the control group (Supplementary Figure 6). Eight studies reported compression depth as an outcome of interest ($n = 2625$). The average compression depth was $4.59 \text{ cm} \pm 0.91 \text{ cm}$ in the intervention group and $4.24 \text{ cm} \pm 1.29 \text{ cm}$ in the control group, with a nationally recommended compression depth of 5-6 cm in the average adult[53]. Neither group had an average compression depth that met AHA guidelines. However, a significant difference was seen between the two

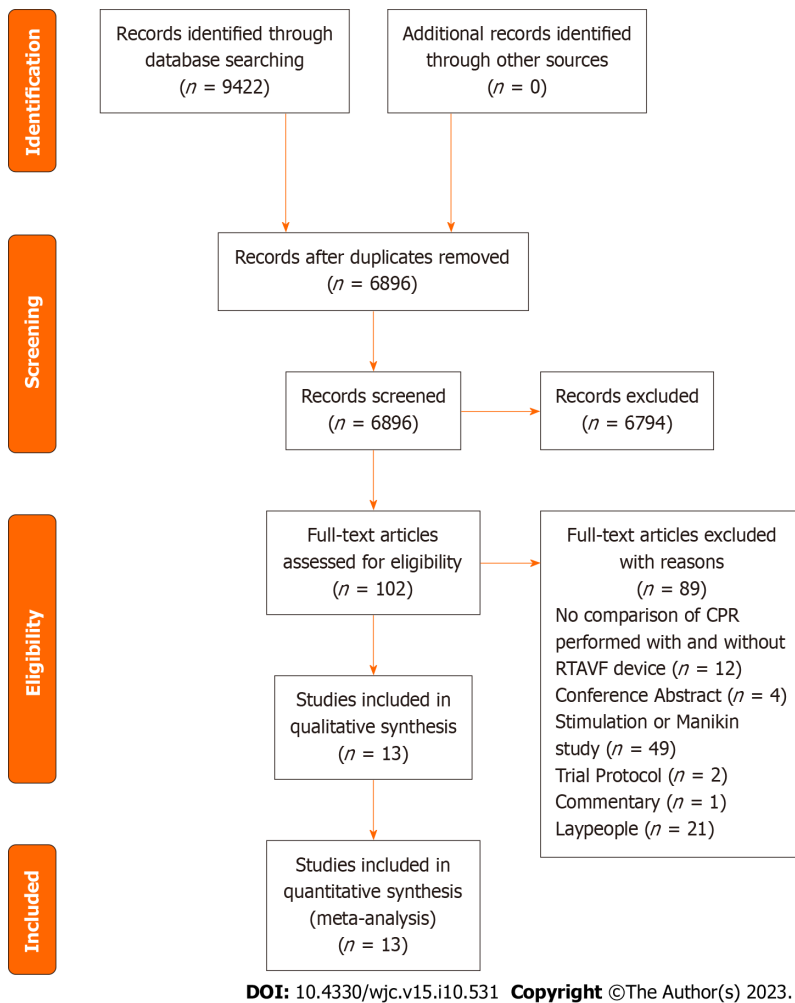


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of included and excluded articles.

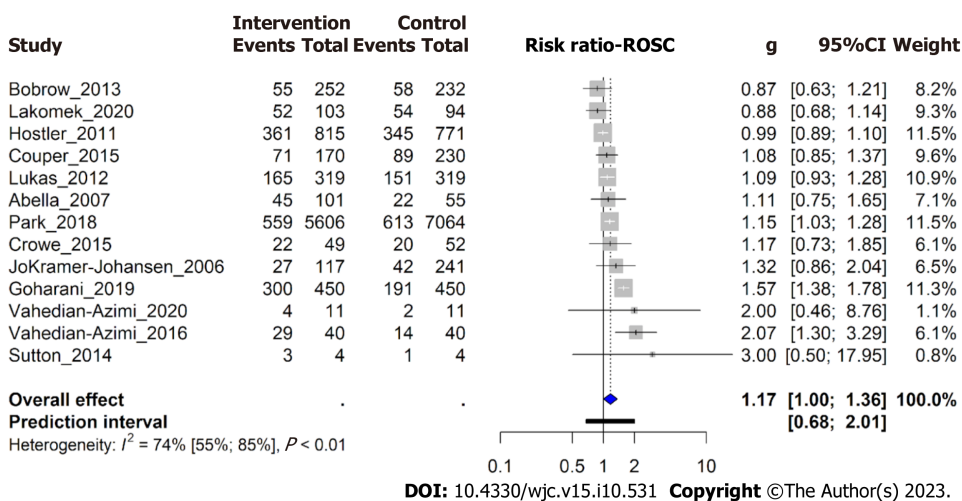


Figure 2 Forest plot of return to spontaneous circulation. ROSC: Return of spontaneous circulation.

groups, with patients in the intervention group receiving a higher compression depth, closer to AHA guidelines [SMD 1.6 (0.02-3.1); $P = 0.047$] (Supplementary Figure 7).

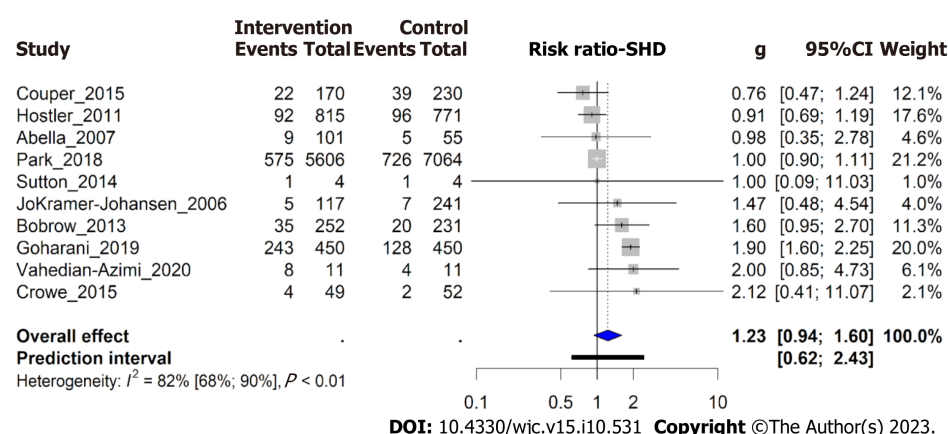


Figure 3 Forest plot of survival to hospital discharge. SHD: Survival to hospital discharge.

DISCUSSION

This manuscript analyzed the most recent evidence with regards to the efficacy of real-time audiovisual feedback devices in improving CPR quality and patient outcomes. A total of 13 studies ($n = 17600$) were included, making it the largest study of this topic to date.

Currently, patient outcomes after cardiac arrest remain poor. This meta-analysis found an average ROSC of 37%, which is consistent with previous literature findings ranging between 13% and 72% [54-59].

The AHA mandated that beginning January 2019, all AHA courses that teach adult CPR will be required to use a real-time audiovisual feedback device. These devices typically measure one or more of the following CPR metrics: Chest compression rate, depth, hand position, recoil, ventilation volume, ventilation rate, and hands-off time. Multiple types of feedback devices exist, including manikins with integrated sensors, devices that can be added to existing manikins, and hand-held devices that can be easily transferred from patient to patient [60]. As this meta-analysis examined the effect of using RTAVF devices during CPR on patient outcomes, the only type of RTAVF devices that were analyzed were hand-held devices that can be used during CPR on patients, rather than manikin-based RTAVF devices.

Thirteen studies with a total of 17600 patients were analyzed. These studies were a mixture of 4 RCT, 2 non-RCT, 4 cohort studies, 2 before-after studies, and 1 matched pair registry study. Studies took place across the globe with only 5 in the United States. These studies were both clinically and statistically heterogenous, with varying protocols and outcomes. Despite this heterogeneity, all studies did examine the primary outcome of ROSC with ten of thirteen also examining SHD.

Contrary to prior literature reviews, this analysis found that the use of real-time audiovisual feedback devices did significantly improve ROSC in cases of IHCA. This may be because prior meta-analyses included only three human intervention studies, while this meta-analysis had a larger number of studies and patients [31,32]. In addition, Kirkbright *et al* [32] 2013, Gugelmin-Almeida *et al* [31] 2021, and Lv *et al* [61] 2022 included only 1, 2, and 5 studies focusing on IHCA, respectively. This meta-analysis found that the location of cardiac arrest played a significant role in whether RTAVF devices influenced ROSC, with a significant increase in ROSC seen in cases of IHCA and no such increase seen in cases of OHCA. This could be another reason why prior reviews found no significant impact of RTAVF devices on ROSC. In particular, Lv *et al* [61] 2022 found that RTAVF-assisted CPR did not improve ROSC across all studies, but did not differentiate between ROSC outcomes in IHCA and OHCA settings. These findings suggest that hospitals should prioritize the rollout and adoption of RTAVF devices in areas most likely to see IHCA, such as intensive care units, telemetry units, and EDs, rather than with paramedics or ambulances [62,63]. This difference in survival may be due to the inherent rushed nature of CPR for patients suffering OHCA. Unlike cases of IHCA where a dedicated HCW can focus exclusively on performing high quality CPR, in cases of OHCA, paramedics may be obligated to multi-task, performing CPR while also keeping track of the other required tasks to bring the patient into the hospital safely. As such, the quality of CPR may be reduced in cases of OHCA *vs* IHCA. Another explanation could be tied to the fact that the time-to-CPR from arrest is lower in cases of IHCA *vs* OHCA, and as such CPR quality may play a more important role in IHCA than in OHCA [64, 65].

Despite the increase in ROSC when using RTAVF devices, no similar increase was seen in SHD. This insignificance may relate to how CPR quality plays little role in the improvement of survival after ROSC. It could also be due to the presence of comorbidities including heart failure, sepsis, and myocardial infarction and that effective CPR is one factor among many steps required for improved survival. Without additional improvements in other steps required in the care of post-cardiac arrest patients, the increase in CPR quality may be insufficient to translate into improved SHD.

Repeated studies in the literature have shown that CPR quality when performed on manikins improves when using a RTAVF device [31,32]. Consistent with existing literature, this meta-analysis also found that CPR quality was increased in RTAVF-assisted CPR. The average compression rate in both groups fell within AHA guidelines, while the average compression depth in both groups fell outside of AHA guidelines [53]. However, for both compression rate and depth, the RTAVF group was more likely to have a higher proportion of compressions falling within guidelines compared to the conventional CPR group, showing that RTAVF-assisted CPR was superior to conventional CPR. Prior studies have shown

the importance of proper compression depth in patient outcomes[10,16,66]. In CPR training courses being taught with RTAVF devices, a larger focus should be put on achieving adequate compression depth.

Overall, the evidence suggests that RTAVF-assisted CPR is of superior quality than conventional CPR. In addition, RTAVF-assisted CPR has a small benefit in patient outcomes, specifically improving ROSC in cases of IHCA. However, this meta-analysis has multiple limitations. First, the studies examined were both statistically and clinically heterogeneous, with varying study parameters, outcomes, and designs, limiting the internal validity of the meta-analysis. This was partially accounted for using a random-effects model and by subgroup analysis, but not all heterogeneity could be accounted for. This may partially be due to the limitations of I^2 as a metric for heterogeneity. This study contained relatively larger studies than most examining this topic, and prior literature has documented that as sampling error decreases, I^2 tends to increase, which can erroneously lead to assumptions that clinical heterogeneity has also increased. In addition, as this meta-analysis examined the class of all RTAVF devices used in CPR, some degree of clinical heterogeneity is expected, as the expected effects of individual devices can vary. Second, nine of these thirteen studies were not RCT, which can introduce sources of both confounding and selection bias. However, ROSC outcomes of cardiac arrest patients are dependent upon many non-controllable factors that cannot undergo randomization including time from arrest to CPR initiation and presence of shockable rhythm which may limit the advantage an RCT would have over other nonrandomized studies designs. Third, this meta-analysis only examined RTAVF devices that could be used during CPR on patients rather than RTAVF devices that are built into manikins. As such, these results cannot be extrapolated to that class of RTAVF devices. Fourth, this meta-analysis only reviewed publications in the literature until 2020, precluding studies published thereafter from inclusion in this analysis. Fifth, this meta-analysis was limited by the evidence that could be extracted from prior reports in the literature, and evidence on long-term patient outcomes and neurological function from RTAVF-assisted CPR is lacking. Future research should examine such cohorts and associated long-term outcomes. In addition, further research into why the improvements seen in ROSC with RTAVF-assisted CPR were not translated into improvements in SHD is warranted, along with research examining which RTAVF device provides the highest improvement in patient outcomes and CPR quality.

CONCLUSION

This meta-analysis examined 13 studies ($n = 17600$) and found that RTAVF-assisted CPR resulted in a significantly increased rate of ROSC, specifically in cases of IHCA but did not improve SHD. This is a novel finding, with prior meta-analyses finding that the use of RTAVF devices did not significantly improve patient outcomes. Consistent with what has been found previously, the use of RTAVF devices resulted in improved CPR quality, as measured by compression rate and depth.

ARTICLE HIGHLIGHTS

Research background

Cardiac arrest is a leading cause of mortality in America and continues to grow in prevalence. Cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest; however, healthcare workers often do not perform CPR within recommended guidelines. Real-time audiovisual feedback (RTAVF) devices provide live feedback on CPR performance and subsequently improves the quality of CPR performed.

Research motivation

Effective CPR in cardiac arrest is critical to emergent management and stabilization. RTAVF-assisted CPR devices may improve performance, compliance with recommended guidelines, and survival, therefore, this systematic review and meta-analysis seeks to compare the effect of RTAVF-assisted CPR devices with conventional CPR on patient outcomes in the setting of in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA).

Research objectives

To investigate the impact of RTAVF-assisted CPR on patient outcomes and CPR quality with respect to in- and OHCA.

Research methods

The literature search was conducted on PubMed, SCOPUS, the Cochrane Library, and EMBASE from inception to July 27, 2020, for studies reporting patient outcomes and/or CPR quality metrics between an RTAVF-assisted CPR and conventional CPR in the setting of IHCA or OHCA. The primary outcomes of interest extracted and analyzed were return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD). Data was analyzed using R statistical software 4.2.0. Results were statistically significant if $P < 0.05$.

Research results

Thirteen studies ($n = 17600$) were included after deduplication, screening, and full-text analysis. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. Overall pooled ROSC was 37% among all studies. RTAVF-assisted CPR significantly improved ROSC in the case of IHCAs and improved chest compression depth. No significant

improvements were seen in ROSC in cases of OHCA, SHD, or compression rate.

Research conclusions

This meta-analysis found that RTAVF-assisted CPR increases ROSC in the setting of IHCA but has no significant effect on ROSC in the setting of OHCA or SHD. Consistent with previous manikin simulation studies, the meta-analysis found that RTAVF-assisted CPR results in improvements in both chest compression rate and depth.

Research perspectives

Cardiac arrest remains a leading cause of mortality with increasing prevalence. The findings of this study suggest that RTAVF-assisted CPR may improve ROSC in the setting of IHCAs but not in the setting of OHCA. Hospitals should prioritize implementing RTAVF devices in areas with the highest rates of IHCA rather than to paramedics or ambulances.

FOOTNOTES

Author contributions: Sood N, Sangari A, and Goyal A contributed equally to this work; Sood N and Sangari A designed the research study; Sood N, Sangari A, and Goyal A performed the research; Sood N performed the statistical analysis; Sood N, Sangari A, Goyal A, Sun C, Horinek M, Hauger JA, and Perry L analyzed the data and wrote the manuscript; Sood N, Sangari A, Goyal A, Sun C, Horinek M, Hauger JA, and Perry L reviewed the manuscript before submission; All authors have read and approved the final manuscript.

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Systemic right ventricle complications in levo-transposition of the great arteries: A case report and review of literature

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Abstract

BACKGROUND

Congenitally corrected levo-transposition of the great arteries (L-TGA) is a congenital heart disease in which the ventricles and great arteries are transposed from their typical anatomy. In L-TGA, the double discordance, atrioventricular and ventriculoarterial, create an acyanotic milieu which allows patients to survive their early decades, however, progressive systemic right ventricle (sRV) dysfunction creates complications later in life. sRV dysfunction and remodeling predisposes patients to intracardiac thrombus (ICT) formation.

CASE SUMMARY

A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure. In childhood, he had surgical repair of a ventricular septal defect. In adulthood, he developed sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and left-bundle branch block for which he underwent cardiac resynchronization therapy. Transthoracic echocardiogram showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV ICT. ICT was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. Our patient was optimized with guideline-directed medical therapy and diuresis. Anticoagulation was achieved with a vitamin K antagonist (VKA) and he was later referred for evaluation by advanced heart failure and heart transplant services.

CONCLUSION

Anticoagulation with VKA is the mainstay of treatment in the absence of conclusive data supporting direct oral anticoagulant use in ICT in patients with

congenital heart disease. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring with dedicated cardiac imaging to identify complications.

Key Words: Levo-transposition of the great arteries; Systemic right ventricle; Congenital heart disease; Intracardiac thrombus; Anticoagulation; Direct oral anticoagulant; Case report

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Core Tip: Patients with congenital heart disease such as levo-transposition of the great arteries experience progressive cardiac dysfunction and remodeling which manifests as heart failure. This predisposes patients to the formation of intracardiac thrombus (ICT). We present a case of progressive systemic right ventricle (sRV) dysfunction resulting in an apical thrombus. Review of literature identified no cases of sRV thrombus making this one of the first reports. Guidelines do not exist for anticoagulation in patients with congenital heart disease and ICT. Therefore, clinical decisions are extrapolated from anticoagulation principles in patients without congenital heart disease. Considerations for direct oral anticoagulants in this population should be individualized and involve shared decision making.

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INTRODUCTION

Congenitally corrected transposition, or levo-transposition of the great arteries (L-TGA) is a rare congenital heart disease with an estimated prevalence of 0.4%-1.0% among patients with congenital heart disease[1,2]. The double discordance, atrioventricular and ventriculoarterial, creates an acyanotic milieu in which both pulmonary and systemic circulations exist and freely communicate[3]. This phenomenon, which is alluded to as “congenitally corrected”, allows patients to survive their early decades with minimal cardiac complications. A large prospective survival study found that 95.5% of patients survive the first month of life; 72.7% survive to the age of 3 and this percentage of patients continues to live to the age of 15[1]. Survival data among adults is variable due to the presence of different associated cardiac lesions and the heterogeneous surgical interventions these patients undergo[4]. Among all patients with L-TGA, a minority survive beyond the fifth decade of life due to cardiac complications[5]. In those who undergo surgical correction as children, the 10-year survival rate ranges from 60%-70%[6,7].

The natural history of L-TGA involves a wide spectrum of cardiac complications that manifest during early adulthood. The atypical anatomy and pathophysiologic circulation with the systemic right ventricle (sRV) in L-TGA predisposes patients to progressive sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and conduction defects including heart block[8]. Patients commonly present with clinical manifestations of heart failure as the lifetime prevalence is 34% in L-TGA as opposed to 1%-2% across the general population[9,10].

A large multicenter study found that by the age of 45, heart failure develops in 67% of patients with L-TGA and associated cardiac lesions whereas it develops in 25% of patients with L-TGA and no associated cardiac lesions[9]. Anatomical surgical repair, which aims to correct the double discordance by making the morphologic left ventricle the systemic ventricle and the morphologic right ventricle the pulmonary ventricle, is associated with higher survival rates and lower morbidity[11-13]. Physiologic surgical repair, which targets associated cardiac lesions without correcting the double discordance, is associated with higher rates of sRV dysfunction and mortality in adulthood[14].

We report a case of sRV thrombus in a patient with L-TGA who presented with acute decompensated heart failure (ADHF) and discuss the state of current literature regarding anticoagulation management.

CASE PRESENTATION

Chief complaints

A 40-year-old male with L-TGA presented to the hospital with ADHF. Upon review of systems, he had no chest pain, palpitations, lightheadedness, or syncope; he also denied cough, sputum production, or fever. He was not recently ill and had no sick contacts.

History of present illness

Symptoms started three-weeks prior to presentation with progressive shortness of breath on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bilateral lower limb swelling. His symptoms were severe enough to make conversation difficult and limited his activities of daily living.

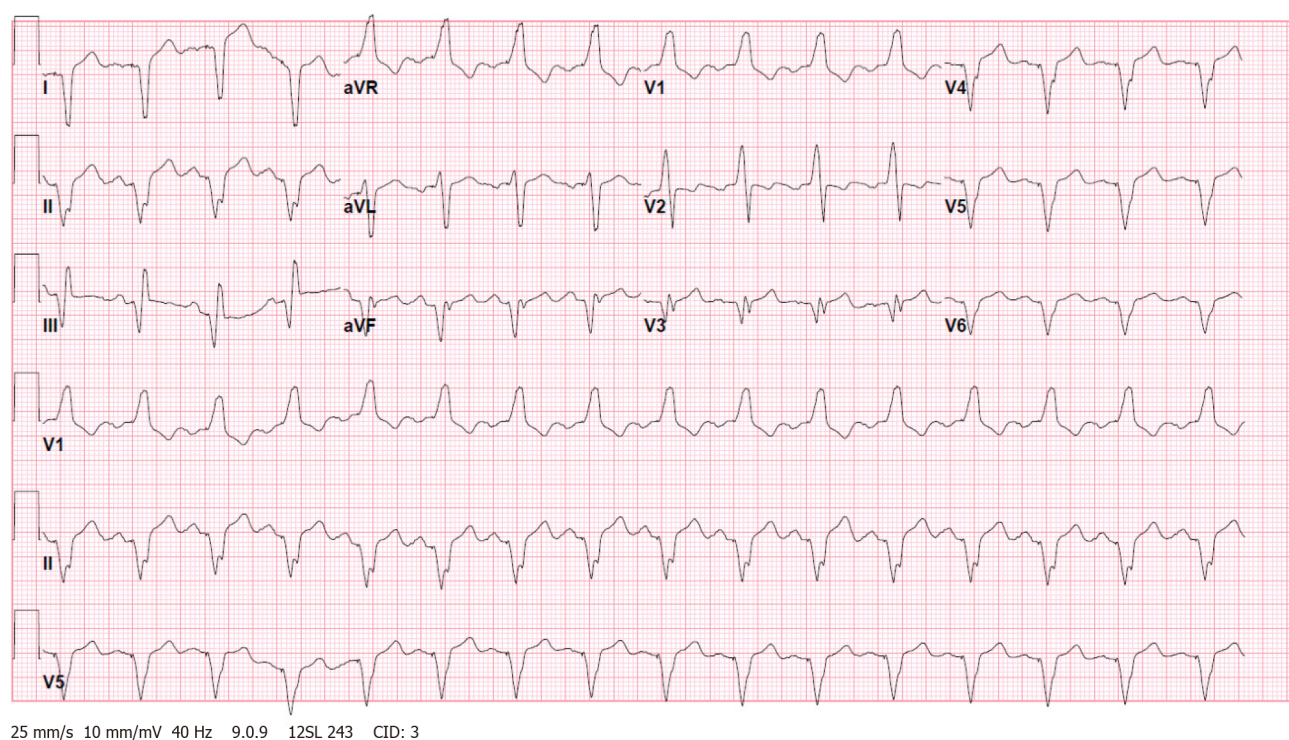


Figure 1 Electrocardiogram showing an atrial-sensed ventricularly-paced rhythm without acute abnormalities.

History of past illness

His medical history was remarkable for L-TGA with an associated ventricular septal defect, he underwent physiologic surgical closure of the septal defect at three years of age. He was monitored by a pediatric cardiologist in childhood and early adulthood during; he remained free of cardiac symptoms during this time and was eventually lost to follow-up. At the age of thirty-five, he was hospitalized for ADHF and was found to have sRV dysfunction with severely reduced global systolic function and severe sTV regurgitation. He was also noted to have a progressive conduction disease as his previously known first degree atrioventricular block was replaced by a newly identified left-bundle branch block. He was medically managed for heart failure and underwent cardiac resynchronization therapy with biventricular pacemaker implantation. He followed with the advanced heart failure and transplant service but was then lost to follow-up for several years until this latest presentation to the hospital.

Personal and family history

The patient did not have a family history of congenital heart disease, heart failure, or respiratory illness.

Physical examination

During this presentation, the patient was tachycardic (108 beats per minute) and tachypneic (25-40 breaths per minute); blood pressure was 104/68 mmHg and he was not hypoxic on room air. Height was 168 cm and weight was 92 kg. Physical exam was positive for decreased bilateral breath sounds with mild crepitation. Jugular venous distension was present and pitting edema was noted in the bilateral lower limbs.

Laboratory examinations

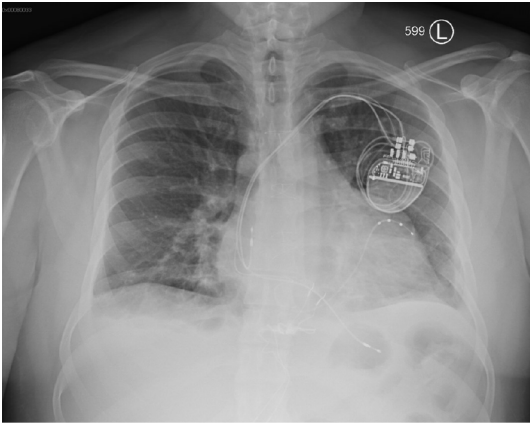
Laboratory tests were notable for a brain natriuretic peptide of 472 pg/mL, high-sensitivity troponin of 16 ng/L, venous lactate of 1.2 mmol/L, and creatinine of 0.80 mg/dL (Table 1). Electrocardiogram showed an atrial-sensed ventricularly-paced rhythm without acute abnormalities (Figure 1).

Imaging examinations

Chest X-ray was remarkable for cardiomegaly with small bilateral pleural effusions (Figure 2). Chest pulmonary angiography was negative for pulmonary embolism, pericardial effusion, or pneumothorax (Figure 3). His cardiac anatomy of L-TGA is visualized on chest computed tomography (Figure 4).

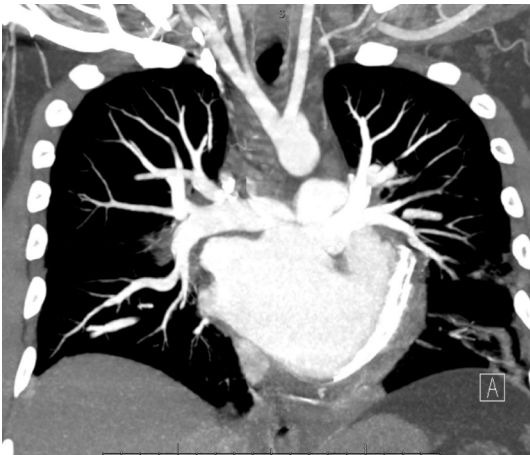
FURTHER DIAGNOSTIC WORK-UP

Our patient was managed for ADHF with guideline-directed medical therapy including diuresis with intravenous



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Figure 2 Chest X-ray showing cardiomegaly with small bilateral pleural effusions with unremarkable pulmonary vasculature. Biventricular pacemaker is present at the right chest.



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Figure 3 Chest pulmonary angiography demonstrating a levo-transposition of the great arteries cardiac anatomy. Examination was negative for pulmonary embolism, pericardial effusion, or pneumothorax.

furosemide 40 mg once daily, oral metoprolol succinate 50 mg once daily, oral losartan 50 mg once daily, and oral dapagliflozin 10 mg daily. He had rapid clinical improvement with resolution of his symptoms and was transitioned to oral diuretic as needed.

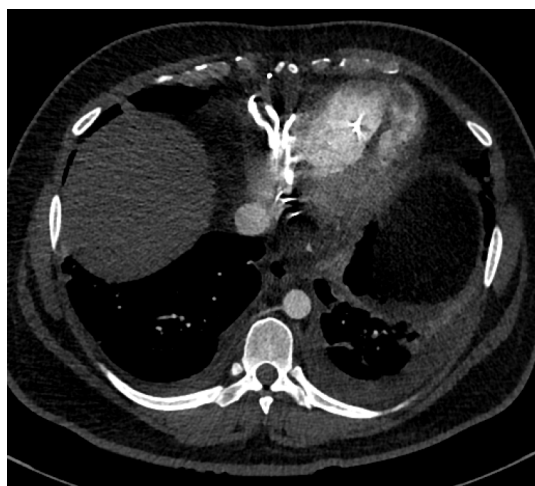
Transthoracic echocardiogram obtained prior to discharge showed a mildly reduced global sRV ejection fraction of 40%, severe sAV regurgitation, and a newly identified apical thrombus in the sRV (Figures 5-8). Transesophageal echocardiogram confirmed this finding with visualization of a 2.07 cm by 1.43 cm well-circumscribed mass.

FINAL DIAGNOSIS

The final diagnosis was ADHF complicated by a systemic right ventricular thrombus in the setting of L-TGA.

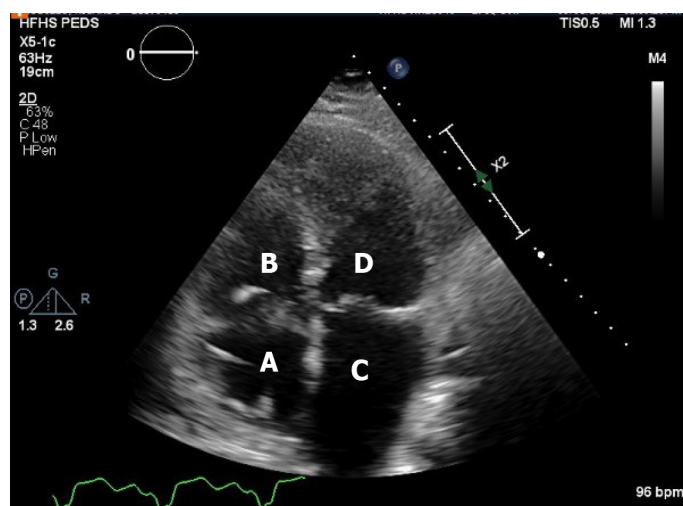
TREATMENT

The presence of a sRV thrombus posed a dilemma given the limited literature on this topic. Our patient was anticoagulated with a vitamin K antagonist (VKA) and later referred for evaluation by advanced heart failure and heart transplant services.



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Figure 4 Computed tomography of the chest detailing the patient's cardiac anatomy of levo-transposition of the great arteries. Venous circulation consists of the right atrium, left ventricle, and pulmonary artery. Systemic circulation consists of the pulmonary vein, left atrium, right ventricle, and aorta. Patient has a left-sided aortic arch with typical configuration.



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Figure 5 Transthoracic echocardiography demonstrating the patient's classic levo-transposition of the great arteries anatomy. A: Right atrium; B: Venous left ventricle; C: Left atrium; D: Systemic right ventricle. Visualized is an apically displaced systemic tricuspid valve opening into systemic right ventricle.

OUTCOME AND FOLLOW-UP

On subsequent follow-up visits, our patient's symptoms of heart failure continued to improve with medical optimization and cardiac rehabilitation. Transthoracic echocardiogram was performed 5 mo after the index echocardiogram that identified the sRV thrombus; it demonstrated interim resolution of the sRV thrombus with improvement in sAV regurgitation and estimated pulmonary artery systolic pressure (Table 2). Cardiopulmonary exercise testing (CPX) provides objective measures of cardiovascular fitness and allows them to be tracked over time; our patient's peak oxygen uptake (peak VO_2), a strong prognostic indicator in heart failure, showed improvement (Table 3). Tables 2 and 3 allow readers to understand the natural history and progression of L-TGA in adults by demonstrating findings from CPX and echocardiography from the patient's initial visit in 2016 to the last known follow-up in 2022.

DISCUSSION

Intracardiac thrombus (ICT) involves the formation of a blood clot within the heart chambers. It typically occurs in the setting of acute myocardial infarction, left ventricular aneurysm, and cardiomyopathy with dilated chambers[15]. Pathophysiology of thrombus formation involves an interplay of prothrombotic state, tissue endothelial injury, and blood

Table 1 Pertinent laboratory investigations

Investigation	Patient result	Reference range
Sodium (mmol/L)	138	135-145
Potassium (mmol/L)	4.1	3.5-5.0
Chloride (mmol/L)	104	98-111
Carbon dioxide (mmol/L)	22	21-35
Blood urea nitrogen (mg/dL)	19	10-25
Creatinine (mg/dL)	0.80	< 1.28
Venous lactate (mmol/L)	1.2	< 2.1
High-sensitivity troponin (ng/L)	16	< 18
Brain natriuretic peptide (pg/mL)	472	< 50

Table 2 Cardiopulmonary exercise testing trend over time

Date of CPX	Peak HR (bpm)	Duration (min)	Peak VO ₂ (ml/kg/min)	VO ₂ at anerobic threshold (ml/kg/min)	Peak VO ₂ (% of age predicted)	Peak RER	Actual METS achieved	VE-VO ₂ slope	Peak double product	O ₂ pulse rest	O ₂ pulse peak
June 16, 2016	85 (46% predicted max)	12.0	18.2	13.5	47	1.28	5.2	28.0	11900	4	16
February 16, 2017	145 (78% predicted max)	13.5	22.4	16.4	59	1.23	6.4	25.6	22040	4	12
September 6, 2018	173 (94% predicted max)	10.5	20.1	-	58	1.20	5.7	28.8	25258	3	11
June 13, 2022	173 (96% predicted max)	9.5	19.5	-	56	1.17	5.6	22.8	21106	3	11

CPX: Cardiopulmonary exercise testing; HR: Heart rate; METS: Metabolic equivalent of task; RER: Respiratory exchange ratio; VE: Ventilatory efficiency.

stasis as described by Virchow's triad[16-18]. Systemic embolization of left-sided ICT results in clinical manifestations of stroke and transient ischemic attack, mesenteric ischemia and infarction, renal infarction, and acute limb ischemia. Pulmonary embolization of right-sided ICT results in pulmonary embolism. Diagnostic gold standard is identification of a thrombus on cardiac magnetic resonance imaging, although echocardiography with the use of echocardiographic contrast agents is a widely used initial modality[19].

ICT of the sRV is sparsely covered in the literature with limited data and guidelines available regarding the approach to management. Clinicians resort to extrapolating from practice standards for systemic left ventricular (sLV) thrombus. A review of literature identified no published case reports of sRV thrombus.

Current American and European guidelines for ICT in patients with structurally typical hearts are covered by class IIa, LOE C recommendations. Standard of care consists of anticoagulation with a VKA for 3-6 mo with an international normalized ratio (INR) target range of 2.0-3.0 followed by repeat imaging to assess for thrombus resolution[20,21]. Anticoagulation in this population has been shown to decrease major cardiovascular events including cerebral and systemic sequela of thrombus embolization[22]. Patients who have interval resolution of ICT on repeat imaging typically have anticoagulation discontinued, although some experts continue anticoagulation as a preventative measure in select patients with persistent and significant sLV wall hypokinesis due to the higher risk of recurrence[23]. In the absence of data on this population, patients with sRV dysfunction who develop right ventricular thrombus, such as our patient, can be similarly managed with anticoagulation using a VKA followed by repeat imaging.

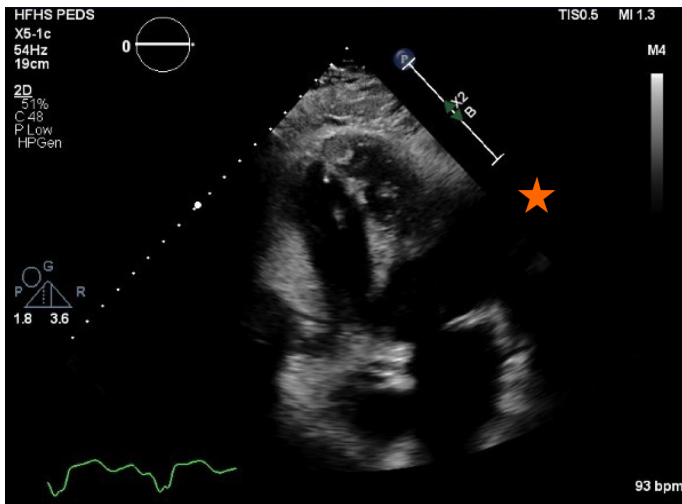
Oral anticoagulant (OAC) agent of choice for the treatment of ICT has classically been a VKA as opposed to a direct OAC (DOAC), as early available literature demonstrated clinically significant difference in outcomes between the two agents. The largest study to date, a multicenter cohort study compared 514 patients with sLV thrombus and demonstrated a higher risk for stroke and systemic embolism with DOAC therapy compared to VKA which suggests against efficacy equivalence[24]. However, more recent data derived from small-scale randomized controlled trials, cohort studies, and case series report similar outcomes and support the use of DOAC for sLV thrombus which has led experts to adopt it as an off-label alternative[23,25-31]. A recent scientific statement by the American Heart Association carried out a comprehensive meta-analysis of all published studies that compared VKA and DOAC use in sLV thrombus, it

Table 3 Echocardiography trend over time

Date of study	Type of study	sRV parameters	sAV valve parameters	vLV parameters	vAV valve parameters	LA parameters	RA parameters	PA pressure (mmHg)	Other details
April 13, 2016	Transthoracic	Severely reduced global RV SF. Moderately enlarged RV	Severe Reg (sAV Reg Vmax 4.17 m/s)	Mildly reduced LV SF (41%). Restrictive pattern of diastolic filling (G3)	Moderate-Severe Reg (vAV Reg Vmax 346.72 cm/s)	Mildly dilated	Normal	51	Side by side great arteries, anterior aorta consistent with L Transposition of the Great Arteries (congenitally corrected). S/P VSD repair with intact patch in basal septum
November 10, 2016	Transthoracic	Normal size and global systolic function (RV % FAC, A4C: 54.5%)	Moderate-Severe Reg (sAV Reg Vmax 5.28 m/s)	Mildly reduced LV SF (41%). Moderate hypokinesis of entire septal wall. Normal pattern of LV diastolic filling	Moderate Reg (vAV Reg Vmax 246.26 cm/s). Mildly thickened	Mildly dilated	Dilated	N/A	S/P BiV PPM
February 16, 2017	Transthoracic	Mildly reduced global RV SF (RV % FAC, A4C: 44.7%). RV wall thickness is moderately increased	Severe Reg (sAV Reg Vmax 5.00 m/s)	Mildly reduced LV SF (48%). Normal size	Mild-moderate Reg (vAV Reg Vmax 332.84 cm/s)	Moderately dilated	Normal	52	Interim mild improvement in systemic RV function but persistent systemic AV valve severe regurgitation with moderate pulmonary hypertension
February 27, 2017	Transthoracic	EF 54% (biplane)		EF 51% (A4C)					Limited study to quantify ventricular function
September 25, 2018	Transthoracic	Mild dysfunction. RV wall thickness is moderately increased	Moderate-Severe Reg (sAV Reg Vmax 4.74 m/s)	Mildly reduced LV SF (47%). Normal size	Mild Reg (vAV Reg Vmax 243.67 cm/s)	Mildly dilated	Normal	32	Overall no major changes noted compared to prior studies except for mild fluctuations in systemic RV function.
May 1, 2022	Transthoracic	Mildly reduced global RV SF (40%)	Moderate-Severe Reg (sAV Reg Vmax 4.71 m/s)	EF 45%	Moderate Reg (vAV Reg Vmax 328.85 cm/s)	Moderately dilated	Normal	46	There is a 1.3 cm × 1.3 cm, well circumscribed mass with echolucent center, seen apically, and likely represents a thrombus. Saline contrast bubble study -ve
May 4, 2022	Transesophageal	N/A	Moderate-Severe Reg (sAV Reg Vmax 2.46 m/s)	Moderately reduced LV SF (35%). Normal thickness	Moderate-Severe Reg (vAV Reg Vmax 383.31 cm/s)	N/A	N/A	N/A	Well-circumscribed mass measuring 2.07 cm × 1.43 cm in the morphologic RV/Systemic ventricle with central echolucency. Saline contrast bubble study was negative
September 30, 2022	Transthoracic	Mildly reduced global RV SF (40-45%). Mildly enlarged sRV	Mild-Mod Reg	Low-normal LV SF function	Moderate-Severe Reg (vAV Reg Vmax 228.43 cm/s)	Upper normal	Normal	24	Interim resolution of small systemic RV apical thrombus. Extensive trabeculation related to systemic RV hypertrophy noted

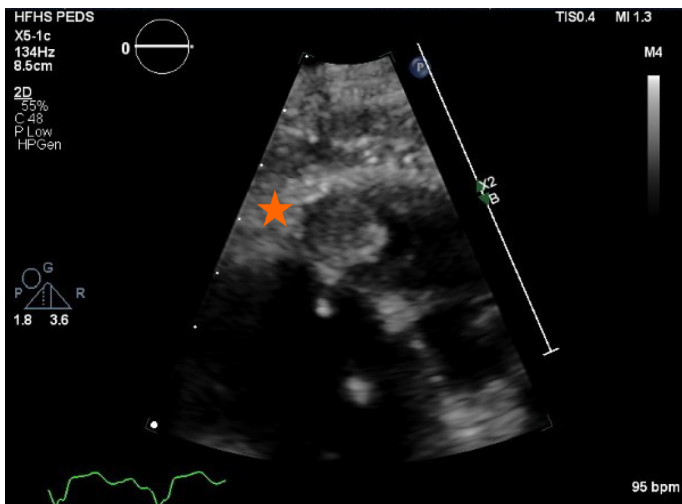
A4C: Apical 4 chamber; EF: Ejection fraction; FAC: Fractional area change; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; PPM: Permanent pacemaker; RA: Right atrium; RV: Right ventricle; SAV: Systemic atrioventricular valve; SF: Systolic function; S/P: Status post; SRV: Systemic right ventricle; vAV: Venous atrioventricular valve; vLV: Venous left ventricle; VSD: Ventricular septal defect; N/A: Not applicable.

demonstrated no differences in therapeutic efficacy and safety; the statement concluded that the use of DOAC for sLV thrombus is a reasonable alternative to VKA[32]. This practice-changing statement is a yet to be reflected in society guidelines and adopted by other organizations.



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Figure 6 Transthoracic echocardiography in apical four chamber view showing an systemic right ventricle apical thrombus. This view highlights the importance of visualizing the true apex of the systemic right ventricle as the thrombus is not seen in Figure 5 where the apex is foreshortened.

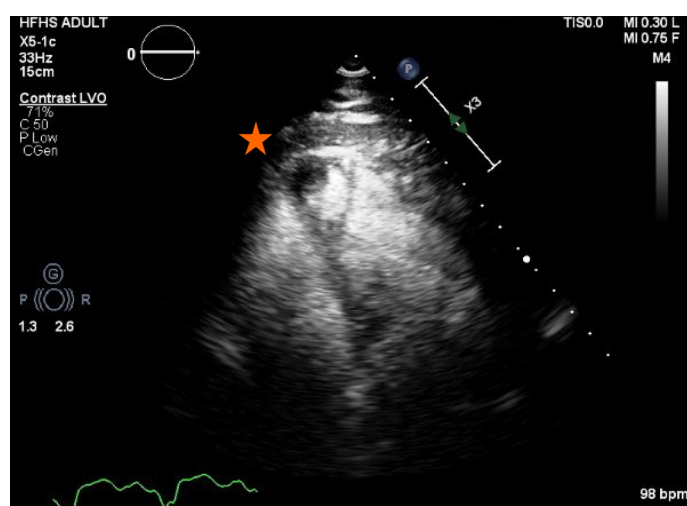


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Figure 7 Transthoracic echocardiography highlighting the systemic right ventricle apical thrombus. A 1.3 cm × 1.3 cm well circumscribed mass with an echolucent center.

Clinical consensus for the management of sRV thrombus in patients with congenital heart disease has been derived from the management principles of sLV thrombus in patients without congenital heart disease; it consists of OAC, interval repeat imaging, and case-by-case evaluation of anticoagulation duration. The advent of DOAC therapy has seen it become the OAC agent of choice for most anticoagulation indications which has raised questions regarding its applicability in the treatment of sRV thrombus in the setting of the limited data. The international NOTE registry evaluated 530 adults with congenital heart disease treated with OAC for various indications and concluded non-inferior efficacy and safety of DOAC use compared to VKA; subgroup analysis of 76 patients with sRV found high efficacy and safety rates[33, 34]. Another similar study of 215 patients with different congenital heart diseases quoted high efficacy rates but non-negligible bleeding risks[35]. However, a retrospective cohort review of a German nationwide registry of 6504 adults with congenital heart disease on OAC determined that DOAC use was associated with higher rates of thromboembolism, bleeding, major adverse cardiac events, and all-cause mortality compared to VKA[36]. The discrepancy of results between the former and latter studies raises concerns can be explained by the significant heterogeneity including differences in age and complexity of lesions in the latter's study population. In the absence of conclusive data supporting DOAC use in sRV thrombus in patients with congenital heart disease, VKA remains the OAC of choice.

Patients with sRV thrombus are typically younger than those with sLV thrombus given the earlier development of heart failure in the setting of congenital heart disease. The structural cardiac anomalies and abnormal hemodynamics are likely contributors to abnormal flow and blood stasis, this predisposes patients to thrombus formation. Younger patients are more likely to have educational and workplace commitments that cause time constraints. VKA therapy is particularly challenging in this population as dietary restrictions and frequent laboratory testing results in difficulty achieving and



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Figure 8 Transthoracic echocardiography with intravenous contrast demarcating the apical thrombus in the systemic right ventricle.

maintaining therapeutic INR levels; lower time in therapeutic range is associated with higher risk of stroke in patients with sLV[37]. Further studies evaluating the safety and efficacy of DOAC agents in sRV thrombus are necessary.

CONCLUSION

Systemic right ventricular thrombus is a rare complication of congenital heart disease. We describe the first reported case of sRV thrombus in a patient with L-TGA who presented with ADHF. Management of this condition is driven by expert opinion and extrapolation of treatment principles from ICT in patients with structurally normal hearts.

In the absence of conclusive data supporting DOAC use in sRV thrombus in patients with congenital heart disease, VKA bridged with intravenous heparin or subcutaneous low-molecular weight heparin and remains the time-honored approach particularly in patients with recent large thrombi and in the setting of dysfunctional ventricles or slow flow states. Transitioning to a DOAC in these cases should be individualized to a patient characteristics and imaging features; it should involve shared decision making regarding limited and conflicting literature. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring in this patient population to prevent and treat complications.

FOOTNOTES

Author contributions: Almajed MR, Almajed A, Khan N, Obri M, Ananthasubramaniam K contributed equally to this work; All authors evaluated the case, reviewed the literature, and wrote the manuscript; All authors have read and approve of the final manuscript.

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Cardiovascular implications of inflammatory bowel disease: An updated review

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Abstract

Emerging data highlights the heightened risk of atherosclerotic cardiovascular diseases (ASCVD) in patients with chronic inflammatory disorders, particularly those afflicted with inflammatory bowel disease (IBD). This review delves into the epidemiological connections between IBD and ASCVD, elucidating potential underlying mechanisms. Furthermore, it discusses the impact of current IBD treatments on cardiovascular risk. Additionally, the cardiovascular adverse effects of novel small molecule drugs used in moderate-to-severe IBD are investigated, drawing parallels with observations in patients with rheumatoid arthritis. This article aims to comprehensively evaluate the existing evidence supporting these associations.

To achieve this, we conducted a meticulous search of PubMed, spanning from inception to August 2023, using a carefully selected set of keywords. The search encompassed topics related to IBD, such as Crohn's disease and ulcerative colitis, as well as ASCVD, including coronary artery disease, cardiovascular disease, atrial fibrillation, heart failure, conduction abnormalities, heart blocks, and premature coronary artery disease. This review encompasses various types of literature, including retrospective and prospective cohort studies, clinical trials, meta-analyses, and relevant guidelines, with the objective of providing a comprehensive overview of this critical intersection of inflammatory bowel disease and cardiovascular health.

Key Words: Inflammatory bowel diseases; Cardiovascular disorders; Pericarditis;

myocarditis; Thromboembolism; Chronic inflammation; Oxidative stress; Endothelial dysfunction

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Core Tip: A substantial association has been established between cardiovascular disorders (CVD) and inflammatory bowel diseases (IBD), with a notably higher prevalence of CVD in IBD patients compared to the general population. Potential mechanisms underlying CVD in IBD involve chronic inflammation, oxidative stress, altered platelet function, endothelial dysfunction, hypercoagulability, gut dysbiosis, and drug-related side effects. This review comprehensively synthesizes the latest evidence on the epidemiology, pathophysiological mechanisms, and cardiovascular manifestations in IBD.

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INTRODUCTION

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions affecting the gastrointestinal tract, characterized by a relapsing-remitting disease course. Extraintestinal symptoms may occur either concomitantly with or independently of luminal symptoms[1-4]. An association has been established between cardiovascular disorders (CVD) and IBD, with a notably higher prevalence of CVD in IBD patients compared to the general population. The cardiovascular manifestations in IBD patients encompass pericarditis, myocarditis, venous and arterial thromboembolism, atherosclerotic CVD, heart failure, arrhythmias and conduction disorders, infective endocarditis, valvulopathy, and rarely, Takayasu arteritis[5-7]. Potential mechanisms underlying CVD in IBD involve chronic inflammation, oxidative stress, altered platelet function, endothelial dysfunction, hypercoagulability, gut dysbiosis, and drug-related side effects[8]. This review comprehensively synthesizes the latest evidence on the epidemiology, pathophysiological mechanisms, and cardiovascular manifestations in IBD.

PATHOPHYSIOLOGY OF CVD IN IBD

The intricate pathogenesis linking IBD and CVD remains an enigma, characterized by a complex interplay of diverse factors. Dysregulated immune responses, endothelial dysfunction, a pro-thrombotic state, accelerated atherosclerosis, and genetic polymorphisms collectively contribute to this intricate web connecting IBD with CVD.

Chronic low-grade inflammation, marked by alterations in both innate and adaptive immunity, plays a pivotal role in the pathogenesis of atherosclerotic CVD[9]. In IBD, the stimulation of inflammatory T cell pathways, mediated by T helper (Th) 17 and Th1 responses fosters a pro-inflammatory milieu, leading to increased production of cytokines, including interleukin (IL)-1b, IL-6, IL-23, tumor necrosis factor (TNF), and interferon-gamma. Elevated expression of Toll-like receptors (TLR)-2 and TLR-4 further contributes to the pro-inflammatory state by amplifying IL-6 and IL-12 production[10,11]. These pro-inflammatory cytokines, *via* oxidative stress, provoke inflammation, tissue damage, and proliferation of endothelial and mesenchymal cells, synergistically contributing to the pathogenesis of CVD[12]. Furthermore, TNF, IL-1, IL-6, vascular endothelial growth factor (VEGF), and reactive oxidative species promote endothelial dysfunction by increasing the expression of cell adhesion molecules like ICAM-1, MCP-1, E selectin and intensify endothelial cell apoptosis, micro- and macrovascular dysfunction, tissue remodelling, angiogenesis, lymphangiogenesis, and fibrosis[13-15]. C-reactive protein (CRP), a marker of inflammation, is elevated in IBD and contributes to atherogenesis, correlating with increased CVD risk. Elevated CRP levels, especially exceeding 5 mg/L, serve as predictors of cardiovascular events. Notably, CRP levels rise with IBD disease activity, heightening cardiovascular risk during active disease[16,17].

Gut microbial dysbiosis, an important risk factor for IBD development, is also associated with CVD and increased thromboembolic event risk, particularly in younger age groups[12,18,19]. Alterations in the *Firmicutes/Bacteroidetes* ratio are linked to hypertension, while enrichment in Enterobacteriaceae, including *Escherichia coli*, is observed in patients with IBD and CVD[20-23]. *Streptococcus spp.* increase CVD risk, and opportunistic bacteria like *Enterobacter* and *Oscillibacter* are associated with ischemic stroke and transient ischemic attacks[24-26].

Gut dysbiosis can also increase gut permeability, leading to elevated absorption of lipopolysaccharide (LPS) from the intestines. The LPS, in turn, heightens pro-inflammatory cytokine secretion, exacerbating atherosclerosis, inducing macrophage activation, vascular endothelitis, and increasing CRP[27]. Gut bacterial metabolites, such as indole and phenyl derivatives, also exacerbate atherosclerosis and lead to hypertension[26]. Additionally, the gut bacteria-derived metabolite, Trimethylamine-N-oxide (TMAO), contributes to atherogenesis and hypertension, serving as a predictor of coronary artery disease. TMAO promotes platelet responsiveness, thrombosis, and cardiovascular risk through the

expression of pro-inflammatory cytokines, ox-low density lipoprotein (LDL) deposition, and cardiac mitochondrial dysfunction[25,28,29]. The drugs used for treatment in IBD, through various mechanisms, are also associated with cardiovascular side effects and are discussed in the subsequent sections[30]. The pathogenesis of CVD in IBD is outlined in Figure 1.

CARDIOVASCULAR MANIFESTATIONS AND ITS MANAGEMENT IN IBD

Cardiovascular manifestations in IBD may be infrequent, yet they carry significant clinical implications when left unaddressed. We discuss the common CVD seen in patients with IBD.

Pericarditis and myocarditis

Pericarditis and myocarditis account for 70% and 10% of cardiac extra-intestinal manifestations (EIMs) respectively. Patients with IBD are at a greater risk of developing myopericarditis as compared to the general population[31,32]. Notably, pericarditis displays a higher incidence in males with UC[30-32]. On the other hand, myocarditis, constituting around 10% of cardiovascular EIMs in IBD, is more prevalent in patients diagnosed with CD[33].

Pathogenesis

It is difficult to determine whether the complications are secondary to the systemic disease or therapy related adverse events. Two possible mechanisms that are responsible for pericarditis and myocarditis in patients with IBD include immune mediated, secondary to the exposure of autoantigens, and cardiotoxicity associated with aminosalicylates and its derivatives[34-36].

Experimental models suggest that exposure to autoantigens produced during an acute flare of IBD, *via* inflammatory cytokines and an activated immune response, can lead to direct cytotoxicity of the cardiac myocytes[37]. This process may involve both the myocardium and pericardium and lead to myopericarditis. Continued inflammation and remodeling may result in chronic myocarditis which may cause valvular abnormalities (*via* papillary muscle fibroses and dysfunction), chamber dilation resulting in systolic dysfunction and decreased ejection fraction or arrhythmias[38,39].

Pericarditis almost exclusively occurs as a drug induced adverse event, in particular with 5-amino salicylic acid (ASA) derivatives such as sulfasalazine, mesalamine, and balsalazide[40-42]. The underlying mechanisms responsible for pericarditis associated with mesalamine include IgE-mediated allergic reactions, direct cardiac toxicity, cell-mediated hypersensitivity, or a humoral antibody response against 5-ASA derivatives[43].

Clinical features and diagnosis

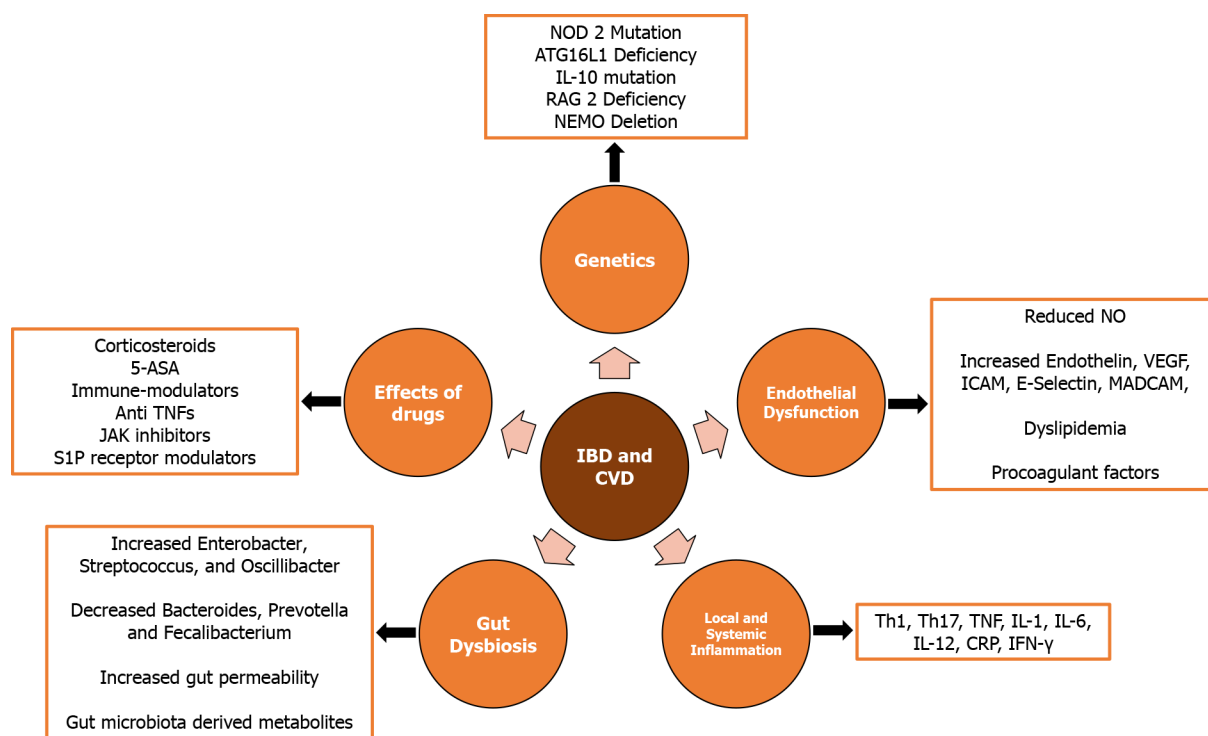
Patients with 5-ASA induced pericarditis usually develop symptoms within two weeks of initiation of therapy[44]. Myopericarditis may present as acute coronary syndrome, new onset or decompensated heart failure, arrhythmias, cardiogenic shock or sudden death[45]. The electrocardiogram may show ST segment and T wave changes or conduction disorders. Leucocytosis, elevated levels of erythrocyte sedimentation rate, CRP and cardiac biomarkers such as troponin, creatine kinase-MB, B-type natriuretic peptide and N-terminal pro-brain natriuretic peptide may be present[30,46]. Echocardiographic features of myocarditis such as left ventricular dysfunction, anomalies of parietal kinetics, low ejection fraction, or pericardial effusion may be present. The cardiovascular magnetic resonance (CMR) imaging in a patient with myocarditis may reveal myocardial (regional or global) oedema, myocardial hyperaemia, and focal fibrosis or necrosis with non-coronary artery distribution[46]. The endomyocardial biopsy is the gold standard but is seldom performed in view of its invasive nature and availability of non-invasive CMR. The endomyocardial biopsy is however indicated in patients where CMR is not feasible or in life threatening conditions to establish the diagnosis and aetiology of myocarditis[39]. Histologically, two forms of IBD-associated myocarditis are known: The acute/chronic lymphocytic myocarditis and the giant cell myocarditis. Giant cell myocarditis is associated with a poor prognosis[47].

Management

The two major goals of treatment are optimal care of heart failure and arrhythmias, regardless of etiology and disease-specific therapy. Patients with fulminant myocarditis and hemodynamic instability should be shifted to intensive care units (ICU) with facilities of advanced cardiopulmonary support such as mechanical ventilation and extracorporeal membrane oxygenation[36,48].

Discontinuation of the causative drug remains the mainstay of treatment for pericarditis and resolution occurs within 2 wk. For inflammatory myocarditis associated with IBD, immune-suppressive treatment should always be considered especially in the presence of ventricular systolic dysfunction and severe arrhythmias[49-52]. The commonly used immune suppressive agents for treatment of inflammatory myocarditis are corticosteroids, azathioprine, cyclosporine, or immunoglobulins[53]. Interestingly, these agents are also used for treatment of IBD and therefore no specific alteration in therapy may be required in majority of the patients. The current guidelines also discourage patients with myocarditis from participating in competitive and leisure sports[54].

If pericarditis arises as an EIM, steroids are indicated after ruling out sepsis[55-57]. Alternatively, indomethacin, aspirin and colchicine can be used. However, their use can exacerbate underlying IBD and caution is recommended. Pericardial effusion and tamponade can complicate pericarditis which can be managed with pericardiocentesis or pericardiectomy[30,58].



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Figure 1 Factors implicated in development of cardiovascular disease in patients with inflammatory bowel disease. JAK: Janus kinase; ASA: Amino salicylic acid; TNF: Tumor necrosis factor; CVD: Cardiovascular diseases; IBD: Inflammatory bowel disease; VEGF: Vascular endothelial growth factor; IFN- γ : Interferon-gamma; CRP: C-reactive protein; S1P: Sphingosine-1-phosphate; IL: Interleukin.

VENOUS THROMBOEMBOLISM (VTE)

IBD patients are at an increased risk for VTE. Systematic reviews and meta-analyses report that patients with IBD are at a two-fold increased risk for VTE as compared to general population (RR = 2.20; 95%CI: 1.83-2.65)[59,60]. The most common reported VTE events include deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The involvement of portal, the superior mesenteric, the splenic, the internal jugular, and the cerebral veins has also been reported[61]. The reported frequency is higher in patients with active IBD and directly proportional to the extent and severity of the disease in the absence of provoking factors[62]. In a retrospective study, VTE was more common in patients with UC (pancolitis more than left sided colitis or proctitis). In CD, VTE is more frequent in patients with ileocolonic or colonic involvement than with ileal disease alone[62].

The risk of in-hospital and post-hospitalisation VTE in patients with IBD is increased with intestinal or non-intestinal surgery when compared to non-IBD patients (OR = 2.03; 95%CI: 1.52-2.70 and OR = 4.45; 95%CI: 1.72-11.49, respectively). The risk factors for VTE include emergency surgery, open procedure, longer operative time, ileostomy formation, anastomotic leak, ileus, diagnosis of UC (higher risk as compared with CD), age > 65 years, and obesity[59,63,64]. Patients with IBD are also at a significantly high risk of recurrent VTE (HR = 2.5; 95%CI: 1.4-4.2; $P = 0.001$)[65].

Pregnant females with IBD (UC > CD, active disease) are also at two to three times increased risk of VTE during pregnancy and postpartum period (RR = 2.13; 95%CI: 1.66-2.73 and RR = 2.61; 95%CI: 1.84-3.69, respectively)[66,67].

Pathogenesis

The pathogenesis of VTE in IBD patients is multifactorial. The various mechanisms that contribute to thrombosis in IBD include genetic predisposition, inflammation, gut dysbiosis, spontaneous platelet aggregation, vascular thrombotic events secondary to flares, surgery, drug therapy and compounding risk factors such as pregnancy. Altered intestinal microbiota reduces mucus secretion and fibre fermentation that promotes inflammation *via* endothelial damage[68]. Genetic mutations in NOD2, ATG16L1, recombination activating gene 2, IL-10 receptor deficiency, and nuclear factor kappa beta essential modulator also lead to a pro-inflammatory state[36,69-71]. Inflammatory cytokines such as TNF and IL-1 result in a prothrombotic state due to increased levels of thrombin (which initiates the coagulation cascade through tissue factor) and simultaneous suppression of antithrombotic factors (such as endothelial thrombin and protein C)[72,73]. Another contributory mechanism is hyperhomocysteinemia secondary to inflammation induced malabsorption, and vitamin B and folate deficiency. Increased factor V thromboxane A2, arachidonic acid peroxidation product 8-iso-prostaglandin F2, tissue factor and mRNA synthesis further promote platelet activation and inhibit thromboregulation [74,75]. Estrogen based oral contraceptives and hormone replacement therapy promote production of coagulant factors leading to increased risk of VTE[76,77]. There is increased production of fibrinogen and decreased production of protein S during pregnancy which increases the risk of VTE[78].

IBD drugs and impact on VTE

5-ASA: No VTE or related complications have been reported with 5-ASA. In vitro studies have shown that 5-ASA inhibits platelet activation by thrombin, and therefore could have a role in preventing VTE. However further studies are required to evaluate the beneficial effect of 5-ASA in reducing the VTE risk[79-81].

Corticosteroids: Corticosteroids are potent anti-inflammatory drugs that also exert an independent thrombogenic effect (via increase in the serum levels of the clotting factors and fibrinogen)[82]. Systemic glucocorticoids and endogenous production of cortisol are associated with an increased risk of VTE. The risk of VTE is increased in patients who are treated with corticosteroids, more so with higher doses [incidence risk ratio (IRR) = 2.31, 95%CI: 2.18-2.45][83,84].

Immunomodulators: There has been no reported risk of VTE with immunomodulatory drugs[85-87]. Although, it has been hypothesized that thiopurines reduce VTE risk by decreasing platelet aggregation and inhibiting platelet-leucocyte aggregation in vitro, more studies are required to confirm this hypothesis[88].

Biologics: TNF- α directly promotes endothelial dysfunction resulting in increased thrombus formation[89]. Patients treated with anti-TNF- α agents are therefore likely to have a decreased risk of VTE (OR = 0.267; 95%CI: 0.106-0.674, P = 0.005)[83]. It has been demonstrated that clot lysis profile normalises and there is a reversal of clotting abnormalities in patients receiving infliximab, suggesting benefit to reduce the VTE risk[63,72,82,90].

The overall risk of VTE with vedolizumab is low[91,92]. Pooled safety analysis from Phase 2/3 studies on ustekinumab reported no significant difference in VTE risk in patients treated with ustekinumab compared to placebo (0.75/100 person years vs 0.34/100 person years, respectively)[93-95].

Janus kinase (JAK) inhibitors: A safety study done in patients older than 50 years with rheumatoid arthritis and more than one cardiovascular risk factor showed that VTE, DVT and PE was higher for tofacitinib when used in the dose of 10 mg twice daily[95]. Similar to these observations, in the OCTAVE open study, with a follow-up of 7 years, 10 mg tofacitinib group had 0.1% and 0.7% prevalence of DVT and PE, respectively [IR = 0.06 (95%CI: 0.00-0.31) and 0.28 (95%CI: 0.09-0.65)]. There were no cases of DVT or PE in 5 mg tofacitinib group. Overall IR for tofacitinib was 0.06 (95%CI: 0.00-0.31) and 0.28 (95%CI: 0.09-0.65), for DVT and PE, respectively. Majority of the patients with thromboembolic complications had one or more underlying risk factors for DVT, except one patient with no pre-existing risk factors [96]. In IBD, therefore, tofacitinib appears to have an acceptable safety profile from VTE point of view, though The United States Food and Drug Administration has issued a black box warning recommending avoidance of JAK inhibitors in patients at risk of DVT, VTE and PE[97]. These risk factors include history of recent surgery, trauma, stroke or myocardial infarction (MI) in previous 3 mo, age > 50 years, morbid obesity, use of oral contraceptive pills, long flights and previous history of DVT, PE or acute thromboembolic event[98]. In case, when no therapeutic alternatives are available, a close coordination with cardiologist is required. The 10 mg twice daily dose is restricted to a maximum of 3 mo (for induction of remission) with de-escalation to 5 mg twice daily as soon as possible[99]. The randomized controlled trials (RCTs) of upadacitinib and filgotinib did not report a higher rate of VTE[100,101].

Management

All patients with IBD hospitalised for any cause, should receive a prophylactic dose of low-molecular-weight heparin (LMWH) or fondaparinux. LMWH is recommended over unfractionated heparin in critically ill patients[102]. Thromboprophylaxis during hospitalisation reduces the risk of VTE in IBD after discharge by 54% and should be maintained during the inpatient period[103]. Older age, *Clostridioides difficile* infection in index admission, longer hospital stay (> 7 d), ICU admission, previous VTE, and coronavirus disease are indications of extended prophylaxis (at least 2 mo after discharge) as these conditions are associated with increased the risk of post-discharge VTE[104]. IBD patients treated in the outpatient settings with moderate to severe flare and a high risk profile for VTE may benefit from thromboprophylaxis until resolution[105].

Guidelines recommend that the treatment of VTE should follow the general antithrombotic therapy guidelines. Direct oral anticoagulants are first line drugs and should be used at a therapeutic dose in IBD, LMWH is an alternative. In case of unprovoked VTE, the duration of treatment is indefinite. For provoked VTE secondary to an identifiable risk factor, anticoagulation is continued for 3 mo beyond the resolution of the risk factor. It is essential to know that thromboprophylaxis does not increase the risk of further IBD-related gastrointestinal bleeding in patients with active disease. It is important to remember that controlling the disease activity is most critical to prevent the recurrence of VTE[102,105,106]. The duration of anticoagulation is summarized in Figure 2.

ATHEROSCLEROTIC AND ATHEROTHROMBOTIC CARDIOVASCULAR DISEASE (ASCVD)

In addition to VTE, there is a moderate increase in the risk of arterial thrombotic events, such as acute myocardial infarction (MI), mesenteric ischemia, and stroke, in IBD, albeit lower than the VTE risk. Interestingly, this risk is comparable between UC and CD patients[14]. The risk of ischemic heart disease (IHD) is slightly elevated in younger age groups and women, peaking within the first year of IBD diagnosis[12,13,107,108].

Pathogenesis

The pathogenesis involves a multifaceted interplay between inflammatory cytokines, endothelial dysfunction, smooth muscle proliferation mediated by VEGF, ICAM-1, MADCAM-1, E-selectin, reduced vasodilator nitric oxide, and NOD2

Symptomatic VTE	• A minimum 3 mo of anticoagulant therapy
Active IBD, first event of VTE	• Continue until IBD has been in remission for at least 3 mo
Unprovoked VTE presenting during clinical remission	• Indefinite anticoagulant therapy
If there is a reversible risk factor	• At least three months until a risk factor has resolved
Residual thrombus (partial recanalization) at 3-6 mo	• Extended anticoagulation treatment

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Figure 2 Duration of anticoagulation in inflammatory bowel disease patients with venous thromboembolism. IBD: Inflammatory bowel disease; VTE: Venous thromboembolism.

polymorphisms[106].

The incidence of CVD and cerebrovascular accidents is higher in females with IBD, and could be due to inherent differences in distribution of risk factors in males and females, including greater immune response and higher levels of CRP in females[109,110]. The role of sex hormones in the development of ASCVD in IBD patients remains inconclusive. Moreover, younger IBD patients exhibit an increased relative risk of ASCVD, possibly stemming from earlier disease onset and a more severe disease course that results in prolonged exposure to chronic inflammation. Notably patients with IBD have similar prevalence traditional risk factors for coronary artery disease such as hypertension, diabetes, smoking, and obesity[111] (Figure 3).

Despite the lack of conventional risk factors for coronary artery disease, both UC and CD are independently associated with an increased risk of acute MI[112]. The IBD patients with CVD have been reported to have a higher level of high sensitive-CRP and fibrinogen, and greater prevalence of NOD-2 mutations[113]. Paradoxically, IBD patients tend to have lower levels of total cholesterol and LDL-cholesterol, with unaffected high density lipoprotein (HDL)-cholesterol and triglyceride concentrations. In CD patients, ileal resection and ileoanal anastomosis are inversely correlated with plasma total cholesterol and LDL-cholesterol levels[114,115].

The overall level of serum lipids in IBD patients is negatively associated with disease severity[113,116]. On the contrary, disease activity has been reported to be an independent risk factor for development of CVD[117-119]. This quandary is explained on the basis of presence of a more pro-atherogenic lipid profile characterized by small dense LDL-cholesterol particles and dysfunctional HDL-cholesterol in chronic inflammation associated with IBD[120]. The extent and location of inflammation is also associated with CVD risk. Patients with colonic involvement, in both UC and CD, have a threefold higher risk of developing MI[112].

Subclinical atherosclerosis

The occurrence of subclinical atherosclerosis is more frequent in individuals with IBD. To identify subclinical atherosclerosis, various diagnostic measures are employed, including assessing arterial stiffness through pulse-wave velocity between the carotid and femoral arteries (carotid-femoral pulse wave velocity, calculated as Δ distance/ Δ time), measuring carotid intima-media thickness, evaluating flow-mediated dilation of arteries, and determining the coronary artery calcium score[106].

IBD drugs and impact on ASCVD

5-ASA: As with nonsteroid anti-inflammatory drugs such as aspirin, 5-ASA shares anti-inflammatory, anti-platelet and antioxidant properties. Thus 5-ASAs may be associated with a decreased risk of IHD in patients with IBD[121,122]. IBD patients using 5-ASA were reported to have a lower risk of IHD than non-users (IRR = 1.16; 95%CI: 1.06-1.26 and IRR = 1.36; 95%CI: 1.22-1.51 P = 0.02, respectively). In long-term users of 5-ASA, the risk of IHD was even lower (IRR = 1.08; 95%CI: 0.98-1.19)[103,123].

Corticosteroids: Corticosteroid users are at a higher risk of developing IHD compared to non-users[123-125]. Corticosteroids predispose to risk factors such as hypertension, obesity, dyslipidemia and insulin resistance which may exacerbate IHD in IBD[126]. However, a direct causal association cannot be established.

Thiopurines: Thiopurines are not associated with acute arterial events in IBD and the effect of methotrexate on IHD in IBD is unknown. However in a beneficial effect on arterial stiffness has been demonstrated in various other chronic inflammatory disorders[127,128]. Thiopurines also decrease the production of transforming growth factor-beta and IL-10, which are responsible for endothelial dysfunction, and hence may have some protective role, though there is very limited data to make any conclusive recommendations at the moment[129,130].

Biologics: *In vitro* studies on infliximab have suggested an atheroprotective effect in monocytes by increasing both ABCA1 and LXR gene expression and removing excess cholesterol and preventing foam cell formation[127,129,131].

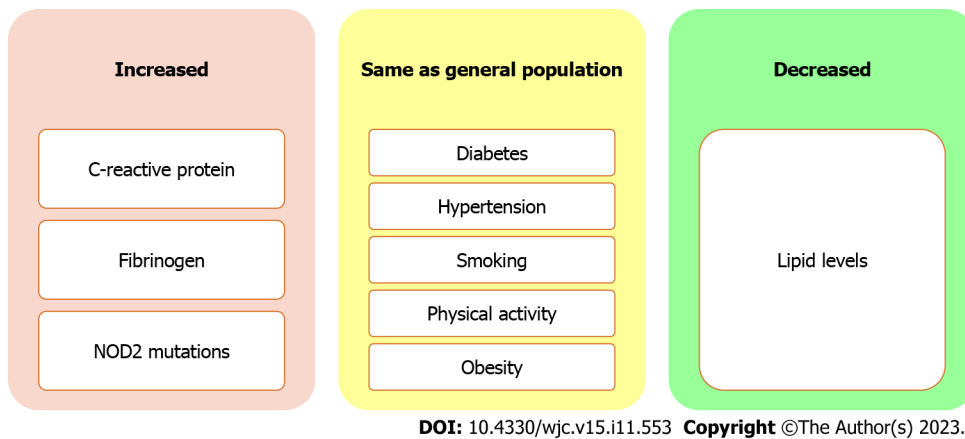


Figure 3 Prevalence of risk factors for atherosclerotic cardiovascular disease in patients with inflammatory bowel disease.

However, the *in vivo* biological mechanisms are very complex. TNF- α is proatherogenic. Contradictory results have been reported with regards to the effect of anti TNF- α agents on the lipid profile. While some studies report an increase the levels of HDL-cholesterol and apoprotein-A1, others report an increase in the small dense LDL-cholesterol and total cholesterol. Also, TNF- α inhibition increases abdominal fat, leading to increased risk of ASCVD. On the contrary, the anti TNF- α agents exert beneficial effect by improving insulin sensitivity, endothelial function, arterial stiffness and fibrinolysis[89,132,133]. The anti-TNF- α agents may be associated with reduced risk of new-onset acute arterial events and prevent recurrence when used in patients with previous history of acute arterial events. Vedolizumab and ustekinumab have not reported any augmented risk of ASCVD[134,135].

JAK inhibitors: Small molecules tend to increase the risk of cardiovascular diseases by causing dyslipidaemia. Tofacitinib is associated with reversible changes in the lipid profile specifically total cholesterol, HDL-cholesterol and LDL-cholesterol[136,137]. Clinical trials in rheumatoid arthritis showed that tofacitinib is associated with higher rates of major adverse cardiovascular events (MACE). Older patients aged > 50 years with at least one cardiovascular risk factor had higher risk of MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) as compared with anti TNF agents (HR = 1.33; 95%CI: 0.91-1.94)[138]. However, the same has not been shown in the clinical trials in IBD. In the OCTAVE trials, one patient with several risk factors had acute coronary syndrome, one died of dissecting aortic aneurysm and one patient with a history of cardiovascular disease had congestive heart failure. During the maintenance phase, one subject with several risk factors receiving tofacitinib 5 mg twice daily had an adjudicated MACE (myocardial ischaemia/ myocardial infarction), and one patient, also with multiple risk factors, receiving tofacitinib 10 mg twice daily had an adjudicated MACE (haemorrhagic stroke). The overall incidence rate for MACE in the OCTAVE trials was 0.16 (95%CI: 0.04-0.42). Multiple real life studies of tofacitinib also did not demonstrate increase in the risk for MACE compared to anti TNF agents[96,139,140].

In a meta-analysis assessing safety of JAK inhibitors in IBD and other immune-mediated inflammatory diseases evaluated MACE in 32765 patients on JAK inhibitors (17 tofacitinib; 6 upadacitinib; 4 baricitinib; 3 filgotinib), the incidence rate of MACE was 0.67 per 100 patient-years[141]. Real life safety data on upadacitinib and filgotinib are lacking, however in the registry trials, MACE were infrequent and no difference was reported compared to placebo[142, 143]. Though the risk of MACE appears low, JAK inhibitors should be used cautiously in patients over the age of 50 years with concomitant risk factors for CVD.

Management of ASCVD

Current risk assessment tools for predicting CVD, such as the Framingham risk score and the ASCVD risk calculator, lack validation for individuals with chronic inflammatory conditions, potentially leading to an underestimation of their CVD risk. European guidelines suggest incorporating a 1.5-fold multiplier when assessing the 10-year CVD risk in patients with rheumatoid arthritis. However, there remains an information void regarding whether a similar adjustment is warranted for patients with IBD.

Controlling inflammation in IBD is the key to reduce the risk of CVD[105]. Adequate treatment of underlying IBD with the aim to achieve and maintain remission is important. Additionally, the patients should be screened for atherosclerotic risk factors such as obesity, smoking, hypertension, diabetes, dyslipidaemia and positive family history[144]. Definitive role of statins in IBD is controversial, but statins in addition to the lipid lowering function have pleiotropic effects, including modulation of the immune system[145,146]. IBD is not a contraindication to low-dose aspirin for primary and/or secondary prevention.

HEART FAILURE

The risk of heart failure is twice as higher in IBD than non IBD subjects when adjusted for traditional cardiovascular risk factors with the highest risk reported in females with UC[112].

Heart failure in individuals with IBD may manifest as either new-onset (de novo) or as a consequence of deteriorating health in those with pre-existing conditions. These underlying conditions, which predispose individuals to heart failure, encompass IHD, hypertension, dyslipidemia, diabetes, smoking, valvular heart disease, congenital heart disease, *etc.* The frequent triggers for decompensation leading to heart failure involve infections or inadequate adherence to prescribed treatment regimens.

Pathogenesis

Heart failure in IBD could be a consequence of the chronic inflammation or the drug therapy used. The compromised integrity of the intestinal barrier and ongoing intestinal inflammation are contributing factors to the development of heart failure. This can be attributed to the translocation of bacterial LPS, which triggers the production of TNF- α . Both LPS and TNF- α are implicated in inducing structural changes in the heart that progress to heart failure[147,148]. Additionally, several other proposed mechanisms may contribute to the development of heart failure in these patients. These mechanisms include myocardial fibrosis due to altered collagen metabolism, impaired nitric oxide-mediated vasodilation, deficiencies in essential vitamins and trace elements, heart muscle atrophy resulting from prolonged corticosteroid use, total parenteral nutrition, myocarditis, endocarditis, and valvulopathy[30,149-151].

Anti-TNFs and heart failure

There have been case reports and studies of anti TNF induced heart failure[152,153]. The biological effects of TNF- α are mediated *via* two distinct cell surface receptors. TNFR1 is cardiotoxic and antagonising its action attenuates ventricular dysfunction and improves post MI survival whereas TNFR2 is cardioprotective and its inhibition upregulates TNFR1 and increases ventricular dysfunction and remodelling[154,155]. The effects of TNF- α are concentration dependent and involve two pathways. In lower concentrations, survival activating factor enhancement pathway is activated, while higher concentration leads to stimulation of death-promoting pathway functions[156,157]. Chung *et al*[158] evaluated the effect of infliximab in patients with New York heart association (NYHA) Class III or IV heart failure with ejection fraction $\leq 35\%$ and found that patients in the 10 mg/kg infliximab group were more likely to die or be hospitalized for heart failure than patients in the placebo group or 5 mg/kg infliximab group (HR = 2.84, 95%CI: 1.01-7.97; $P = 0.043$).

Prevention

Routine screening tests for cardiovascular diseases prior to the administration of biologics is not recommended. However, employment of an echocardiogram prior to initiation of anti TNF therapy to evaluate baseline cardiac function is vital [105,157]. Although there are no specific guidelines for the use of anti TNF in heart failure, it is suggested to avoid anti TNF agents in patients with NYHA class III or IV disease and switching to an alternative non-TNF inhibitor in patients with patients who develop acute heart failure on anti TNFs[105,157,159,160].

ARRHYTHMIAS AND CONDUCTION DISORDERS

As with other chronic inflammatory disorders, IBD carries a risk of major cardiac arrhythmias, which include atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation. The risk of arrhythmias correlates with the disease activity[43,161]. A large population-based cohort study found that risk of atrial fibrillation was increased in patients with IBD with a higher risk in CD and was particularly increased in younger patients with age < 45 years[21].

Pathogenesis

Although the pathogenesis of arrhythmias is incompletely understood, chronic inflammation is hypothesized to predisposes to rhythm disorders and conduction abnormalities in patients with IBD[30,162]. Also, patients on systemic steroids, immunomodulators or biologics had a higher risk, highlighting the role of moderate-to-severe active disease. Atrial electromechanical conduction delay, a predictor of atrial fibrillation, has been shown to be significantly prolonged in patients with IBD, especially those with active disease and longer disease duration.

IBD drugs and arrhythmias

Sphingosine-1-phosphate (S1P) receptor modulators (ozanimod) have been implicated in cardiac arrhythmias. S1PRMs have 5 G protein coupled receptor subtypes S1PR1 to S1PR5. The S1PR1, which is extensively expressed on cardiomyocytes and vascular endothelial cells, is the target of S1P modulators. In phase 3 RCT of ozanimod in UC, five cases of bradycardia were reported during the induction period and none during the maintenance period[163-165]. In the TOUCHSTONE open label long term extension study of ozanimod 1 mg per day in patients with UC, no bradycardia nor evidence of atrioventricular (AV) block was reported at 44 wk[163,166]. In the OASIS trial, a phase 2 induction trial of etrasimod which selectively target S1P1, S1P4, and S1P5, no such cardiac events were reported[167,168]. In the ELEVATE UC study, 5 patients receiving etrasimod reported bradycardia and 1 patient had first degree AV block that resolved without interventional treatment. The real-world studies, though scarce, did not report cardiac conduction abnormalities after 26 wk of treatment exposure of ozanimod.

Recommendations for patients with IBD to mitigate cardiovascular risk

The probability of experiencing cardiovascular events is inherently intertwined with the presence of systemic inflammation and the level of disease activity in individuals with IBD. It is imperative to adopt a proactive approach by conducting regular screenings and monitoring of cardiovascular risk factors for all IBD patients. Those identified as being at risk should adhere to established recommendations applicable to the general population. Collaborative efforts with cardiologists are vital in managing these risks effectively. Considering that these risk factors may evolve over time, especially with advancing age, routine screening and monitoring are indispensable for sustaining optimal cardiovascular well-being. It is of paramount importance to provide counseling and education to patients regarding their specific cardiovascular risks. Encouraging the adoption of healthy lifestyle modifications is crucial in this regard[169]. A concise summary of practical guidance for managing CVD in individuals with IBD is presented in [Table 1](#).

Table 1 Practical guide to management of cardiovascular diseases in inflammatory bowel disease

Cardiovascular disease	Risk factors	Suggested testing	Therapeutic considerations
Pericarditis and myocarditis	Disease related	Onset of symptoms within 2-4 wk of starting 5-ASA	Discontinuation of therapy
	Disease activity		
	Drugs	ECG: ST-T changes	Immunosuppressives for inflammation associated myocarditis
	5-ASA	2D Echocardiography: LV dysfunction, pericardial effusion	Pericardiocentesis or pericardial window, if cardiac tamponade
		Cardiac MRI	Control IBD disease activity
Venous Thromboembolism		Endo-myocardial biopsy, if cardiac MRI contraindicated or life threatening disease	
		Elevated cardiac biomarkers	
	Patient related	Screening for genetic risk factors in patients with recurrent venous thromboembolic events	Thromboprophylaxis
	Elderly age		All IBD patients during hospitalization of any cause
	Females		Ambulatory patient with active IBD and known risk factors for VTE
	Obesity		Prophylaxis should be maintained during the inpatient period
	Malnutrition		
	Disease related		Treatment
	Disease activity		LMWH
	Colonic disease location		Direct oral anticoagulants
	UC > CD		Cautious use of JAK inhibitors
	Hospitalization		Aim the lowest effective dose to maintain remission
	Emergency surgery		
	Longer operative time		
	Open surgery		
	Drugs		
	JAK inhibitors		
	Corticosteroids		
Atherosclerotic cardiovascular disease	Patient related	Lipid profile at baseline, end of induction and every 6 mo	Treatment of ASCVD is similar to non IBD patients and should be done in close collaboration with an expert cardiologist
	Younger age		
	Females		
	Disease related	Test for subclinical atherosclerosis	Control IBD disease activity
	Disease activity	Carotid intima media thickness	

	Colonic disease location	Pulse-wave velocity between the carotid and femoral arteries	
	Increased hs CRP	Coronary artery calcium	
	Increased fibrinogen		
	Drugs	2D echocardiography/ stress echocardiography/TMT	Cautious use of JAK inhibitors
	Corticosteroids		
	JAK inhibitors		
		Coronary angiography	Treat JAK inhibitor induced dyslipidemia/hyperlipidemia with statins
Heart failure	Patient related	2D Echocardiography	Avoid anti TNF in NYHA Class III or IV heart failure, especially with ejection fraction $\leq 35\%$
	Females	Ventricular dysfunction	
	Underlying cardiac structural diseases	Structural abnormalities	
	Diabetes		
	Hypertensive heart disease		
	Chagas disease		
	Deposit diseases		
	Valvular heart disease		
	Disease related		
	UC > CD		
	Drugs		
	Anti TNF agents in high dose		
Arrhythmias and conduction abnormalities	Patient related	ECG	Control disease activity
	Age > 65 yr	Increased P-wave dispersion	Caution with S1P receptor modulators
	Previous arrhythmias or cardiac conduction abnormalities	Increased QTc dispersion	Caution in patients with risk factors
	Ischemic heart disease	Prolonged QTc interval	
	Cardiomyopathy with septal involvement		
	Drugs (e.g: beta-blockers, calciumchannel inhibitors, antiarrhythmics)		
	Uncontrolled hypertension		
	Previous cardiac surgery		
	Surgical/percutaneous treatment of valvular disease		
	Disease related		
	Disease activity		
	Drugs		
	S1P receptor modulators		

ASA: Amino salicylic acid; ECG: Electrocardiogram; LV: Left ventricular; MRI: Magnetic resonance imaging; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; VTE: Venous thromboembolism; LMWH: Low-molecular-weight heparin; JAK: Janus kinase; ASCVD: Atherosclerotic cardiovascular diseases; CRP: C-reactive protein; TMT: Treadmill test; TNF: Tumor necrosis factor; NYHA: New York heart association; S1P: Sphingosine-1-phosphate.

Future directions

The pathophysiology of CVD in IBD needs further elaboration. The current knowledge gaps include the following: Immunological mechanisms at play in both the development of IBD and the formation of atherosclerosis, prevalence of cardiometabolic risk factors, risk stratification and identification of IBD patients at the highest risk for cardiovascular

complications, allowing for more targeted preventive measures, role of pre-emptive screening for subclinical atherosclerosis and its cost effectiveness, long term outcomes in patients with CVD and IBD, and effective strategies for monitoring cardiovascular risk factors in IBD patients, and how often should such monitoring occur.

CONCLUSION

The prevalence of cardiovascular manifestations in patients with IBD, though rare, is higher when compared to the general population. The CVD in IBD represent a complex and multifaceted relationship between chronic gastrointestinal inflammation and cardiovascular health. The inflammatory cytokines, immune responses and chronic systemic inflammation associated with disease activity contributes to the development and progression of CVD. Individual patient factors, such as age, gender, pre-existing cardiovascular conditions, and genetics, also play a significant role in determining the cardiovascular impact. The spectrum of CVD in IBD is wide. Additionally, the cardiovascular effects of drugs used in IBD are multifaceted and depend on various factors, including the specific medicines involved and individual patient characteristics.

In individuals with IBD who are at an elevated risk of cardiovascular issues, there is a need to shift the focus of care from a reactive approach to a proactive one, emphasizing preventive measures for cardiovascular management. To minimize cardiovascular risk a multidisciplinary approach involving gastroenterologists and cardiologists is often necessary. This will ensure that IBD treatment is optimized while minimizing cardiovascular risk.

FOOTNOTES

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Acute myocardial infarction in myeloproliferative neoplasms

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Abstract

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematologic malignancies characterized by an abnormal proliferation of cells of the myeloid lineage. Affected individuals are at increased risk for cardiovascular and thrombotic events. Myocardial infarction (MI) may be one of the earliest clinical manifestations of MPNs or may be a thrombotic complication that develops

during the natural course of the disease. In the present review, we examine the epidemiology, pathogenesis, clinical presentation, and management of MI in MPNs based on the available literature. Moreover, we review potential biomarkers that could mediate the MI-MPNs crosstalk, from classical biochemical tests, *e.g.*, lactate dehydrogenase, creatine kinase and troponins, to pro-inflammatory cytokines, oxidative stress markers, and clonal hematopoiesis.

Key Words: Myeloproliferative neoplasms; Polycythemia vera; Essential thrombocythemia; Myelofibrosis; Myocardial infarction; Acute coronary syndrome; Biomarker; Clonal hematopoiesis

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Core Tip: Patients diagnosed with myeloproliferative neoplasms (MPNs) are at risk of developing thrombotic complications, among which acute coronary syndromes are of relevance. Myocardial infarction (MI) can emerge as the initial event in the diagnosis of MPNs or occurs during the evolution of the disease. Here, we examine the interplay between MI and MPN, with a focus on the epidemiology, presentation, risk factors, diagnosis, and management of MI in MPNs, as well as discuss potential biomarkers of MI in MPNs, as well as the role of inflammation and clonal hematopoiesis.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a heterogeneous class of blood disorders characterized by an abnormal proliferation of cells of the myeloid lineage[1]. They comprise a group of chronic myeloid malignancies with various phenotypes, marked by the clonal proliferation of hematopoietic stem cells and excessive proliferation of terminally differentiated myeloid blood cells[2]. The four classic types of MPNs include chronic myeloid leukemia, essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)[1]. Furthermore, chronic neutrophilic leukemia, chronic eosinophilic leukemia, and unclassified MPN are also included in the classification presented by the World Health Organization (WHO)[1]. Among these, PV (characterized by an absolute increase in erythrocytes due to the proliferation of the erythroid lineage[3]), ET (marked by the excessive proliferation of hyperlobulated mature megakaryocytes in the bone marrow along with persistent peripheral blood thrombocytosis[4]) and PMF (characterized by abnormal differentiation of the megakaryocytic clone, ultimately resulting in excessive proliferation of reactive fibroblasts and fibrosis[5]) are BCR-ABL1 negative and will remain the focus of this review. The major cause of morbidity and mortality in MPNs are thrombo-hemorrhagic complications. This review aims to describe the complex pathogenesis, risk stratification, diagnostic criteria, and management of acute coronary syndrome (ACS) in MPNs.

Patients with MPNs have a higher risk of cardiovascular events[6]. It is important to note that ACS can be one of the first clinical manifestations of MPN[7], or it can be a thrombotic complication of ET and PV. PV typically affects the large arteries of the cardiovascular and cerebrovascular system, while ET tends to involve the microcirculatory system[7]. Previously published literature suggests that the reported incidence of cardiovascular complications related to MPNs ranges from 4% to 21%[7]. In patients diagnosed with ET, the incidence of thrombosis was reported to be 25%, with arterial thrombosis occurring more frequently than venous thrombosis[8]. During the follow-up of patients with PV, over a 10-year period, coronary events were frequently observed, with a reported rate of 11.4%[3]. Among a total of 1213 PV patients, thrombosis was identified in 19% of cases over a 20-year period, with 21.7% thrombotic events resulting in myocardial infarction (MI)[9]. In patients diagnosed with ET and PV, the mortality rate attributed to cardiovascular disease was 26% and 25%, respectively, higher than the mortality rate caused directly by the disorder itself[10]. Cerebral venous thrombosis, although a rare complication of PV, has been reported to cause the death of 8.3% of patients[11]. Furthermore, complications of MI may develop in 12 mo after the diagnosis of ET or PV[12].

Pathogenesis

The mechanisms responsible for the increased tendency for thrombosis in MPNs are not yet fully understood. ACS in myeloproliferative diseases is mostly attributed to coronary thrombosis due to hyperviscosity and thrombocytosis. The etiology of MPN-related hemostatic conditions is complex and multifactorial, involving a combination of quantitative and qualitative changes[12]. Pathophysiological mechanisms likely involve complex interactions between blood components and vascular cells, together with hemodynamic changes[13]. These, coupled with risk factors such as advanced age, a history of thrombotic events, leukocytosis, and cardiovascular risk factors such as hypertension, smoking, diabetes mellitus, have been observed to increase the risk associated with developing thrombosis in the context of myeloproliferative diseases. Factors that contribute to the thrombophilic state in MPNs include: Increased cell mass resulting from

the clonal expansion of hematopoietic stem cells[11]; prothrombotic state induced by increased platelet accumulation, along with the release of activation products and increased expression of surface activation markers[5]; elevated leukocyte count, which has been documented to be a stronger predictor of thrombogenesis than platelet count or hematocrit/hemoglobin levels[13]; elevated blood viscosity that pushes platelets centrifugally, causing them to adhere to the vessel wall, consequently initiating the process of thrombus formation; increased tendency of erythrocytes to attach to the endothelium; inflammatory response resulting from increased cytokine expression; and an elevated level of microparticles exhibiting procoagulant activity[14].

Furthermore, in most patients with MPN, driver mutations are observed in the pro-inflammatory JAK-STAT signaling pathway, with *JAK2* mutations the most prevalent. MPN patients carrying *JAK2* mutations are at higher risk of developing arterial thrombosis[6], which is evident in reports that around > 95% PV and approximately 50% of patients with ET and PMF have a mutation of the *JAK2* gene, *i.e.*, *JAK2V617F*[2,11]. In addition to mutations in exon 14 of the *JAK2* gene, deletions, and mutations in exon 12 of the *JAK2* gene have been observed. Furthermore, mutations in *MPL*, the thrombopoietin receptor gene, as well as in *CALR*, the calreticulin gene, have been identified along with several mutations in non-driver genes, for example, the ten-eleven translocation 2 gene[2,14]. Although a susceptibility haplotype to *JAK2* mutations, 46/1, haplotype, has been reported, the presence of a *JAK2* mutation is not strictly associated with the initialization of MPN[2].

RISK FACTORS FOR ACS/MI IN MPNS

Patients with MPNs have an overall increased risk of developing cardiovascular disease, especially under the spectrum of ACS[15,16]. The incidence of ACS in these patients has been attributed to significant morbidity and mortality, with up to 76% of deaths due to cardiovascular events and approximately 32% having major adverse cardiovascular events up to 1 year post-ACS[6]. As discussed above, the basis for ACS and MPNs comorbidity is largely due to the prothrombotic, pro-inflammatory, and profibrotic states seen in patients with MPNs secondary to gain of function mutations in the *JAK* signaling pathway[14,16].

Risk factors for ACS in MPNs are chiefly based on the level of ischemic risk, classified as either; high, intermediate or low, based on a set of established criteria[17-19]. Increasing age, previous thrombosis, and diabetes have been identified as consistent and independent predictors of cardiovascular events in MPNs and therefore have been classified as the main risk factors for ischemic events in MPNs[17]. Minor risk factors in this criterion include smoking, hypertension, and hypercholesterolemia. Therefore, a high-risk patient is often < 60 years of age, has a history of thrombosis, or diabetes. Intermediate-level risk patients have ages between 40 and 60 years along with one of the minor risk factors or an age < 40 years with two minor risk factors. Patients with a low-risk level do not have any identifiable risk factors[4]. A schematic representation of the risk factors that contribute to the development of ACS in MPNs is depicted in Figure 1.

The European Collaboration on Low-Dose Aspirin in Polycythemia (ECLAP) study reported higher incidences of cardiovascular complications in patients with PV > 65 years (5% patient-years) and in those with a history of thrombosis (4.93% patient-years) compared to younger patients without a history of thrombosis (2.5% patient-years)[20]. Similarly, Barbui *et al*[21] based on the results of an epidemiological study of 1638 patients with PV, observed an 8:6 hazard ratio in patients > 60 years compared to younger patients. Carobbio *et al*[22] observed a similar trend in an international study of 891 patients with emergency department (ED) where individuals over 60 years of age and with a thrombotic history had risk ratios (RR) of 1.5 and 1.93, respectively, to develop major thrombosis when followed for about 6.2 years.

Another risk factor for the thrombosis and MI in MPN patients is leukocytosis[17]. A study using data from the ECLAP database assessed the association between hematological variables and risk of MI[23]. They observed a 70% increased risk of thrombosis in patients with PV with a white blood cell (WBC) count > $15 \times 10^9/L$. The proposed mechanism of thrombosis is believed to involve endothelial inflammation from activated WBCs. Consequently, the consensus recommends that as part of the cytoreduction in PV and ET, the WBC count should remain within the normal range[24]. It is noteworthy, however, that this association has not yet been proven in randomized clinical trials. Interestingly, while elevated platelet levels can be assumed to be the leading risk factor for MI in these patients, the findings of the ECLAP study showed that neither the proposed therapeutic target ($400 \times 10^9/L$) nor other platelet count thresholds served as a predictor of increased risk of the aforementioned complication[25].

Most minor risk factors for the occurrence of MI in MPNs constitute conventional atherosclerosis risk factors and serve as accentuators in the background of the aforementioned major risk factors leading to the transition from low to intermediate or high-risk levels[26,27]. The International Prognostic Score for Thrombosis categorizes cardiovascular risk factors as part of the variables that are significantly and independently associated with increased rates of thrombosis in patients with ED[26]. Genetic interplay in the causality of MI in MPNs is also to be considered as key risk factors. A study evaluating PV patients observed a higher risk of cardiovascular events (RR = 7.1; $P = 0.003$) in patients harboring > 75% of the mutant allele *JAK2V617F*[28]. Similarly, a systematic review showed a twice as high odds (odds ratio = 1.92; 95% confidence interval: 1.45-2.53) in patients with similar mutations in ET, although heterogeneity between included studies [29]. The coexistence of this mutation with leukocytosis results in the highest levels of fatal and non-fatal thrombosis[30].

CLINICAL PRESENTATION

Approximately 0.27% and 0.1% of MI-related hospitalizations due to thrombosis are attributed to ET and PV, respectively [31]. Thus, despite the relatively high incidence of this vascular complication in MPNs, it contributes very little to the

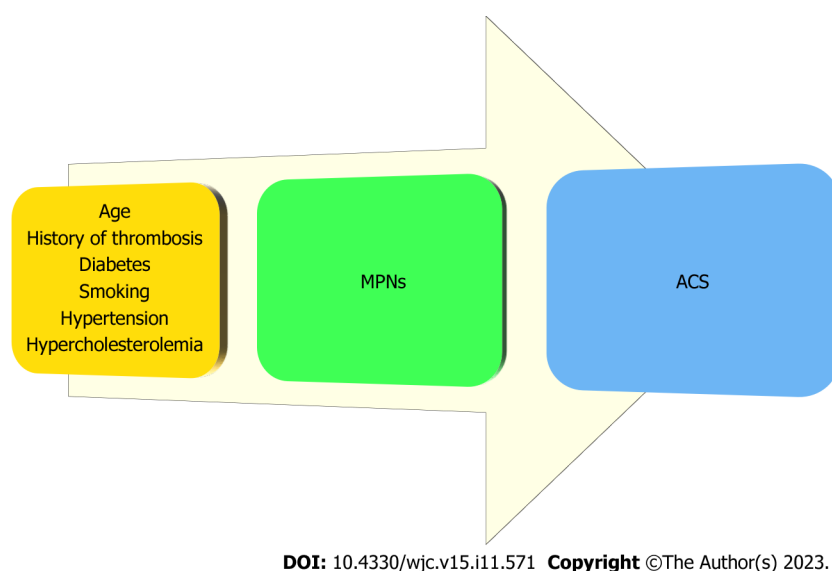


Figure 1 Schematic representation of the risk factors that contribute to the development of acute coronary syndromes in myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes.

etiology of MIs. ACS has been reported as the initial presentation in some patients with MPN; however, most incidences of MI develop within one year after diagnosis of ET and PV[12]. This usually occurs despite the initiation of MPN treatment. Patients usually present with the typical symptoms associated with MI, that is, severe retrosternal chest pain radiating to the shoulder that is squeezing in character, exertional chest pain, dyspnea combined with profuse sweating. These patients often lack a history of risk factors associated with ACS, *e.g.*, hypertension, diabetes, or hyperlipidemia; however, one or more may be present[32]. They may or may not have a family history of coronary artery disease or a history of smoking with varied pack-years. Other associated symptoms include headache prior to acute condition, nausea, general malaise, and diaphoresis[32].

Examination and lab findings often vary from patient to patient. Vital signs including heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation often remain stable within the reference ranges. Lung auscultation is often clear throughout both lungs, however, cardiac examination at times reveals an S4 gallop[33] and splenomegaly may at times be palpable on abdominal examination[34]. The peripheries do not show edema, but erythromelalgia of the hands is positive in some cases[33]. Lab tests reveal elevated platelets, troponins, D-dimers, triglycerides and hematocrit with low potassium levels and normal urea, electrolytes, and creatinine[35,36].

On radiological investigation, the thrombus in ET is often located within the left anterior descending artery; however, right coronary involvement has also been reported in the literature[36,37]. Electrocardiography usually shows a regular sinus rhythm with elevation of the ST or non-ST segment[33,34]. Notably, as part of treatment, an oral imidazoquinazoline drug, anagrelide, has been observed to cause ACS in some (1%-5%) patients with ED by directly inducing coronary artery vasospasm[4]. The incidence of ACS increases with increasing age; therefore, most of the presenting patients are over 60 years of age and those with a history of thrombosis or in the background of mutations in the *JAK2* or *MPL* genes[35].

DIAGNOSIS

For ACS, risk factors such as age, family history of coronary artery disease, hypertension, diabetes, dyslipidemia, or smoking should be considered[7]. An electrocardiogram should be performed to assess the type of MI to guide emergency management. Cardiac markers may be elevated[38]. Coronary angiogram may reveal the coronary artery involved, of which the most reported in MPNs is the left anterior descending artery[7]. Echocardiography may be performed to assess ventricular ejection fraction[7].

The complete blood cell count becomes an important baseline investigation, particularly in this case. Lab tests may reveal an increase in platelet count, an increase in hematocrit, and/or leukocytosis. However, reactive thrombocytosis and leukocytosis can be observed due to an inflammatory response in the case of acute MI, resulting in a delayed or missed diagnosis of MPN[7]. The international normalized ratio and prothrombin time may be normal[39]. In addition, giant platelets and megakaryocyte fragments can be seen in the peripheral blood smear[39].

Diagnosis of ET according to the criteria issued by the WHO is given by a persistent elevation of the platelet count of $\geq 450 \times 10^9$ platelets/L, presence of typical mutations associated with ET, a negative translocation of BCR-ABL1 and bone marrow biopsy for histopathological confirmation. Molecular biology studies for *JAK2* mutations confirm the diagnosis, as evidence of the *JAK2V617F* mutation has been observed in 60% of patients with ET[7]. In the analysis of the *CALR* or *MPL* mutations, mutations of the *CALR* exon 9 and *MPL* exon 10 have been reported in 30% of patients who are *JAK2V617F* negative[7]. Cellular bone marrow with maturing trilineage hematopoiesis and large atypical hypolobulated

megakaryocytes may be seen in bone marrow biopsy, as reported in previously published literature[39].

Furthermore, the abdomen should be examined for hepatosplenomegaly, which may be indicative of thrombocytosis, leukocytosis, or polycythemia, followed by abdominal ultrasound if indicated[7]. The following three 'red flags' have been reported in previous literature that should raise suspicion of ET in ACS and should therefore inform relevant investigations, including bone marrow biopsy and genetic testing for driver mutations[40]: (1) There are few or no coronary artery disease-related risk factors present in ACS patients; (2) Platelet count $> 450 \times 10^9/L$. A mild increase above this level should also warrant investigation; and (3) In coronary angiography, severe atherosclerotic narrowing is not reported. However, thrombotic occlusion may sometimes be observed.

PV is diagnosed when the three main criteria are met, or when the patients meet the first two main criteria and the minor criterion defined by the WHO[3]. The main criteria for PV issued by the WHO include: (1) Hemoglobin level > 16.5 g/dL in males, and > 16.0 g/dL in women or a hematocrit $> 49\%$ in males and $> 48\%$ in women or increased red cell mass; (2) Hypercellularity for age with trilinear growth observed on bone marrow biopsy; (3) Detection of *JAK2* mutations (V617F or exon 12 mutations). The minor criterion includes a decreased serum erythropoietin level[3]. In patients with PMF, circulating platelets exhibit an activated state and demonstrate notably elevated levels of protein kinase Cepsilon (PKCepsilon)[41]. Furthermore, in patients with MF, PKCepsilon levels in platelets were found to be associated with high-risk disease and a history of major cardiovascular events[41].

MANAGEMENT

For patients with ACS, emergency management should begin depending on the specific type of MI. ACS management in ET involves initiating cytoreductive therapy, administration of antithrombotic drugs, and revascularization based on risk-oriented recommendations. Thus, risk stratification of thrombosis becomes important to guide management. Patients are classified as 'high risk' when any of the three specified criteria is met: (1) Age ≥ 60 years; (2) A previous history of thrombosis or major bleeding; and (3) A blood platelet count of $\geq 1500 \times 10^9/L$ [40]. Patients are labeled low risk if their age is less than 60 years and there is no history of previous thrombotic event[12].

As all patients with ACS with ET are classified as 'high risk'[40], their management involves monitoring the associated risk factors and initiating cytoreductive therapy. The first-line drug is hydroxyurea and the objective of the therapy is to maintain a platelet target of less than $400 \times 10^9/L$ [42]. Platelet target count of $400 \times 10^9/L$ is generally considered acceptable by most hematologists; however, a target count of $600 \times 10^9/L$ may be appropriate to avoid anemia and leukocytopenia, and in particularly younger patients, malignant transformation possibly related to intensive cytoreductive therapy can be prevented[40]. With long-term administration of hydroxyurea, irreversible gonadal toxicity has been reported[42]. Therefore, in younger patients with reproductive intentions, interferon alpha is preferred[42]. In addition, limited information is available on the safety of cytoreductive therapy in very elderly patients[12].

Given the risk of thrombosis with the *JAK2V617F* mutation and cardiovascular risk factors, cytoreductive therapy may be combined with antiplatelet therapy with low-dose acetylsalicylic acid. The combination of cytoreductive therapy with antiplatelet agents or oral anticoagulants has also been reported to be more effective than the administration of single drugs[43]. Furthermore, the *JAK1/2* inhibitor ruxolitinib has also been used in the management of ET[44]. Platelet reducing agents such as anagrelide can also be prescribed[43]. Anagrelide (imidazoquinazoline) selectively affects megakaryocytes by inhibiting cyclic-AMP phosphodiesterase III activity, resulting in inhibition of platelet aggregation. Although it is recommended for patients resistant to or intolerant to hydroxyurea, it can induce spasm of the coronary arteries, leading to cardiovascular events such as ACS, heart failure, and/or arrhythmias[4].

The estimate of the rate of recurrence of thrombosis after cytoreductive therapy was halved in the overall cohort of 494 patients with PV and ET[43]. In addition, the use of tirofiban, a glycoprotein IIb/IIIa receptor blocker, has also been highlighted in the treatment of acute MI in an ET patient[45]. Thrombotic complications in PV are substantially reduced by cytoreductive management of blood hyperviscosity either by phlebotomy or chemotherapy along with antiplatelet therapy using low-dose aspirin to achieve target hematocrit levels below 45%[44].

Other treatment options for ED include aspiration thrombectomy and distal protection revascularization to prevent distal embolization. Percutaneous coronary intervention has been described as an effective approach to revascularization in patients with ER, however, an increased incidence of complications such as stent thrombosis and restenosis has been reported[8]. However, cytoreduction is advised before revascularization to prevent platelet activation and future thrombotic events[39]. The management of ACS in MPNs is therefore a combination of aggressive pharmacotherapy and an appropriate revascularization approach.

PROGNOSIS

Thrombosis remains the most common complication of MPNs. There is an increased risk of in-hospital mortality due to MI associated with ET and PV. It has been reported that around 4% of patients with MPNs die from MI[46]. The incidence of recurrence of thrombosis after previous arterial or venous thrombosis is high, with studies reporting a rate of 33%[47]. Furthermore, in patients with ACS due to this pathological hypercoagulable state, a diagnosis may be missed in the absence of marked thrombocytosis as clinicians focus on the restoration of normal cardiac function and coronary vessel revascularization and thus may overlook this rare etiology[46]. Thus, recurrence can further worsen the prognosis for this condition. The prognosis also worsens with increasing age, the presence of atherosclerotic risk factors, the presence of a previous thrombotic event, and comorbid conditions[32]. Treatment must therefore involve a multidisciplinary team in

order to treat the underlying etiology, prevent recurrence, and decrease the risk of additional thrombotic complications.

FUTURE PERSPECTIVES: CAN WE QUEST FOR BIOMARKERS?

In the era of genomic and precision medicine, it is warranted to identify biomarkers that could predict the onset of thrombotic complications or link ACS and MPN. Lactate dehydrogenase is of poor utility in the ACS-MPNs interaction, as it is not an ideal biomarker for the heart and is also frequently detected in elevated concentrations in MPN[48]. Furthermore, creatine kinase, a potential marker of myocardial damage useful for its low execution costs as opposed to other more heart-specific biochemical panels, has been shown to exhibit a low mean creatinine kinase activity compared to ACS, healthy individuals and subjects diagnosed with a wide range of chronic disorders. However, Pan *et al*[49] have highlighted that creatinine kinase activity was the best biomarker for MPNs among 36 disorders, including ACS, stroke, diabetes, leukemia, lymphoma, multiple myeloma, and several solid cancers. Increased troponin concentrations have rarely been reported in MPNs. Tortorella *et al*[50] investigated cardiovascular risk factors and events in ET subjects prescribed anagrelide, discovering that only 2 of 55 analyzed patients had elevated troponin values. However, therapy with this platelet-lowering agent did not influence troponin concentrations nor the risk of MI, and the two individuals diagnosed with ET who also developed MI did not require discontinuation of anagrelide.

Oxidative stress could be a mediator of MPN-ACS crosstalk. Ischemia-modified albumin has been detected at elevated concentrations in both MI[48] and MPN[51-53]. Regardless of the disease subtype, MPN subjects showed increased albumin values modified by ischemia compared to healthy controls, with notable elevations exhibited by individuals with PMF and *ASXL1*-mutated MPN[51]. Similarly, Karahan *et al*[52] have highlighted that subjects living with PV show elevated levels of ischemia-modified albumin compared to healthy counterparts and that ischemia-modified albumin is an excellent predictor of tissue ischemia in PV. Additionally, prescription of ruxolitinib has been reported to decrease levels of oxidative stress in PMF. After one month of therapy, ischemia-modified albumin values decreased in PMF patients regardless of their mutational landscape. Subjects with PMF mutated with *ASXL1*, *JAK2V617F*, and *CALR*-mutated PMF ($P = 0.001$ for all), followed by *MPL*-mutated ($P = 0.005$) and triple negative PMF ($P = 0.028$)[53].

S100A, a myeloid-related protein, has also been reported in elevated values in ACS[48] and MPN. S100A is inhibited by pro-inflammatory cytokines and may emerge as a potentially relevant biomarker of inflammation in the diagnosis of MPN[54]. Furthermore, S100A proteins interact with cell signaling pathways in MPNs *via* Toll-like receptor 4 and RAGE in a burden-dependent manner of the *JAK2V617F* and *CALR* alleles, respectively[55]. Choline-related metabolites have been detected at high levels in ACS[48], however, Gómez-Cebrián *et al*[56] noted that there are low concentrations of these biomarkers in MPN.

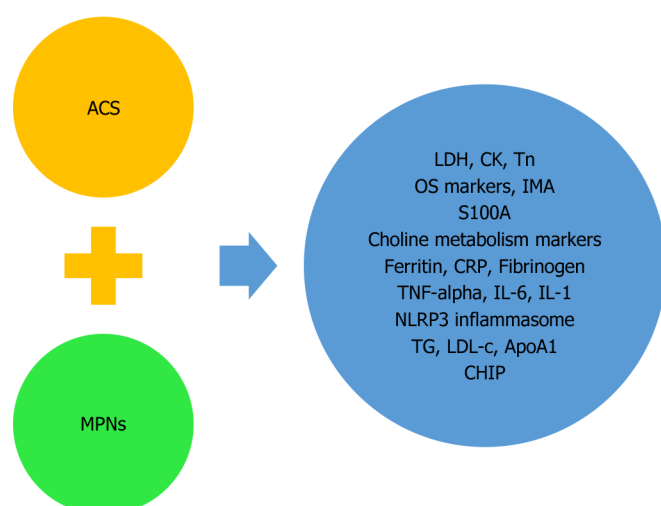
Inflammation markers remain elevated in both ACS[48] and MPNs[57,58]. MPN inflammation is dependent and independent of the mutational landscape of the disease and is influenced not only by genetics, but also by the immune system, diet, metabolism, and comorbidities[59]. Furthermore, researchers have pointed out that both MPN patients[58] and MI subjects have elevated concentrations of ferritin[60,61], C-reactive protein[62,63], and fibrinogen[64]. Pro-inflammatory cytokines, such as tumor necrosis factor- α , interleukin (IL)-6 and IL-1, and the NACHT, LRR, and PYD domains-containing protein 3 inflammasome have been reported to contribute to the pathogenesis of both MI[65-67] and MPN[58,59,68-70].

Dyslipidemia is recognized as a contributor to the development of MI[48]. In addition, several assessments have also delineated the role of lipid alterations in MPN. Furuya *et al*[71] have revealed that elevated levels of triglycerides and low-density lipoprotein-cholesterol are associated with thrombotic complications and survival in ET. Apolipoprotein A1 levels were also associated with the burden of the *JAK2V617F* allele in people with PV[72].

Clonal hematopoiesis of indeterminate potential has also emerged as a contributing factor to the onset of MI[73-75]. Moreover, inflammation has depicted as a possible link between the hematologic malignancies, thrombosis, and ACS in particular[76]. A schematic representation of potential biomarkers linking ACS and MPNs is depicted in Figure 2.

As new instruments are continuously being developed to evaluate cardiovascular risk, we may experience the beginning of an improved prognostication of thrombotic events in MPNs. For example, Mehta *et al*[77] have assessed the QRISK3 score in a cohort of 438 individuals diagnosed with MPNs, revealing that subjects with a history of arterial thrombosis have an elevated burden of cardiovascular risk factors and thus an increased cardiovascular risk warranting for a more aggressive management of associated comorbidities. The QRISK3 tool takes into consideration age (25-84 years), sex, ethnicity, smoking status, presence of comorbidities (diabetes, atrial fibrillation, chronic kidney disease stage 3-5, migraines, lupus, rheumatoid arthritis, severe mental illness, erectile dysfunction), family history of angina or AMI in a 1st degree relative aged < 60 years, use of several medications (antihypertensive agents, antipsychotics, oral corticosteroids, treatment for erectile dysfunction) and several other variables (body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, systemic blood pressure values and the standard deviation of at least two most recent systolic blood pressure readings)[77]. Moreover, Skov *et al*[78] have highlighted that in MPNs there is a dysregulation of the genes involved in the onset of premature/accelerated atherosclerosis, depicting an aberrant expression of 45-56 out of 84 investigated genes. Thus, their findings might explain the crosstalk between inflammation and thrombosis in MPNs and the contribution of this axis to the onset of atherosclerosis and ACS in these blood cancers.

Nevertheless, Leiva *et al*[79] reported that 76% MPN patients are likely to experience another major cardiovascular event or even death following an episode of ACS. The researchers examined 41 individuals with MPNs and a history of ACS who were followed-up for 80 mo, demonstrating that the presence of leukocytosis [leukocyte count ≥ 20000 leukocytes/ μ L; hazard ratio (HR) = 9.10], the occurrence of ACS in the first year after the established diagnosis of MPN (HR = 3.84), the presence of *JAK2* gene mutations (HR = 3.71) and history of cardiovascular disease (HR = 2.60) were risk



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Figure 2 Potential biomarkers linking acute coronary syndromes and myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes; LDH: Lactate dehydrogenase; CK: Creatine kinase; Tn: Troponin; OS: Oxidative stress; IMA: Ischemia-modified albumin; CRP: C-reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin-6; IL-1: Interleukin-1; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; CHIP: Clonal hematopoiesis of indeterminate potential.

factors for another major cardiovascular event or death in this MPN subpopulation[79]. These results are particularly interesting as the same group of scientists have previously reported that according to their propensity score analysis MPN patients who suffer an episode of AMI are less likely to experience in-hospital death and cardiac arrest but elevated rates of hemorrhages *vs* individuals who experienced an AMI but do not associate MPNs[80]. Therefore, based on these findings, we suggest a close monitorization and follow-up of individuals diagnosed with MPNs and who experience an episode of AMI.

CONCLUSION

MI remains a potentially fatal complication of MPNs and may be the presenting event in MPN diagnosis or develop during the natural course of the disease. Patients who develop MI and have persistent hematological abnormalities warrant screening for MPN. Driver mutations, inflammation, and clonal hematopoiesis may contribute to the pathogenesis of MI in MPN. Future investigations should focus on the discovery of biomarkers that could predict the development of MI in MPN subjects, as well as indicate which MI patients could also suffer from blood cancers.

FOOTNOTES

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Case Control Study

Novel predictors of permanent pacemaker implantation following transcatheter aortic valve replacement

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Abstract

BACKGROUND

Conduction and rhythm abnormalities requiring permanent pacemakers (PPM) are short-term complications following transcatheter aortic valve replacement (TAVR), and their clinical outcomes remain conflicting. Potential novel predictors of post-TAVR PPM, like QRS duration, QTc prolongation, and supraventricular arrhythmias, have been poorly studied.

AIM

To evaluate the effects of baseline nonspecific interventricular conduction delay and supraventricular arrhythmia on post-TAVR PPM requirement and determine the impact of PPM implantation on clinical outcomes.

METHODS

A retrospective cohort study that identified patients with TAVR between January 1, 2012 to December 31, 2019. The group was dichotomized into those with post-TAVR PPM and those without PPM. Both groups were followed for one year.

RESULTS

Out of the 357 patients that met inclusion criteria, the mean age was 80 years, 188 (52.7%) were male, and 57 (16%) had a PPM implantation. Baseline demographics, valve type, and cardiovascular risk factors were similar except for type II diabetes mellitus (DM), which was more prevalent in the PPM cohort (59.6% *vs* 40.7%; $P = 0.009$). The PPM cohort had a significantly higher rate of pre-procedure right bundle branch block, prolonged QRS > 120 ms, prolonged QTc > 470 ms, and supraventricular arrhythmias. There was a consistently significant increase in the odds ratio (OR) of PPM implantation for every 20 ms increase in the QRS duration above 100 ms: QRS 101-120 [OR: 2.44; confidence intervals (CI): 1.14-5.25; $P = 0.022$], QRS 121-140 (OR: 3.25; CI: 1.32-7.98; $P = 0.010$), QRS 141-160 (OR: 6.98; CI: 3.10-15.61; $P < 0.001$). After model adjustment for baseline risk factors, the OR remained significant for type II DM (aOR: 2.16; CI: 1.18-3.94; $P = 0.012$), QRS > 120 (aOR: 2.18; CI: 1.02-4.66; $P = 0.045$) and marginally significant for supraventricular arrhythmias (aOR: 1.82; CI: 0.97-3.42; $P = 0.062$). The PPM cohort had a higher adjusted OR of heart failure (HF) hospitalization (aOR: 2.2; CI: 1.1-4.3; $P = 0.022$) and nonfatal myocardial infarction (MI) (aOR: 3.9; CI: 1.1-14; $P = 0.031$) without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; $P = 0.796$) at one year.

CONCLUSION

Pre-TAVR type II DM and QRS duration > 120, regardless of the presence of bundle branch blocks, are predictors of post-TAVR PPM. At 1-year post-TAVR, patients with PPM have higher odds of HF hospitalization and MI.

Key Words: Transcatheter aortic valve replacement; Balloon-expandable valve; Self-expandable valve; Myocardial infarction; Left bundle-branch block; Nonspecific inter-ventricular defect; Coronary artery bypass graft; Coronary artery disease

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Core Tip: This study found that patients with pre-transcatheter aortic valve replacement (TAVR) type 2 diabetes mellitus and QRS duration > 120 ms regardless of the presence of right or left bundle branch block, are at increased risk of permanent pacemaker implantation post-TAVR. The study also demonstrated a linear association between post-TAVR permanent pacemakers (PPM) incidence for every 20 ms prolongation in QRS duration > 100 ms. The study also showed post-TAVR PPM is associated with greater risks of heart failure hospitalization and non-fatal myocardial infarction in our study cohort. In light of the expanded indication of TAVR and the clinical and economic impact of PPM implantation, multidisciplinary heart teams should meticulously risk stratify pre-TAVR patients regarding PPM requirements using novel evidence.

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INTRODUCTION

Patients with untreated symptomatic severe aortic valve stenosis within the first two years have 50% mortality[1]. Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive therapeutic option with proven survival benefits for the management of these patients regardless of their surgical risks after evaluation by a multidisciplinary heart valve team[2,3]. Since the TAVR idea was conceptualized in 1989 and the first-in-human procedure successfully performed thirteen years later by Alain Cribier in France, TAVR procedure has caused a therapeutic paradigm shift, is a safer, non-inferior alternative to surgical aortic valve replacement which is contraindicated in about a third of patients due to prohibitive surgical risks[4-8].

Despite improvement in TAVR procedure techniques over the last two decades to optimize patient safety, cardiac conduction abnormalities requiring permanent pacemakers (PPM) implantation are some post-TAVR complications observed in about 5%-20% of patients[7,9-11]. These conduction abnormalities have been shown to be dependent on patient and periprocedural factors[6,8,9-12]. The atrioventricular (AV) conduction system courses posterior-inferiorly to the non-coronary cusp of the aortic valve annulus as it passes through the membranous septum and the central fibrous body as the bundle of HIS before bifurcation as it enters the interventricular septum[12,13]. This anatomic proximity of the conduction system to the aortic annulus and subarticular region poses a risk of a procedural, mechanical injury during TAVR through direct trauma during catheter insertion, balloon pre-dilation, valve deployment, or perimplantation swelling[10,14-16]. The resultant post-procedural electrical conduction abnormalities, though may be

transient and self-resolving, sometimes may require permanent pacemaker implantation[15,17]. The prevalence of these conduction abnormalities can vary depending on the valve type implanted and have been shown to be more common with the self-expandable Medtronic CoreValve revealing system (MRCS) with a 24%-33% PPM implantation rate compared to the balloon-expandable Edwards Sapien valve (ESV) (5%-12%)[6,8,16]. The flaring, self-expanding nature coupled with the greater radial force generated when deploying the MRCS has been thought to contribute to a higher rate of conduction abnormalities and pacemaker placement than balloon-expandable valves (BEV)[8,17].

In order to reliably risk-stratify patients with respect to post-TAVR pacemaker requirements, several studies have identified several pre-procedural, electrocardiographic (EKG), anatomic, and procedural factors that could predict pacemaker implantation. Although pre-existing conduction abnormalities like AV block, right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior fascicular hem-block, potential risk factors like baseline QRS duration without RBBB or LBBB (nonspecific interventricular conduction delay), supraventricular arrhythmia or type 2 diabetes mellitus (DM) have not been well studied[6,8,12,16,18,19]. Also, although studies in non-TAVR patients have shown an association of isolated right ventricular pacemakers with adverse outcomes like increased heart failure (HF) hospitalization and mortality due to electro-mechanical dyssynchrony, studies on whether post-TAVR PPM patients is associated with adverse clinical outcomes have remained controversial[6,16,20-24].

Therefore, in this study, we intend to retrospectively evaluate the effects of baseline type 2 DM, nonspecific interventricular conduction delay, and supraventricular arrhythmia on post-TAVR PPM requirement and determine the impact of PPM implantation clinical outcomes in a tertiary referral center in Central Wisconsin, United States.

MATERIALS AND METHODS

Study population

This retrospective cohort study included all patients who underwent TAVR for symptomatic aortic stenosis from January 1, 2012 to December 31, 2019. TAVR was offered to patients after evaluation by a comprehensive multidisciplinary heart team according to guideline requirements[25].

Preoperative risks were determined after a thorough review by interventional cardiologists and cardiothoracic surgeons, and patients were classified based on the Society of Thoracic Surgeons risk score for prediction of mortality [26]. Preoperative risk was classified into low risk (< 4%), intermediate-risk (4%-7%), and high risk (> 8%) or inoperable if the multidisciplinary heart team considered the patient inoperable for other clinical reasons. Only the first TAVR procedure during index hospitalization was considered. Patients with a prior history of PPM placement, international classification of disease (ICD) placement, unsuccessful procedures, who died during the procedure, and who had a conversion to open procedures were excluded from the study (Figure 1). The study population was then dichotomized into two cohorts: (1) Patients who required PPM post-TAVR within one year post-TAVR; and (2) Patients who did not require PPM. All the patients were followed up for one year.

Data collection

The patients' data were extracted both electronically and manually from the Marshfield Clinic health system (MCHS), electronic health records obtained by mapping with ICD versions 9 and 10 billing codes for TAVR. Baseline EKG and transthoracic echocardiographic data done within 1 mo prior to the TAVR procedure were manually abstracted by trained physicians after reviewing EKGs and transthoracic echocardiogram reports interpreted and approved by board-certified cardiologists. Similarly, postoperative EKG and echocardiographic data were abstracted from the first postoperative EKGs and complete transthoracic echocardiography, which was performed within one month post-TAVR. All other data were electronically abstracted. 15% of the manually and electronically abstracted data were re-verified by three independent physician reviewers and were found to be over 99% accurate. The MCHS IRB committee granted Institutional Review Board approval prior to patients' electronic medical record review in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Study variables

Baseline demographics, comorbid conditions, pre-procedural, intra-procedural, and post-procedural EKG and echocardiographic data were collected. Demographic data obtained included patient sex, age, and race. Some of the pre-procedure clinical characteristics obtained include body mass index (BMI), society of thoracic surgeons (STS) preoperative risk score, comorbidities like a history of atrial fibrillation, coronary artery disease (CAD), history of myocardial infarction (MI), HF, New York Heart Association (NYHA) class, coronary artery bypass graft, preoperative balloon valvuloplasty (BV), hypertension, diabetes, chronic obstructive pulmonary disease, cancer and others outlined in Table 1. Preprocedural and post-procedural EKG data collected include supraventricular arrhythmias (atrial fibrillation, atrial flutter, and junctional rhythm), conduction abnormalities like RBBB, LBBB, AV blocks, left anterior fascicular block, left posterior fascicular block, bifascicular or trifascicular blocks, intervals including P-R, QRS, QTc. Nonspecific interventricular conduction defect was defined at QRS > 120 ms without RBBB or LBBB morphology. Baseline and postprocedural transthoracic Echocardiographic variables obtained include aortic valve area, peak velocity, mean gradient, peak gradient, aortic valve mitral and tricuspid valve regurgitation, aortic annulus area, and sinus diameter, left ventricular ejection fraction (LVEF), pulmonary artery pressure, left ventricular diastolic diameter, and left ventricular outflow tract (LVOT). Preoperative computed tomography (CT) annulus diameter was also obtained.

Table 1 Demographics and clinical characteristics of the patient population

Characteristics	No PPM	PPM	P value
	n = 300 (%)	n = 57 (%)	
Age	81.0 (8.2)	80.3 (7.6)	0.530
Male	158 (52.7)	30 (52.6)	1.00
BMI	30.5 (6.6)	31.4 (6.6)	0.380
STS risk score			0.168
High ($\geq 8\%$)	194 (64.7)	41 (73.2)	
Intermediate (4%-7%)	72 (24)	12 (21.4)	
Low (< 4%)	34 (11.3)	3 (5.4)	
Cardiovascular history			
AF	128 (42.7)	28 (49.1)	0.385
CAD	260 (86.7)	51 (89.5)	0.670
MI	62 (20.7)	16 (28.1)	0.223
HF	280 (93.3)	54 (94.7)	1.00
NYHA HF class			0.495
1	4 (1.5)	1 (1.9)	
2	101 (38.1)	18 (34)	
3	148 (55.8)	30 (56.6)	
4	12 (4.5)	4 (7.5)	
PCI or stent	134 (44.7)	29 (50.9)	0.469
CABG	47 (15.7)	13 (22.8)	0.182
Previous AV replacement	24 (8.0)	1 (1.8)	0.151
Hypertension	284 (94.7)	56 (98.2)	0.493
Dyslipidemia	271 (90.3)	51 (89.5)	0.810
Diabetes	122 (40.7)	34 (59.6)	0.009
PVD	73 (24.3)	20 (35.1)	0.101
Stroke/TIA	32 (10.7)	8 (14)	0.491
Balloon valvuloplasty	149 (50)	35 (62.5)	0.108
Other comorbidities			
COPD	89 (29.7)	11 (19.3)	0.147
Liver disease	4 (1.3)	1 (1.8)	0.583
Cancer	142 (47.3)	26 (45.6)	0.885
Anemia	259 (86.3)	51 (89.5)	0.670
Dialysis	15 (5)	4 (7)	0.521

P values and mean $\pm$ SD from a 2-sample *t*-test were reported for continuous variables. Counts (%) and P values from Fisher's exact test were reported for categorical variables. Kruskal-Wallis test was used for ordinal variables (STS and NYHA HF class). BMI: Body mass index; PPM: Permanent pacemaker; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack; PVD: Peripheral vessel disease; PCI: Percutaneous coronary intervention; HF: Heart failure; MI: Myocardial infarction; AF: Atrial fibrillation; STS: Society of thoracic surgeons; PPM: Permanent pacemakers; NYHA: New York Heart Association; CABG: Coronary artery bypass graft.

The valve index, which is a relation of the valve size in relation to the aortic annulus, was calculated as valve size/LVOT diameter $\times 100$ [27,28]. Other periprocedural variables obtained include procedure urgency, valve type (BEV and SEV), valve size, access site, and post procedure complications.

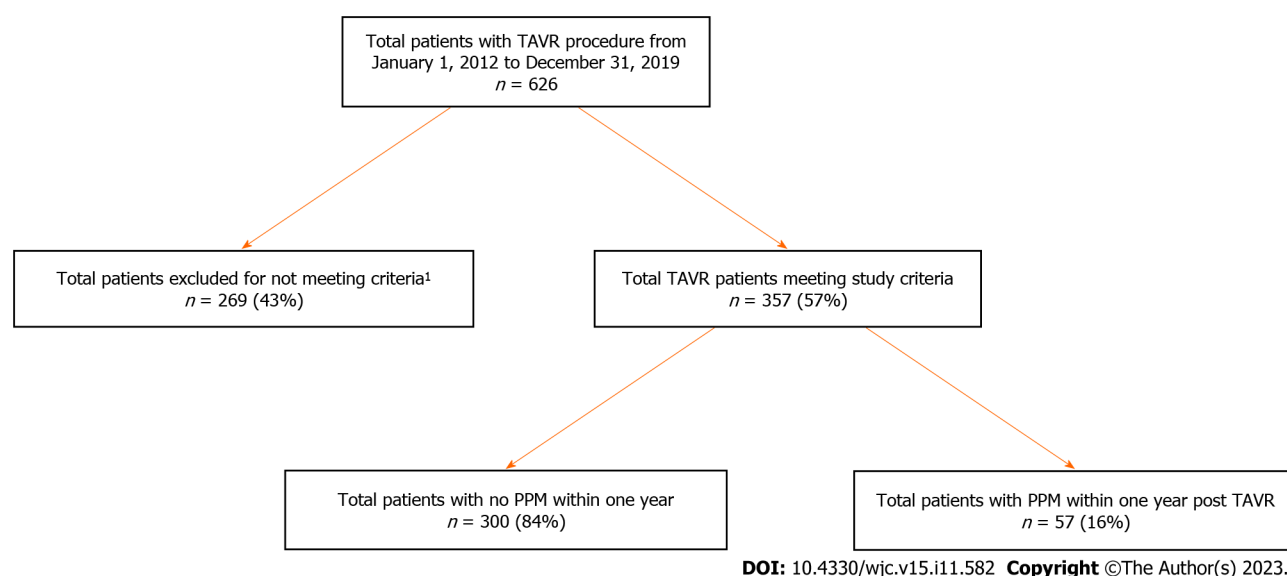


Figure 1 Study cohort distribution. ¹Patients with prior history of permanent pacemakers placement, international classification of disease placement, unsuccessful procedures, died during the procedure, had a conversion to open procedures were excluded from the study. PPM: Permanent pacemakers; TAVR: Transcatheter aortic valve replacement.

Follow-up and clinical outcomes

The patients were followed up one year postprocedure and clinical outcome data were evaluated at in-hospital, 30-d, and at 1-year post-TAVR. In-hospital outcomes data included length of hospital stay. 30-d and 1-year outcomes studied will include all-cause mortality, HF admission, and hospitalization for MI or stroke as defined by the Valve Academic Research Consortium two endpoint criteria[29-34]. The causes of mortality were also evaluated to determine whether they were cardiovascular or non-cardiovascular.

Statistical analysis

Patient characteristics were described using mean $\pm$ SD for normal continuous variables, medians and interquartile range (IQR) for non-normal continuous variables, and counts and percentages for categorical and ordinal variables. Characteristics of patients who received PPM implantation within one year and those who did not receive PPM implantation within one year were compared using a *t*-test, Wilcoxon-rank sum test, Fisher's exact test, or the Kruskal-Wallis test as appropriate.

Incidence of PPM implantation was reported by age group, sex, preoperative risk, valve type, prior BV, procedure time, preoperative EKG findings, QRS intervals, QTc intervals, and prior conduction defects. *P* values reported were derived from Fisher's exact test or the Kruskal-Wallis test. Unadjusted odds ratios (OR) for PPM implantation were calculated for variables selected a priori, which were thought to be independently associated with pacemaker placement. Variables selected a priori with significant unadjusted OR and variables with $P < 0.10$ in a univariate comparison were considered for a multivariable logistic regression model to predict PPM implantation.

The collinearity between prior RBBB, QRS intervals, and QTc intervals was examined. Abnormal QRS intervals were strongly associated with PPM implantation among patients with RBBB but also among patients without RBBB. As such, we kept both terms in the model. Prolonged QTc interval also appeared to be a strong predictor of PPM implantation. However, there was not a significant association between QTc interval and PPM implantation after stratifying by abnormal QRS interval. Adjusted ORs, 95% confidence intervals (CI), and *P* values were reported. The significant *P* value was set to < 0.05 .

Clinical outcomes at 30 d and one year were reported among patients with PPM implantation within one year and those without. The median length of stay was compared using a Wilcoxon rank-sum test. All other clinical outcomes were regressed on PPM and adjusted for patient characteristics that were significantly different at baseline (diabetes). Adjusted ORs, 95%CI, and *P* values were reported. Differences in survival in the year following TAVR by cohort (no PPM, PPM) were compared using Kaplan-Meier curves and a log-rank test.

RESULTS

Study population clinical characteristics

The baseline demographic and clinical characteristics of the study cohort are presented in Table 1. The mean age of the population was 80.8 years, comparable for both cohorts (81.0 years for no PPM and 80.3 years for the PPM). 52.7% of the population were male, and the average BMI was 30.7 kg/m². 66% of the population had a high operative risk (STS $> 8\%$), which was comparable between the 2 populations. Over four-fifths had CAD (87.1%) and HF (93.6%), and two-thirds of

the patients had at least NYHA class III HF. Besides type 2 DM, which was more common in the PPM cohort than the non-PPM cohort (59.6% *vs* 40.7%; $P = 0.009$), there were no differences in the comorbidities or cardiovascular risk factors, as shown in [Table 1](#).

Baseline EKG and echocardiographic characteristics

Baseline EKG and echocardiographic findings as shown in [Table 2](#). Compared to patients without PPM, patients with PPM were found to be more likely to have a supraventricular arrhythmia (atrial fibrillation, atrial flutter, or junctional rhythm) (No PPM: 23.7%; *vs* PPM: 36.9%. $P = 0.054$). Baseline RBBB was found to be significantly higher in the PPM patients (No PPM: 11% *vs* PPM: 32%; $P < 0.001$). Prolonged QRS ≥ 120 ms and prolonged QTc (≥ 470 ms) were found to be higher in the PPM cohorts: (No PPM: 21% *vs* PPM: 47%, $P < 0.001$ and No PPM: 23% *vs* PPM: 47%, $P < 0.001$ respectively). There were no significant differences noted in the other conduction abnormalities noted. As shown in [Table 2](#), there was no echocardiographic difference in baseline LVEF or other parameters.

Procedure characteristics and periprocedural complications

The procedure characteristics shown in [Table 3](#) demonstrated that 96.6% of the procedures where elective femoral access was used in 95.2% of the patients, 53.8% of the valve were balloon-expandable with no differences in the two cohorts. Although the PPM patients received a mildly larger mean valve size (27.3 mm *vs* 26.8 mm), this was not statistically significant ($P = 0.266$). The mean valve index was 129.4 and was not different in the two cohorts. However, a marginally significant higher procedure time of 1.6 h in the PPM cohort when compared to the no PPM cohort (1.4 h) ($P = 0.056$).

There was no difference in perioperative complications of stroke (0.3%), atrial fibrillation/flutter (0.6%), bleeding (2.2%), and blood transfusion (0.3%) between the two cohorts. Also, although we observed no difference in the occurrence of type I AV block, perioperative complete heart block occurred at a significantly higher rate in the PPM cohort (40.4%), in comparison with no PPM cohort (0.3%); $P < 0.001$.

PPM implantation timing, indications, and incidence

The study found that 57 out of 357 patients (16%) required PPM placement within one year following TAVR. The median time to implantation was two days. One-fourth of the patients received PPM within one day following TAVR, half received it within two days following TAVR, and three-quarters received it within nine days post-TAVR. A dual-chamber pacemaker was implanted in 56.2% of patients, a single-chamber in 24.6%, and a biventricular pacemaker type were placed in 8.8% of patients. Complete AV block was the predominant indication for PPM placement (66.7%), followed by CHF with LV dysfunction (10.5%), symptomatic bradycardia (8.8%), and symptomatic second-degree AV block (1.8%).

As presented in [Table 4](#), the incidence of PPM was significantly higher in patients with baseline RBBB (35% *vs* 13%, $P < 0.001$), prolonged QRS ≥ 120 (30% *vs* 11%, $P < 0.001$), and prolonged QTc (29% *vs* 12%, $P < 0.001$) in comparison with the no PPM cohort. Further analysis showed that when compared to patients with normal QRS interval (< 100), patients with QRS > 100 ms interval had a higher PPM incidence for every 20ms above the normal QRS interval ([Table 5](#)). Also, the occurrence of preoperative supraventricular arrhythmia (A. fib, a flutter, junctional rhythm), was associated with a higher incidence of PPM when compared to sinus rhythm with marginal significance (22.8% *vs* 13.6%; $P = 0.055$).

Although the self-expanding valve (SEV) had a higher pacemaker incidence of 17.6% compared to the balloon-expandable valve (14.6%), this did not achieve statistical significance ($P = 0.471$). A higher procedure time of 1.5 h or more had a marginally significant higher PPM incidence of 20.6% compared to the procedure time of < 1.5 h ($P = 0.071$). There was also no significant association between age, sex, preoperative risk, or prior BV and a higher incidence of PPM placement in our cohort.

Predictors of PPM implantation

Positive predictors of PPM implantation in the cohort after multivariate analysis is shown in [Table 6](#). As shown in [Table 6](#), age, sex, prior AV replacement, self-expandable valve, valve index, operative risk, and aortic valve area were not significantly predictive of PPM Placement in our cohort. The odds of PPM implantation in patients with prior RBBB was 3.73 times that in patients without prior RBBB (95%CI: 1.92-7.26; $P < 0.001$). QRS interval ≥ 120 ms has 3.45 odds of PPM implantation (95%CI: 1.91-6.23, $P < 0.001$) compared to patients with normal QRS intervals. Although we observed that compared to patients with normal QTc interval, those with prolonged QTc interval had a 2.94 OR of PPM placement (95%CI: 1.64-5.28, $P < 0.001$); due to collinearity between QRS and QTc intervals, after stratification by abnormal QRS interval, there was no significant association between QTc intervals and PPM implantation. Further analysis showed an incremental impact of baseline prolonged QRS duration with reference to the normal value of < 100 ms. There was a consistently significant increase in the OR for every 20 ms increase in the QRS duration above 100 ms as shown in [Figure 2](#).

After further multivariate analysis and adjusting the OR using a logistic regression model of PPM implantation regressed on baseline differences, diabetes, prior RBBB, QRS interval, and preoperative supraventricular arrhythmias, baseline type 2 DM, and abnormal QRS (≥ 120 ms), remained a significant predictor of PPM implantation (aOR: 2.16; CI: 1.18-3.94; $P = 0.012$), (aOR: 2.18; CI: 1.02-4.66; $P = 0.045$) respectively ([Table 7](#)). Baseline supraventricular arrhythmia had marginally significantly higher odds of PPM implantation when compared to sinus rhythm after multivariate-adjusted analysis (aOR: 1.82; CI: 0.97-3.42; $P = 0.062$) ([Table 7](#)).

Follow-up and clinical outcomes

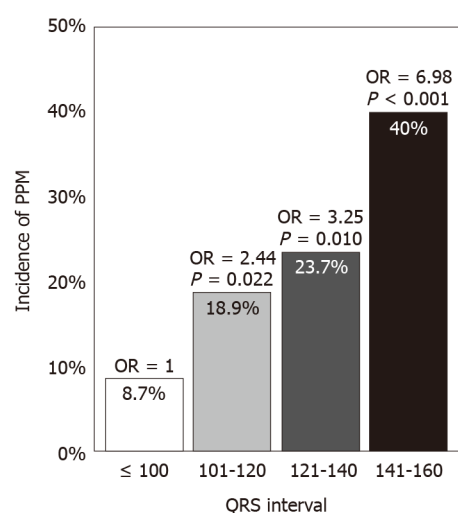
All the patients we have followed up for one year from TAVR or until death using MCHS electronic medical records. For deceased patients, we obtained the primary and secondary causes of death from the hospital records. For those not

Table 2 Baseline electrocardiographic and echocardiogram findings

	All <i>n</i> = 357	No PPM <i>n</i> = 300	PPM <i>n</i> = 57	<i>P</i> value
EKG rhythm abnormalities				0.054
Sinus	265 (74.2)	229 (76.3)	36 (63.2)	
Atrial fibrillation	84 (23.5)	66 (22.0)	18 (31.6)	
Atrial flutter	4 (1.1)	2 (0.7)	2 (3.5)	
Junctional rhythm	2 (0.6)	1 (0.3)	1 (1.8)	
Other	2 (0.6)	2 (0.7)	0 (0)	
Sinus bradycardia	38 (10.6)	35 (11.7)	3 (5.3)	0.229
Sinus tachycardia	3 (0.8)	3 (1)	0 (0)	1.00
Conduction abnormalities				
RBBB	51 (14.3)	33 (11)	18 (31.6)	< 0.001
LBBB	29 (8.1)	24 (8)	5 (8.8)	0.794
AV block I	55 (15.4)	46 (15.3)	9 (15.8)	1.00
AV block IIa	0	0	0	-
AV block IIb	0	0	0	-
AV block III	0	0	0	-
Bifascicular block	5 (1.4)	5 (1.7)	0 (0)	1.00
Left anterior fascicular block	16 (4.5)	12 (4)	4 (7)	0.299
Left posterior fascicular block	1 (0.3)	0 (0)	1 (1.8)	0.16
Abnormal QRS (≥ 120 ms)	89 (25)	62 (20.7)	27 (47.4)	< 0.001
Prolonged QTc (≥ 470 ms)	97 (27.2)	70 (23.4)	27 (47.4)	< 0.001
Echocardiogram findings				
Left ventricular EF	58.1 (12.7)	58.5 (11.9)	56 (16.1)	0.272
AV peak velocity	4.1 (0.7)	4.1 (0.7)	4.1 (0.7)	0.957
AV mean gradient	42 (14.7)	42.1 (14.7)	41.3 (14.8)	0.707
AV peak gradient	68.4 (21.9)	68.4 (21.7)	68.1 (23.2)	0.933
AV regurgitation				0.247
None	147 (43.9)	116 (41.6)	31 (55.4)	
Mild	162 (48.4)	141 (50.5)	21 (37.5)	
Moderate	23 (6.9)	19 (6.8)	4 (7.1)	
Severe	3 (0.9)	3 (1.1)	0 (0)	
MV regurgitation				0.242
None	28 (8.2)	24 (8.4)	4 (7.1)	
Mild	255 (74.8)	208 (73.0)	47 (83.9)	
Moderate	52 (15.2)	48 (16.8)	4 (7.1)	
Severe	6 (1.8)	5 (1.8)	1 (1.8)	
TV regurgitation				0.129
None	19 (5.6)	19 (6.6)	0 (0)	
Mild	272 (79.8)	226 (79.0)	46 (83.6)	
Moderate	43 (12.6)	36 (12.6)	7 (12.7)	
Severe	7 (2.1)	5 (1.7)	2 (3.6)	

Pulmonary artery pressure	46.9 (14.1)	45.9 (13.1)	51.6 (17.7)	0.073
Annulus area	0.8 (0.2)	0.8 (0.2)	0.8 (0.3)	0.968
Aortic sinus diameter	3.2 (0.5)	3.2 (0.5)	3.3 (0.5)	0.074
CT annulus diameter 1	25.1 (4.4)	25 (4.3)	25.2 (4.8)	0.849
CT annulus diameter 2	24.2 (4.2)	24.1 (4.2)	24.8 (4.3)	0.273
LV diastolic diameter	4.7 (0.8)	4.7 (0.8)	4.8 (0.8)	0.290
LVOT	20.9 (1.9)	20.8 (1.9)	21.1 (1.9)	0.354

P values and mean $\pm$ SD from a 2-sample *t*-test reported for continuous variables. Counts (%) and *P* values from Fisher's exact test were reported for categorical variables. RBBB: Right Bundle Branch Block; LBBB: Left Bundle branch block; CT: Computed tomography; AV: Aortic valve; MV: Mitral valve; TV: Tricuspid valve; PPM: Permanent pacemakers; LVOT: Left ventricular outflow tract.



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Figure 2 Incidence and odds ratios for permanent pacemakers implantation by QRS interval. PPM: Permanent pacemakers; OR: Odds ratios.

available within the MCHS, a death certificate was obtained from the state vital statistics record office. Compared to those without a PPM placement, patients with a PPM placement had a significantly longer median length of hospital stay (5 d *vs* 2 d; *P* < 0.001).

30-day and 1-year outcome

Clinical outcomes of any hospitalization, HF hospitalization, nonfatal MI, stroke, and mortality are presented in Figure 3. There was no difference in the clinical outcomes within 30 d. However, at one year, patients with PPM placement had a significantly higher incidence of hospitalization for HF (28% *vs* 14% *P* = 0.022) and nonfatal MI (9% *vs* 2%; *P* = 0.031). There was no significant difference in the incidence of stroke or all-cause mortality, as in Figure 3. Multivariate adjustments adjusted OR for the clinical outcome at one year revealed that compared to the no PPM cohort, the PPM implantation cohorts had a higher adjusted OR of HF hospitalization (aOR: 2.2; CI: 1.1-4.3; *P* = 0.022), and nonfatal MI (aOR: 3.9; CI: 1.1-14; *P* = 0.031) without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; *P* = 0.796) at one year.

DISCUSSION

Incidence, indicators, and dependency of pacemaker

Our study found that 16% of the patients required PPM placement within one year following TAVR with a median time to implantation of 2 days and 75% of the patients receiving the pacemakers within nine days. The balloon-expandable ESV was used in 54% of the procedures, which resulted in a PPM implantation rate of 14.6%. In comparison, the auto-expanding MCRS was implanted in 46%, resulting in a 17.6% PPM implantation rate (*P* = 0.471). This PPM implantation rate was roughly at the median rate observed in a recent systematic review involving 17139 patients that showed a PPM implantation rate between 2.3% and 36.1% [35]. Also, in this study, MCRS resulted in higher PPM implantation rates (16.3%-37.7%), whereas ESV valves resulted in a lower pacemaker rate (4%-24%), which was also comparable to our study [35]. Similarly, Ullah *et al* [6], in a recent large-scale meta-analysis involving 31261 patients with a mean age of 81 $\pm$ 8 years, similar to our population, reported a mean PPM rate of 19.8% and a net rate ranging from 0.16% to 51.1% [6].

Table 3 Procedural characteristics and peri-procedural complications

	All <i>n</i> = 357	No PPM <i>n</i> = 300	PPM <i>n</i> = 57	<i>P</i> value
Urgency				0.699
Elective	344 (96.6)	288 (96.3)	56 (98.2)	
Emergency	12 (3.4)	11 (3.7)	1 (1.8)	
Valve				0.471
Balloon expandable	192 (53.8)	164 (54.7)	28 (49.1)	
Self-expandable	165 (46.2)	136 (45.3)	29 (50.9)	
Valve size	26.9 (3)	26.8 (2.9)	27.3 (3)	0.266
Valve index	129.4 (14.9)	129.3 (15.1)	129.9 (13.5)	0.792
Valve sheath access site				0.270
Right femoral	241 (68.5)	206 (69.8)	35 (61.4)	
Left femoral	94 (26.7)	72 (24.4)	22 (38.6)	
Right subclavian	2 (0.6)	2 (0.7)	0 (0)	
Left subclavian	4 (1.1)	4 (1.4)	0 (0)	
Right radial	2 (0.6)	2 (0.7)	0 (0)	
Transaortic	9 (2.6)	9 (3.1)	0 (0)	
Procedure time	1.5 (0.8)	1.4 (0.8)	1.6 (0.9)	0.056
Perioperative complications				
Atrial fibrillation	1 (0.3)	1 (0.3)	0 (0)	1.00
Atrial flutter	1 (0.3)	1 (0.3)	0 (0)	1.00
AV block I	6 (1.7)	6 (2)	0 (0)	0.595
AV block II	0	0	0	-
Complete AV block	24 (6.7)	1 (0.3)	23 (40.4)	< 0.001
Ventricular tachycardia	0	0	0	-
Ventricular fibrillation	0	0	0	-
Bleeding	8 (2.2)	8 (2.7)	0 (0)	0.365
Stroke	1 (0.3)	1 (0.3)	0 (0)	1.00
Transfusion	3 (0.8)	3 (1)	0 (0)	1.00
Site bleeding	0	0	0	-
Left axis deviation	3 (0.8)	2 (0.7)	1 (1.8)	0.408
LBBB	0	0	0	-
RBBB	0	0	0	-
Left anterior fascicular block	0	0	0	-
Left posterior fascicular block	0	0	0	-
MI	1 (0.3)	1 (0.3)	0 (0)	1.00
Other	31 (8.7)	24 (8)	7 (12.3)	0.305

P values and mean $\pm$ SD from a 2-sample *t*-test reported for continuous variables except for procedure time which was heavily right skewed. Median (IQR) and *P* value from a Wilcoxon rank sum test reported for procedure time. Counts (%) and *P* values from Fisher's exact test reported for categorical variables. The following tests excluded patients due to missing values: Procedure urgency (1), valve index (2), valve sheath access site (5), procedure time (37). RBBB: Right Bundle Branch Block; LBBB: Left Bundle branch block; AV: Aortic valve; MI: Myocardial infarction; PPM: Permanent pacemakers.

Table 4 Incidence of permanent pacemakers implantation

Variable	Group	n	Incidence (%)	P value
Age	< 65 yr	10	0 (0)	0.284
	65-85 yr	235	41 (17.4)	
	> 85 yr	112	16 (14.3)	
Sex	Male	169	27 (16.0)	1.00
	Female	188	30 (16.0)	
Pre-operative risk	Low	37	3 (8.1)	0.168
	Intermediate	84	12 (14.3)	
	High	235	41 (17.4)	
Valve type	Balloon expanding	192	28 (14.6)	0.471
	Self-expanding	165	29 (17.6)	
Prior BAV	Yes	184	35 (19.0)	0.116
	No	170	21 (12.4)	
Procedure time	< 1.5 h	160	20 (12.5)	0.071
	≥ 1.5 h	160	33 (20.6)	
Pre-op EKG rhythm abnormalities	Sinus	265	36 (13.6)	0.054
	Atrial fibrillation	83	18 (21.4)	
	Atrial flutter	4	2 (50.0)	
	Junctional rhythm	2	1 (50.0)	
	Other	2	0 (0)	
RBBB	Yes	51	18 (35.3)	< 0.001
	No	306	39 (12.7)	
LBBB	Yes	29	5 (17.2)	0.794
	No	328	52 (15.9)	
AV block I	Yes	55	9 (16.4)	1.000
	No	302	48 (15.9)	
Bifascicular block	Yes	5	0 (0)	1.000
	No	352	57 (16.2)	
Left anterior fascicular block	Yes	16	4 (25.0)	0.299
	No	341	53 (15.5)	
Left posterior fascicular block	Yes	1	1 (100)	0.160
	No	356	56 (15.7)	
QRS interval	Abnormal (≥ 120 ms)	89	27 (30.3)	< 0.001
	Normal	267	30 (11.2)	
QTc interval	Prolonged (≥ 470 ms)	97	27 (27.8)	< 0.001
	Normal	259	30 (11.6)	

EKG: Electrocardiographic; BAV: Balloon aortic valvuloplasty; RBBB: Right bundle branch block; LBBB: Left Bundle branch block; AV: Aortic valve.

Fadahunsi *et al*[8], in the recent retrospective analysis of 9785 patients from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, reported a median time of 3 d (IQR: 1 d-6 d) from TAVR to PPM implantation which also correlated with our study[8].

The most common indications for post-TAVR PPM implantation reported in several studies are high-grade AV block, new-onset or worsening LBBB, symptomatic bradycardia, unstable nodal conduction, and progressively worsening first-degree AV block with LBBB[16,36,37]. Similarly, in our study, complete AV block was the predominant indication for

Table 5 Incidence of permanent pacemakers implantation by QRS duration

Variable	Group	n	Incidence	P value
QRS interval	≤ 100	194	17 (8.8)	< 0.001
	101-120	74	14 (18.9)	
	121-140	38	9 (23.7)	
	141-160	40	16 (40.0)	
	161-180	10	1 (10.0)	
Pre-op EKG supraventricular arrhythmia	Supraventricular arrhythmia ¹	91	21 (22.8)	0.05
	Sinus rhythm	265	36 (13.6)	

¹Supraventricular arrhythmia includes-atrial fibrillation, atrial flutter and junctional rhythms.
EKG: Electrocardiographic.

Table 6 Odds ratios for permanent pacemakers implantation

	OR	95%CI	P value
Age (per 5 yr)	0.95	0.8-1.12	0.549
Male	1.00	0.57-1.76	0.996
Prior AV replacement	0.21	0.03-1.55	0.125
CAD	1.31	0.53-3.25	0.563
HF	1.29	0.37-4.48	0.693
Self-expanding (Reference: balloon)	1.25	0.71-2.20	0.442
Prior conduction defect-RBBB	3.73	1.92-7.26	< 0.001
Prior conduction defect-LBBB	1.11	0.40-3.03	0.845
Prior conduction defect-LFAB	1.81	0.56-5.83	0.319
Valve index	1.00	0.98-1.02	0.806
Abnormal QRS (≥ 120 ms)	3.45	1.91-6.23	< 0.001
Prolonged QTc (≥ 470 ms)	2.94	1.64-5.28	< 0.001
Aortic valve area > 0.75	1.31	0.73-2.36	0.364
High preoperative risk (Reference: Low)	2.40	0.70-8.17	0.163
Intermediate preoperative risk (Reference: Low)	1.89	0.50-7.14	0.348
Supraventricular Arrhythmia on pre-op EKG (Reference: Sinus)	1.88	1.03-3.43	0.039

EKG: Electrocardiographic; RBBB: Right bundle branch block; LBBB: Left Bundle branch block; AV: Aortic valve; LFAB: Left anterior fascicular block; CAD: Coronary artery disease; HF: Heart failure; OR: Odds ratios.

PPM placement (66.7%), followed by CHF with LV dysfunction (10.5%), symptomatic bradycardia (8.8%), and symptomatic second-degree AV block (1.8%).

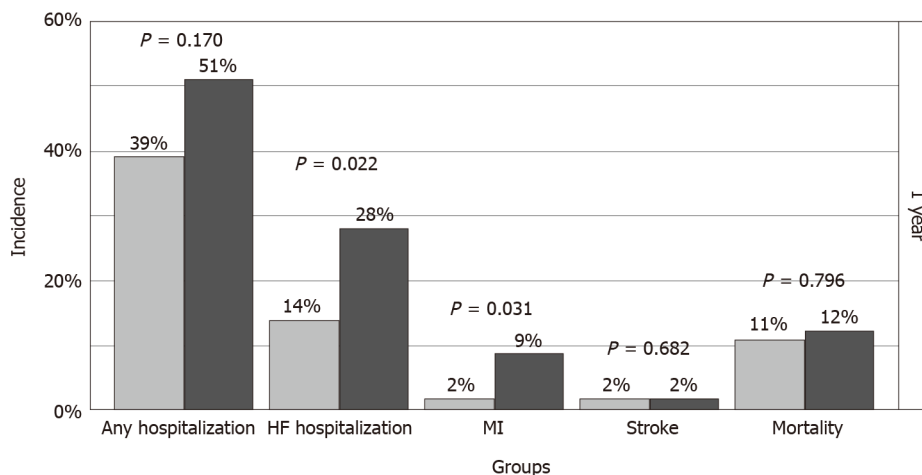
Unlike most other studies, our study went further to evaluate the rate of pacemaker dependency following pacemaker interrogation at 1 mo and found that 78.9% of PPM patients were found to be pacemaker dependent one month after TAVR. This finding is supported by a previous observation that about half of the patients developing conduction abnormalities after TAVR improve over time without PPM implantation due to the resolution of reversible procedural per-aortic edema and inflammation caused during the procedure[16,38]. Although the exact proportion of patients and timing of resolution of this conduction abnormality remains unclear, from our study, it can be inferred that one-fifth of post-TAVR PPM patients may not be dependent on their pacemakers by one month, possibly due to the resolution of their transient abnormalities.

As presented in Table 3, the incidence of PPM was significantly higher in patients with RBBB (35% *vs* 13%, $P < 0.001$), prolonged QRS ≥ 120 without left or right bundle branch morphology, (30% *vs* 11%, $P < 0.001$), and prolonged QTc (29% *vs* 12%, $P < 0.001$). Further analysis showed that when compared to patients with normal QRS interval (≤ 100), patients with prolonged QRS interval had a higher PPM incidence for every 20 ms above the normal QRS interval (Figure 2).

Table 7 Adjusted odds ratios for permanent pacemakers implantation

	aOR	95%CI	P value
Diabetes	2.16	1.18-3.94	0.012
Prior RBBB	2.15	0.91-5.09	0.081
Abnormal QRS (≥ 120 ms)	2.18	1.02-4.66	0.045
Supraventricular arrhythmia on pre-op EKG (Reference: Sinus rhythm)	1.82	0.97-3.42	0.062

Adjusted odds ratios generated from logistic regression model of permanent pacemakers implantation regressed on diabetes, prior right bundle branch block, QRS interval, and pre-operative electrocardiographic Supraventricular arrhythmias. EKG: Electrocardiographic; RBBB: Right bundle branch block; aOR: Adjusted odds ratios.



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Figure 3 Clinical outcomes of transcatheter aortic valve replacement patients for permanent pacemakers and no permanent pacemakers patients. MI: Myocardial infarction; HF: Heart failure.

Novel and traditional predictors of PPM placement

Several studies have reported demographic, clinical, anatomic, EKG, and valve-related risk factors for conduction abnormalities requiring pacemakers after TAVR[6,8,12,16,19,20,37,38]. Siontis *et al*[18] from the systematic review and meta-analysis, reported that male sex, baseline first-degree AV block, RBBB, LBBB, left anterior hemiblock, intraprocedural AV block was associated with a high incidence of PPM placement post-TAVR[18]. Several other similar multiple-center studies, systematic reviews, and meta-analyses have shown similar risk factors for post-TAVR pacemaker requirements. However, none to our knowledge investigated the impact of nonspecific interventricular conduction defect on post-TAVR pacemaker requirement (defined in the study as QRS > 120 without LBBB and RBBB), which we found to be predictive of PPM placement[6,8,12,16,19,20,37,38].

Due to the potential correlation between RBBB, LBBB, and QRS duration, we evaluated PPM incidence by prolonged QRS stratified by prior conduction abnormalities and found that patients without prior RBBB or LBBB but had QRS ≥ 120 ms had a higher PPM incidence compared to those with QRS interval < 120 ms (23% *vs* 11%; $P = 0.05$). Also, stratifying PPM incidence by baseline prolonged QTc interval [> 470 ms], abnormal QRS canceled the effect of QTc on PPM requirement due to collinearity between the QRS duration and QTc interval. Further multivariate analysis revealed a consistently significant increase in the OR of the PPM requirement for every 20 ms increase in the QRS duration above 100 ms, as shown in Figure 2. Overall, in patients with QRS > 120 ms, our study was found to have an adjusted OR of 2.18 (95%CI: 1.02-4.66, $P = 0.045$) for post-TAVR PPM placement.

Another interesting finding in our study is that baseline type 2 DM was a significant predictor of PPM placement with an adjusted OR of 2.16 [95%CI: 1.18-3.94, $P = 0.012$], a finding that was scarcely reported in several studies. Notably, Sammour *et al*[16], in a recent systematic review, reported that type 2 DM was a pre-procedural predictor of new-onset LBBB, which is a known indication for PPM requirement. This further supports the findings of our study[16].

Among the traditional risk factors for PPM implantation, our study found that the odds of pacemaker placement in patients with prior RBBB was 3.73 (95%CI: 1.92-7.26; $P < 0.001$) times those without prior RBBB in the unadjusted model which tended towards significance following multivariate analysis (aOR: 2.15; 95%CI: 0.91-5.09; $P = 0.081$). Contrary to the widely reported increased PPM implantation risk inherent with the use of SEV[8,6,16], our study did not demonstrate a significantly higher risk of PPM placement with the SEV when compared to the balloon-expandable ESV (OR: 1.25; CI: 0.71-2.20; $P = 0.442$). This finding can be explained by the fact that our institution started implanting self-expandable

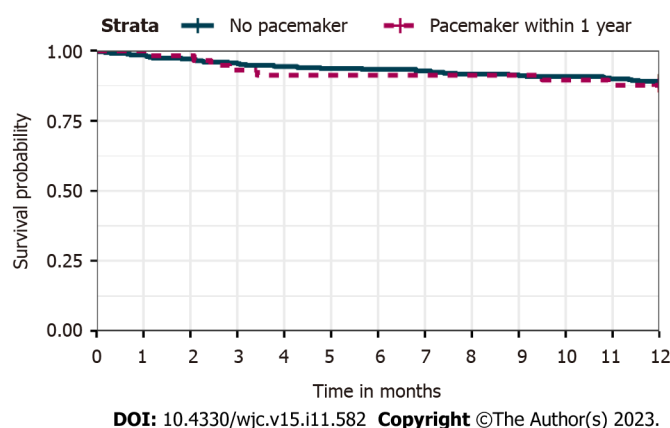


Figure 4 Kaplan-Meier survival curve for one year following transcatheter aortic valve replacement.

valves in 2015, three years after they started the balloon-expandable valve; this delay presumably helps the TAVR operators advance in the learning curve and gain considerable experience with the TAVR procedure[39]. Also, over the last few years, there have been manufacturer-assisted modifications of self-expandable valve implantation techniques in our health system, which emphasize shallow valve implantation depth and cusp overlap in order to avoid the anatomical vicinity of the conduction tissues during TAVR procedures. This performance improvement process, which resulted in lower SEV-related PPM implantation, was informed by contemporary studies that demonstrated that implantation depth relative to membranous septum length is an independent risk factor for post-TAVR PPM implantation[12,40].

An essential clinical significance of the findings of our study is its ability to enhance clinical decision-making prior to TAVR procedures, assist in patients' overall PPM risk evaluation, and choice of valve system to implant. A notable risk prediction score that can be refined by our findings of increased PPM risk for QRS > 100 ms is the Emory risk score for the prediction of PPM requirement following TAVR developed by Kiani *et al*[41]. This scoring system incorporates the history of RBBB (2 points), QRS interval ≥ 140 ms (one-point), syncope (one-point), valve oversizing $\geq 16\%$ (1 point) and has an OR of 2.2 per every point increase ($P < 0.001$)[41]. Adjusting the QRS duration cut-off may increase the sensitivity of this scoring system. However, given the relatively small size of our cohort, further, more extensive studies will be needed to validate this finding.

Clinical outcomes

Although PPM implantation in the non-TAVR population has been associated with complications like device infection, pocket erosion or hematoma, lead failure, right ventricular perforation, and lead-induced tricuspid regurgitation which might lead to higher mortality[42,43], studies on clinical outcomes in TAVR patients with pacemaker have shown conflicting results with the majority of studies showing no mortality impact of PPM implantation at 1 year[6,16].

At 30 d post TAVR, our study showed no significant increase in clinical outcomes of all-cause mortality, hospitalization for HF, nonfatal MI, and stroke. However, at 1 year post-TAVR, relative to the no PPM cohort, the PPM patients had a significantly higher incidence of hospitalization for HF (28% *vs* 14% $P = 0.022$), and nonfatal MI (9% *vs* 2%; $P = 0.031$) with no mortality difference **Figure 3**. Further evaluation of one-year survival using a Kaplan-Meier curve showed no survival difference between the two cohorts (**Figure 4**). This lack of impact of PPM implantation all-cause mortality or survival was also echoed by several multiple studies[44-51].

Similar to our finding of higher odds of HF hospitalization (aOR: 3.9; CI: 1.1-14; $P = 0.031$), López-Aguilera *et al*[52] in a single-center prospective study, and Chamandi *et al*[53] in the multicenter retrospective study both showed an increased risk of hospitalization due to HF in post-TAVR PPM patients[52,53].

Study limitations

This study is a single-center retrospective analysis of our experience as a tertiary cardiology referral health center in the Midwestern United States. Our findings may not reflect the experience in other regions. Also, there was no randomization of the valves to patients based on established criteria but based on the decision of the multidisciplinary TAVR team. As a result, the distribution of valves, patient selection, and valve sizes in each cohort might have been affected. However, the observed relatively equal distribution of these and other patient-related variables between each cohort suggests that this factor might not have significantly contributed to our study findings.

CONCLUSION

Patients with baseline type 2 DM and QRS duration > 100 ms, regardless of the presence of right or left bundle branch morphology, are at increased risk of permanent pacemaker implantation post-TAVR. A linear association may exist between post-TAVR PPM incidence and every 20 ms prolongation in QRS duration > 100 ms. Patients with PPM implantation may have higher risks of HF hospitalization and non-fatal MI at 1 year post TAVR. In light of the expanded

indication of TAVR and the clinical and economic impact of PPM implantation, multidisciplinary heart teams should meticulously risk-stratify pre-TAVR patients regarding PPM requirements using this new evidence.

ARTICLE HIGHLIGHTS

Research background

Conduction abnormalities requiring permanent pacemakers (PPM) are short-term complications following transcatheter aortic valve replacement (TAVR), and their clinical outcomes remain conflicting. Potential novel predictors of post-TAVR PPM, like QRS duration, QTc prolongation, and supraventricular arrhythmias, have been poorly studied.

Research motivation

The evaluation of novel predictors of PPM placement post TAVR light nonspecific interventricular conduction defect, will enhance clinical decision making prior to the TAVR procedure, assist in patient pacemaker risk evaluation, and further refine the indications of pacemaker placement.

Research objectives

To determine the timing, incidence and novel predictors of PPM implantation post TAVR. To evaluate and compare clinical outcomes of length of hospitalization, heart failure (HF) hospitalization, myocardial infarction (MI) and cardiovascular death post TAVR between patients requiring permanent pacemaker implantation and others without pacemaker at 1 year post TAVR procedure.

Research methods

A retrospective cohort study that identified patients with TAVR between January 1, 2012 to December 31, 2019. The cohort was divided into those with post-TAVR PPM and those without PPM. Both groups were followed for one year.

Research results

Of 357 patients that met inclusion criteria, the mean age was 80 years, 188 (52.7%) were male, and 57 (16%) had a PPM implantation. Baseline demographics, valve type, and cardiovascular risk factors were similar except for type II diabetes mellitus (DM), which was more prevalent in the PPM cohort (59.6% *vs* 40.7%; $P = 0.009$). The PPM cohort had a significantly higher rate of pre-procedure right bundle branch block, prolonged QRS > 120 ms, prolonged QTc > 470 ms, and supraventricular arrhythmias. There was a consistently significant increase in the odds ratio (OR) of PPM implantation for every 20 ms increase in the QRS duration above 100 ms: QRS 101-120 (OR: 2.44; CI: 1.14-5.25; $P = 0.022$), QRS 121-140 (OR: 3.25; CI: 1.32-7.98; $P = 0.010$), QRS 141-160 (OR: 6.98; CI: 3.10-15.61; $P < 0.001$). After model adjustment for baseline risk factors, the OR remained significant for type II DM and QRS > 120. The PPM cohort had a higher OR of HF hospitalization and nonfatal MI without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; $P = 0.796$) at one year.

Research conclusions

Pre-TAVR type II DM and QRS duration > 120, regardless of the presence of bundle branch blocks, are predictors of post-TAVR PPM. Post-TAVR, patients with PPM implantation may have higher odds of HF hospitalization and non-fatal MI at 1 year.

Research perspectives

In light of the expanded indication of TAVR to involve lower risk patients and the clinical impact of PPM implantation, risk assessment using the predictors outlined in the study will help optimize pre-procedural risk stratification. Further larger multicenter studies will be needed to further investigate the impact of this number predictors and post-TAVR pacemaker requirement.

FOOTNOTES

Author contributions: Nwaedozie S and Garcia-Montilla R designed the research study; Zhang H and Najjar Mojarab J assisted in the data abstraction; Gabor R did the data analysis; Sharma P, Yeung P, Umukoro P, Anderson K, and Soodi D reviewed and edited the final manuscript.

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Observational Study

Clinical impact of portal vein pulsatility on the prognosis of hospitalized patients with acute heart failure

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Abstract**BACKGROUND**

Heart failure (HF) causes extracardiac organ congestion, including in the hepatic portal system. Reducing venous congestion is essential for HF treatment, but evaluating venous congestion is sometimes difficult in patients with chronic HF. The portal vein (PV) flow pattern can be influenced by right atrial pressure. Ultrasound images of the PV are quite easy to obtain and are reproducible among sonographers. However, the association between PV pulsatility and the condition of HF remains unclear. We hypothesize that PV pulsatility at discharge reflects the condition of HF.

AIM

To evaluate the usefulness of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

METHODS

This observational study was conducted from April 2016 to January 2017 and April 2018 to April 2019 at Shinko Hospital. We enrolled 56 patients with acute HF, and 17 patients without HF served as controls. PV flow velocity was measured by ultrasonography on admission and at discharge. We calculated the PV pulsatility ratio (PVPR) as the ratio of the difference between the peak and minimum velocity to the peak velocity. The primary endpoint was cardiac death and HF re-hospitalization. The observation period was 1 year from the first hospitalization. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups.

RESULTS

On admission, the PVPR was significantly higher in patients with acute HF than

controls (HF: 0.29 ± 0.20 *vs* controls: 0.08 ± 0.07 , $P < 0.01$). However, the PVPR was significantly decreased after the improvement in HF (admission: 0.29 ± 0.20 *vs* discharge: 0.18 ± 0.15 , $P < 0.01$) due to the increase in minimum velocity (admission: 12.6 ± 4.5 *vs* discharge: 14.6 ± 4.6 cm/s, $P = 0.03$). To elucidate the association between the PVPR and cardiovascular outcomes, the patients were divided into three groups according to the PVPR tertile at discharge (PVPR-T1: $0 \leq \text{PVPR} \leq 0.08$, PVPR-T2: $0.08 < \text{PVPR} \leq 0.21$, PVPR-T3: $\text{PVPR} > 0.21$). The Kaplan-Meier analysis showed that patients with a higher PVPR at discharge had the worst prognosis among the groups.

CONCLUSION

PVPR at discharge reflects the condition of HF. It is also a novel prognostic marker for hospitalized patients with acute HF.

Key Words: Heart failure; Venous congestion; Atrial pressure; Ultrasonography; Portal vein; Prognosis

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Core Tip: Although reducing venous congestion is essential for heart failure (HF) treatment, the assessment of venous congestion is sometimes difficult, especially in patients with recurrent HF. Interestingly, a previous study demonstrated a correlation between right atrial pressure and portal vein (PV) flow pattern. However, the association between PV flow and the condition of HF remains unclear. Therefore, we investigated the clinical usefulness of PV pulsatility in hospitalized patients with HF. We found that PV pulsatility reflected not only the condition of HF but also cardiovascular outcomes. Therefore, PV pulsatility may be a novel prognostic marker for hospitalized patients with HF.

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INTRODUCTION

The prevalence of heart failure (HF) is increasing worldwide, especially in the aging population. Previous studies have reported that patients with HF have more severe frailty and a poorer prognosis than patients with several common diseases, including cancer[1,2]. Therefore, prevention of recurrent acute decompensated HF is of paramount importance.

Extracardiac organ congestion is seen in the advanced stages of chronic HF[3]. When severe right-sided HF is present, liver congestion develops followed by an increase in serum liver aminotransferase and total bilirubin concentrations, indicating a poor prognosis[3]. Thus, reducing venous congestion is essential for HF treatment. However, the assessment of venous congestion is sometimes difficult, especially in patients with recurrent HF.

To evaluate venous congestion, right atrial pressure (RAP) measured by right heart catheterization (RHC) is the most reliable parameter. RHC is difficult to repeat because the process is invasive and costly[4]. For non-invasive assessment, measuring the inferior vena cava (IVC) using ultrasound is the standard method. However, the ultrasound image quality of the IVC is often poor in patients with obesity[4]. Although a previous study reported that intrarenal venous flow has been proposed as venous congestion, reproducible images are difficult to obtain[5]. Therefore, there is a strong demand for a non-invasive and easy-to-use technique for reliable measurement of venous congestion.

The portal vein (PV) is interposed between the capillary network of the splanchnic circulation and the hepatic sinusoids[6]. Ultrasound images of the PV are quite easy to obtain and reproducible among sonographers. Interestingly, previous studies have demonstrated a correlation between RAP and PV flow[7,8]. However, the association between PV flow and the condition of HF remains unclear.

In this study, we aimed to identify the changes in PV flow pattern by the condition of HF and to evaluate the ability of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

MATERIALS AND METHODS

Patients

This study was conducted with hospitalized patients with acute HF starting in April 2016, with the total of 56 enrolled by April 2019. The European Society of Cardiology guideline was used to confirm the diagnosis of HF[9]. We also included 17 patients without HF, such as patients with urinary tract infection, dehydration, and other conditions, who were admitted during the same follow-up period as the acute HF patients and who served as controls. Patients in the control group were always in sinus rhythm. We excluded patients with liver cirrhosis, acute coronary syndrome, carbon dioxide narcosis due to chronic obstructive pulmonary disease, a malignant tumor diagnosed in the past 5 years, and renal

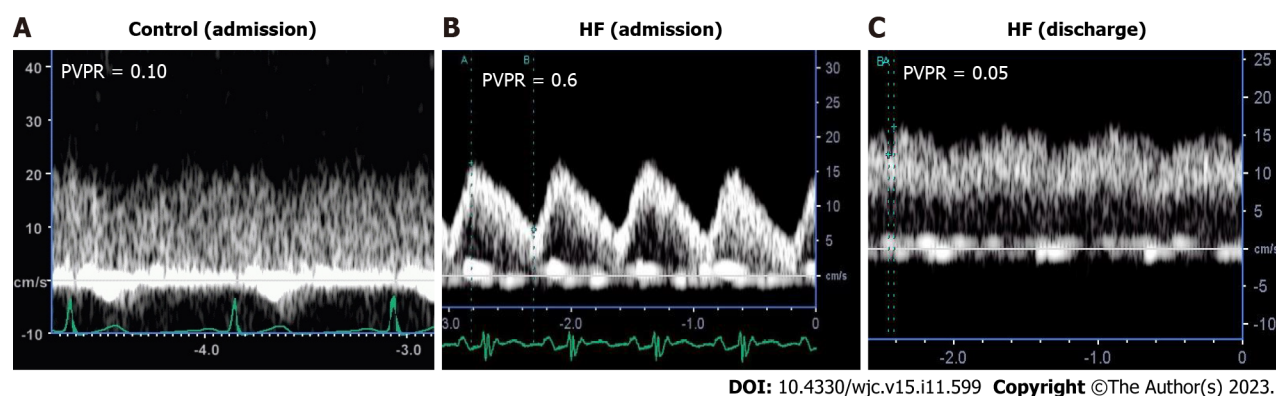


Figure 1 Portal vein flow in the control and heart failure groups. A and B: Representative portal vein (PV) flow waveform in the control (A) and heart failure (HF) (B) groups at admission. Patients with HF had a pulsatile PV flow waveform. Patients in the control group had a continuous PV flow waveform with a significantly higher minimum PV velocity; C: Representative PV flow waveform in a patient with HF at discharge. At discharge, the waveform turned into a continuous pattern. HF: Heart failure; PVPR: Portal vein pulsatility ratio.

replacement therapy.

This study was approved by the Institutional Review Board of Shinko Hospital, and all requirements for written informed consent were waived for the use of the patients' clinical and imaging data.

Study protocol

All of the patients underwent blood tests and ultrasonography on admission and at discharge. The patients with HF were treated according to current guidelines[9]. The treatment goal was to improve clinical HF symptoms and physical examination findings. The primary endpoint was cardiac death and unexpected re-hospitalization for recurrent HF. The observation period was 1 year from discharge. We investigated the prognosis of all patients by outpatient clinic visit and by telephone conversation.

Ultrasound examination

Ultrasound examinations were performed using ultrasound devices (Vivid S5; GE Healthcare, Wauwatosa, WI, United States). Doppler images of PV flow were obtained from right-sided intercostal scanning using a 1.9-6-MHz convex array, and the waveform of PV flow was assessed from the right portal branch (Supplementary Figure 1)[6]. Doppler traces were recorded at the end of expiration. We calculated the PV pulsatility ratio (PVPR) by dividing the difference between the peak velocity and minimum velocity by the peak velocity [(peak velocity - minimum velocity)/peak velocity]. In patients with atrial fibrillation (AF), PV velocity was measured for five heartbeats, and the mean value was used for the analysis.

Statistical analysis

Continuous variables are reported as the mean $\pm$ SD, and categorical variables are reported as number and percentage. For comparisons between groups, we used the Student's *t*-test. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc statistical software, version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Table 1 shows that there were no significant differences in the baseline characteristics between the HF group and the control group, except for age and duration of hospital stay. Among the patients with HF, 32% had a history of HF and 89% had severe symptoms and were classified as New York Heart Association functional class III or IV. Regarding the etiology of HF, 23% of patients with HF had ischemic cardiomyopathy, 25% had non-ischemic cardiomyopathy (including tachycardia-induced cardiomyopathy, idiopathic cardiomyopathy, and cardiac sarcoidosis), and 20% had valvular heart disease.

PV flow reflects RAP[7,8,10]; therefore, we preliminarily confirmed that the minimum PV velocity was negatively correlated with RAP assessed by RHC (data not shown). As shown in Figure 1A and B, the HF group had a pulsatile PV flow waveform, whereas the control group had a continuous PV flow waveform because of the higher minimum PV velocity, indicating a low RAP. Regarding the PVPR, the control group had a significantly lower PVPR than the HF group (Table 2; control: 0.08 ± 0.07 vs HF: 0.29 ± 0.20 , $P < 0.01$).

Next, we investigated how AF affected venous congestion in the setting of HF because AF was a major baseline characteristic in the HF group. There were no significant differences in the tricuspid regurgitation pressure gradient (TRPG), IVC diameter, tricuspid annular plane systolic excursion, and PVPR at admission between the HF group in sinus rhythm

Table 1 Patients' baseline characteristics

Characteristic	HF	Control	P value
No. of patients	56	17	
Age (yr)	78.1 ± 13.1	70.3 ± 12.8	0.03
Male	36 (66)	12 (70)	0.85
Body mass index (kg/m ²)	22.8 ± 4.5	24.4 ± 3.7	0.18
Systolic blood pressure (mmHg)	138.9 ± 33.3	132.2 ± 26.2	0.45
Diastolic blood pressure (mmHg)	84.1 ± 22.3	87 ± 21.3	0.18
Duration of hospital stay (d)	16.9 ± 8.5	8.1 ± 5.2	< 0.01
NYHA classification			
Class II	1 (2)	-	-
Class III	35 (65)	-	-
Class IV	13 (24)	-	-
Atrial fibrillation	29 (51)	0 (0)	-
Etiology of HF			
Ischemic cardiomyopathy	13 (23)	-	-
Non-ischemic cardiomyopathy	14 (25)	-	-
Valvar heart disease	11 (20)	-	-
Other	18 (32)	-	-
History of HF	18 (32)	-	-
In-hospital death	0 (0)	0 (0)	-

Data are *n* (%) or mean ± SD. HF: Heart failure; NYHA: New York Heart Association.

Table 2 Changes in the portal vein pulsatility ratio in control patients and patients with heart failure

Parameter	Control (admission)	HF (admission)	P value
Minimal velocity (cm/s)	14.4 ± 2.3	12.6 ± 4.5	< 0.01
Peak velocity (cm/s)	15.7 ± 2.5	18.6 ± 6.2	0.12
PVPR	0.08 ± 0.07	0.29 ± 0.2	< 0.01

HF: Heart failure; PVPR: Portal vein pulsatility ratio.

and those with AF (TRPG: 29.8 ± 12.5 mmHg *vs* 32.3 ± 10.6 mmHg, respectively, *P* = 0.66; IVC diameter: 15.6 ± 4.1 mm *vs* 17.5 ± 4.3 mm, respectively, *P* = 0.15; tricuspid annular plane systolic excursion: 17.9 ± 5.1 mm *vs* 16.1 ± 3.4 mm, respectively, *P* = 0.18; PVPR: 0.27 ± 0.19 *vs* 0.28 ± 0.23, respectively, *P* = 0.43).

In all patients with HF, clinical symptoms and physical examination findings improved after optimal treatment. At discharge, blood tests showed that total bilirubin and brain natriuretic peptide concentrations were significantly decreased. Transthoracic echocardiography also demonstrated that right heart overload findings, such as the TRPG and IVC diameter, improved significantly after HF treatment (TRPG: 31.3 ± 12.1 mmHg *vs* 25.2 ± 8.9 mmHg, respectively, *P* < 0.01; IVC diameter: 16.5 ± 4.2 mm *vs* 14.2 ± 2.9 mm, respectively, *P* < 0.01) (Table 3).

Figure 1B and C depicts the representative PV flow waveforms of patients with HF before and after optimal treatment, respectively. Figure 2 shows the changes in the PVPR from admission to discharge in patients with HF. The PVPR decreased after the improvement in HF (admission: 0.29 ± 0.20 *vs* discharge: 0.18 ± 0.15, *P* < 0.01) due to the increase in minimum velocity (admission: 12.6 ± 4.5 cm/s *vs* discharge: 14.6 ± 4.6 cm/s, *P* = 0.03). The minimum velocity was negatively correlated with RAP; therefore, RAP also decreased. However, 14% of patients with HF did not demonstrate an improvement in the PVPR, even after HF treatment.

To elucidate the association between the PVPR at discharge and cardiovascular outcomes, we divided the patients with HF into three groups according to the PVPR tertile at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). Surprisingly, the Kaplan–Meier analysis found that patients with a high PVPR at discharge had a

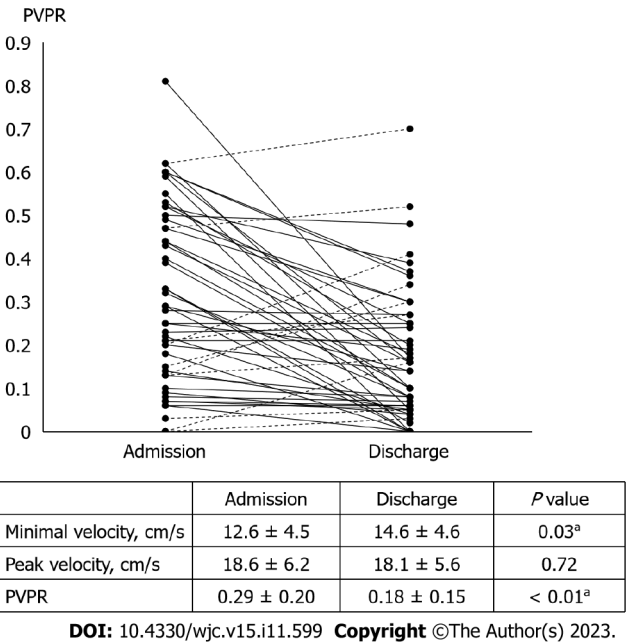


Figure 2 Changes in the portal vein pulsatility ratio from admission to discharge in patients with heart failure. The portal vein (PV) pulsatility ratio (PVPR) was significantly decreased after the improvement in heart failure (HF) due to the significant increase in minimum PV velocity. Some patients with HF (14%) did not demonstrate an improvement in the PVPR at discharge. ^a*P* < 0.05. Solid line: PVPR decreased at discharge. Dotted line: PVPR increased at discharge. PVPR: Portal vein pulsatility ratio.

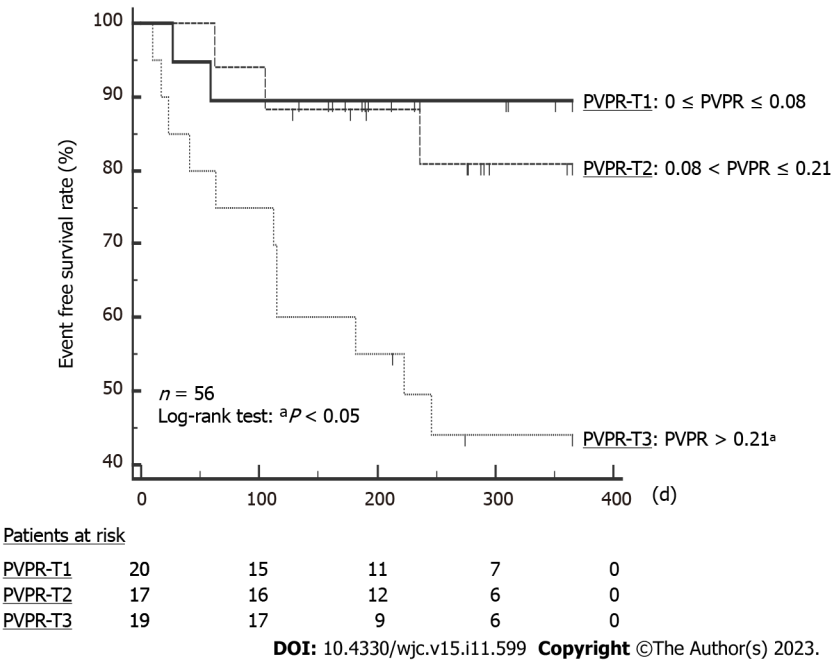


Figure 3 Kaplan-Meier curve for prognosis in patients with heart failure. Patients with heart failure were divided into three groups according to the portal vein pulsatility ratio (PVPR) at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). PVPR-T3 had a worse prognosis than the lower PVPR tertiles (log-rank test: ^a*P* < 0.05 vs PVPR-T1). PVPR: Portal vein pulsatility ratio.

significantly worse prognosis than patients with a low PVPR (*P* < 0.05; **Figure 3**). There were no significant differences in the biochemical and echocardiographic data among the tertiles (**Table 4**).

DISCUSSION

In this study, we showed that the PV flow pattern differed between the control group and the HF group. The high PVPR pulsatile pattern was often seen in the HF group but not in the control group. The PVPR was significantly decreased after

Table 3 Changes in the biochemical and echocardiographic data of patients with heart failure

Parameter	Admission	Discharge	P value
Laboratory data			
Albumin (mg/dL)	3.5 ± 0.4	3.4 ± 0.5	0.14
AST (IU/L)	61.4 ± 17.8	23.8 ± 15.0	0.06
ALT (IU/L)	46 ± 12.4	19 ± 2.0	0.06
Total bilirubin (mg/dL)	1.0 ± 0.6	0.8 ± 0.4	< 0.01
BUN (mg/dL)	28.3 ± 12.1	28.4 ± 12.4	0.50
Creatinine (mg/dL)	1.5 ± 1.4	1.4 ± 0.9	0.30
eGFR (mL/min/1.73 m ²)	43.7 ± 18.1	43.7 ± 18.5	0.99
Hb (g/dL)	11.8 ± 2.5	11.6 ± 2.4	0.30
BNP (pg/mL)	1010 ± 1181	396 ± 626	< 0.01
TTE			
EF (%)	42 ± 16	44 ± 14	0.51
TRPG (mmHg)	31.3 ± 12.1	25.2 ± 8.9	< 0.01
TAPSE (mmHg)	16.5 ± 4.9	17.4 ± 3.7	0.43
IVC (mm)	16.5 ± 4.2	14.2 ± 2.9	< 0.01

Data are mean ± SD. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; IVC: Inferior vena cava; TAPSE: Tricuspid annular plane systolic excursion; TRPG: Tricuspid regurgitation pressure gradient; TTE: Transthoracic echocardiography.

the improvement in HF and venous congestion. Furthermore, patients with a high PVPR at discharge had a significantly worse prognosis than patients with a low PVPR.

Patients with HF had a high RAP and hepatic venous pressure, representing venous congestion[11]. Previous studies have demonstrated that the PV flow pattern is affected by not only hepatic venous pressure but also RAP[7,8,12,13]. These findings are consistent with our preliminary data showing that the minimum PV velocity was negatively correlated with the RAP assessed by RHC. In this study, patients in the control group had a low PVPR with a high minimum PV velocity, whereas patients with congestive HF had a high PVPR with a low minimum PV velocity at admission. After the improvement in HF, the PVPR was significantly decreased due to the increase in the minimum PV velocity, indicating a decrease in RAP. We also found that there was no significant difference in the PVPR between patients with HF in sinus rhythm and patients with AF. This indicated that there was no correlation between AF and high RAP, which is in agreement with the findings of a previous study[14].

The timing of the minimum PV velocity was synchronized with the peak of the v-wave in the right atrium (RA) (Figure 4). The v-wave represents passive venous filling of the RA when the tricuspid valve is closed. In patients with congestive HF, a high RAP obstructs passive venous blood return into the RA. As a result, we speculate that the velocity of venous blood return from the PV and the IVC decreases. Thus, the minimum PV velocity would be low in patients with congestive HF. When RAP decreases along with HF treatment, the velocity of passive venous return from the PV increases, followed by a continuous PV flow pattern. Given that the PV flow pattern reflects RAP, the PVPR would be a promising marker for evaluating the condition of HF.

The PVPR decreased significantly after HF treatment due to the increase in the minimum PV velocity. However, 14% of the patients with HF did not demonstrate an improvement in the PVPR, even at discharge. In other words, a decrease in the PVPR was not seen in every patient with HF. Given that a high PVPR with a low minimum velocity would indicate a high RAP, we compared the cardiovascular outcomes among the PVPR tertiles. Interestingly, patients with a high PVPR at discharge had a significantly poorer prognosis than patients with a low PVPR (Figure 3). This indicated that patients with a high PVPR still had venous congestion at discharge, even after guideline-based optimal treatment.

IVC diameter and TRPG measurements are standard methods for evaluation for venous congestion and RAP. However, our study demonstrated that the IVC diameter and TRPG did not correlate with cardiovascular outcomes in patients with HF (Supplementary Figures 2 and 3). These findings suggest that the PVPR is a simpler and more reliable non-invasive method to identify the condition of HF than traditional measurements.

Limitations

This study had some limitations. This was a retrospective study that was performed without randomization of patient selection. Moreover, although the two groups of patients demonstrated no significant differences in terms of sex, body mass index, and blood pressure, undetermined factors could have influenced the results.

Table 4 Biochemical and echocardiographic data of patients with heart failure categorized by portal vein pulsatility ratio at discharge

Parameter	PVPR-T1	PVPR-T2	PVPR-T3	P value
Age (yr)	81.3 ± 11.6	78.7 ± 13.7	76.6 ± 14.8	0.54
Male	11 (55)	8 (61)	14 (56)	0.92
Laboratory data				
Albumin (mg/dL)	3.4 ± 0.7	3.5 ± 0.5	3.3 ± 0.4	0.84
AST (IU/L)	24 ± 8.7	22.1 ± 6.5	25.2 ± 24.5	0.85
ALT (IU/L)	20.6 ± 17.1	19.6 ± 11.1	17.2 ± 27.4	0.86
Total bilirubin (mg/dL)	0.7 ± 0.3	0.9 ± 0.5	0.7 ± 0.3	0.08
BUN (mg/dL)	31.2 ± 13.1	24.8 ± 12.2	29.0 ± 14.0	0.34
Creatinine (mg/dL)	1.5 ± 0.9	1.2 ± 0.6	1.5 ± 1.1	0.52
eGFR (mL/min/1.73 m ²)	39.4 ± 15.3	48.2 ± 15.6	46.9 ± 23.7	0.28
Hb (g/dL)	11.5 ± 2.4	13.0 ± 2.5	10.6 ± 2.0	0.08
BNP (pg/mL)	200 ± 178	350 ± 342	682 ± 1030	0.12
TTE				
EF (%)	48 ± 13	42 ± 15	42 ± 17	0.40
TRPG (mmHg)	22.1 ± 5.2	27 ± 7.3	26.1 ± 10.9	0.24
TAPSE (mmHg)	22 ± 5.2	22.2 ± 7.5	21.9 ± 10.8	0.84
IVC (mm)	13.3 ± 2.6	14.7 ± 3.0	14.9 ± 3.1	0.21

Data are *n* (%) or mean ± SD. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; IVC: Inferior vena cava; TAPSE: Tricuspid annular plane systolic excursion; TRPG: Tricuspid regurgitation pressure gradient; TTE: Transthoracic echocardiography; PVPR-T1: 0 ≤ portal vein pulsatility ratio ≤ 0.08; PVPR-T2: 0.08 < portal vein pulsatility ratio ≤ 0.21; PVPR-T3: 0.21 > portal vein pulsatility ratio.

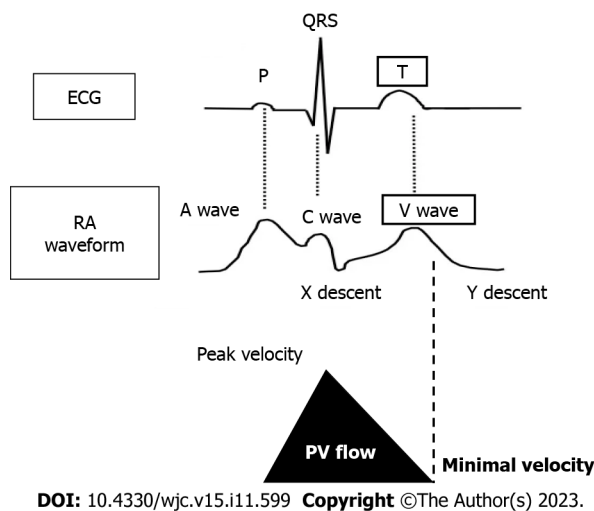


Figure 4 Relationship between electrocardiography, right atrium waveform, and portal vein flow. The timing of minimum portal vein velocity was synchronized with the V-wave in the right atrium. ECG: Electrocardiography; RA: Right atrium; PV: Portal vein.

CONCLUSION

The PVPR at discharge in hospitalized patients with acute HF reflected venous congestion and the condition of HF. Therefore, the PVPR may be a novel prognostic marker for hospitalized patients with acute HF. We also propose that hospitalized patients with acute HF with a low PVPR at discharge require more careful treatment and close follow-up (Figure 5).

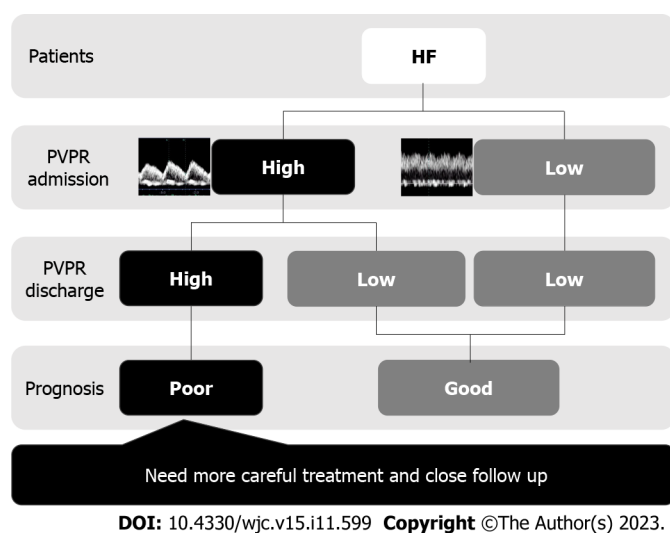


Figure 5 Summary of the study. HF: Heart failure; PVPR: Portal vein pulsatility ratio.

ARTICLE HIGHLIGHTS

Research background

Heart failure (HF) causes extracardiac organ congestion, including in the hepatic portal system. Reducing venous congestion is essential for HF treatment, but evaluating venous congestion is sometimes difficult in patients with chronic HF.

Research motivation

The portal vein (PV) flow pattern can be influenced by right atrial pressure. Ultrasound images of the PV are quite easy to obtain and are reproducible among sonographers. However, the association between PV pulsatility and the condition of HF remains unclear. We hypothesize that PV pulsatility at discharge reflects the condition of HF.

Research objectives

To evaluate the usefulness of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

Research methods

This observational study was conducted from April 2016 to January 2017 and April 2018 to April 2019 at Shinko Hospital. We enrolled 56 patients with acute HF, and 17 patients without HF served as controls. PV flow velocity was measured by ultrasonography on admission and at discharge. We calculated the PV pulsatility ratio (PVPR) as the ratio of the difference between the peak and minimum velocity to the peak velocity. The primary endpoint was cardiac death and HF re-hospitalization. The observation period was 1 year from the first hospitalization. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups.

Research results

On admission, the PVPR was significantly higher in patients with acute HF than controls (HF: 0.29 ± 0.20 vs controls: 0.08 ± 0.07 , $P < 0.01$). However, the PVPR was significantly decreased after the improvement in HF (admission: 0.29 ± 0.20 vs discharge: 0.18 ± 0.15 , $P < 0.01$) due to the increase in minimum velocity (admission: 12.6 ± 4.5 vs discharge: 14.6 ± 4.6 cm/s, $P = 0.03$). To elucidate the association between the PVPR and cardiovascular outcomes, the patients were divided into three groups according to the PVPR tertile at discharge (PVPR-T1: $0 \leq \text{PVPR} \leq 0.08$, PVPR-T2: $0.08 < \text{PVPR} \leq 0.21$, PVPR-T3: $\text{PVPR} > 0.21$). The Kaplan-Meier analysis showed that patients with a higher PVPR at discharge had the worst prognosis among the groups.

Research conclusions

The PVPR at discharge reflects the condition of HF.

Research perspectives

The PVPR is also a novel prognostic marker for hospitalized patients with acute HF.

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FOOTNOTES

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Hypertrophic cardiomyopathy secondary to deficiency in lysosome-associated membrane protein-2: A case report

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Abstract

BACKGROUND

Danon disease (DD), in which mutations in the X-linked lysosome-associated membrane protein-2 (LAMP-2) gene result in hypertrophic cardiomyopathy, is a rare disease, reported primarily in small samples or cases. However, with the development of cardiac magnetic resonance imaging and genetic technology in recent years, the number of reports has increased.

CASE SUMMARY

We report a case of DD in an adolescent male patient, confirmed by genetic testing. The patient was admitted to our hospital with complaints of a three-year history of chest tightness and shortness of breath. His preliminary clinical diagnosis is hypertrophic cardiomyopathy. Our report includes the patient's clinical course from hospital admission to death, step-by-step diagnosis, treatment course, and noninvasive imaging features. We highlight how a noninvasive diagnostic approach, based solely on clinical and imaging "red flags" for DD, can be used to achieve a diagnosis of DD with a high degree of confidence.

CONCLUSION

DD is a very dangerous cardiomyopathy, and it is necessary to achieve early diagnosis and treatment.

Key Words: Danon disease; Lysosome-associated membrane protein-2 gene; Cardiomyopathy; Hypertrophy; Cardiac magnetic resonance imaging; Myocardial strain; Case report

Core Tip: Danon disease (DD) is a rare X-linked disorder caused by a deficiency of lysosome-associated membrane protein-2. DD is clinically characterized by severe cardiomyopathy, skeletal muscle disease, and intellectual disability. The most frequent high-risk form of DD is cardiomyopathy, which can result in arrhythmia(s), early-onset heart failure, and even sudden cardiac death. Our case report intends to raise the awareness of DD and improve the clinical suspicion of DD.

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INTRODUCTION

Danon disease (DD) is a rare, hereditary, X-linked, and dominant lysosomal glycogen storage disease, caused by a deficiency in lysosome-associated membrane protein-2 (LAMP-2)[1]. The disease predominantly affects men, who usually exhibit more severe clinical manifestations and present at an earlier age than women. Clinical manifestations of DD include myocardial enlargement, skeletal myopathy, and mental aberrations[2], and the most frequent high-risk form of DD is cardiomyopathy, which can manifest as arrhythmia(s), early onset heart failure, or even sudden cardiac death. Young male patients with DD typically present with left ventricular hypertrophy, which, unfortunately, is frequently mistaken for hypertrophic cardiomyopathy or other secondary conditions related to left ventricular hypertrophy. Characterized by rapid progression and a propensity for high mortality at an early age, DD may be the most lethal cardiomyopathy in young male patients[3]. In the present case study, we describe the patient's clinical course from hospital admission to death, including all diagnostic work-ups, his treatment course, and any notable noninvasive imaging features. Herein, we emphasize the importance of utilizing unique clinical signs and imaging features for the early recognition and diagnosis of DD.

CASE PRESENTATION

Chief complaints

An 18-year-old adolescent male patient was admitted to our hospital with complaints of a three-year history of chest tightness and shortness of breath.

History of present illness

The patient's symptoms became noticeably worse one week before his admission, with increased chest tightness, an inability to lie supine, and anuria.

History of past illness

The patient was seen at a hospital in Beijing with complaints of chest tightness and was diagnosed with non-obstructive hypertrophic cardiomyopathy, a small pericardial effusion, and chronic bilateral lung inflammation with a few interstitial changes. Additionally, the patient suffered a cerebral infarction during the hospitalization, which improved slightly after treatment.

Personal and family history

The patient denied any family history of genetic disorders or similar conditions.

Physical examination

Upon physical examination, the patient exhibited evidence of hypotension, with a blood pressure of 92/62 mmHg. He exhibited normal development, intelligence, consciousness, and retinal features. Limb muscle strength was graded as level 5 upon the first hospitalization, and muscle tone was normal; however, at the time of the final hospitalization, muscle strength in the right upper limb was grade 4, while muscle strength in the left lower, left upper, and right lower limbs were grade 1. Unfortunately, the hospital staff did not perform electromyography, skeletal muscle magnetic resonance imaging (MRI), or a pathological examination. Atrial/ventricular premature beats and ventricular blocks were visible on resting electrocardiography, although no pre-excitation was observed.

Laboratory examinations

Laboratory testing revealed elevated levels of high-sensitivity cardiac troponin T (0.187 ng/mL) and N-terminal pro-B-type natriuretic peptide (NT-proBNP; 6,554 pg/mL), while liver function tests revealed elevated levels of creatine

kinase (1075 U/L, 1545 U/L, and 936 U/L), creatine kinase-MB (63 U/L, 61 U/L, and 58 U/L), lactate dehydrogenase (728 U/L), alanine transaminase (206 U/L), and aspartate aminotransferase (273 U/L). The patient's troponin T and myocardial enzyme levels were also elevated, suggesting secondary myocardial damage.

Imaging examinations

Left ventricular centripetal and right ventricular hypertrophy were observed on transthoracic echocardiography (ventricular septal thickness, 20–31 mm; lateral wall thickness, 26 mm) (Figures 1A–C). Tissue Doppler imaging revealed increased end-diastolic filling pressure, with an E value of 70 cm/s (Figure 1D), a ventricular septum e' value of 3 cm/s, and a lateral wall e' value of 4 cm/s (Figures 1E and F).

The patient underwent coronary computed tomography (CT) angiography with maximum intensity projection, excluding acute coronary syndrome, which revealed the patency of the lumen of the coronary trunk and its branches (Figure 1G). To further characterize the cardiac phenotype, a cardiac MRI (CMRI) was performed, which revealed bilateral ventricular hypertrophy, severe trabecularization of the biventricular wall, and minor pericardial effusion. Additionally, myocardial strain analyses of the entire left ventricle (Figure 2A), as well as each segment, were performed. The 16-segment bullseye diagram and longitudinal strain map revealed varying degrees of strain reduction in each segment of the patient's left ventricle, indicating myocardial injury (Figures 2B and C). The ventricular myocardium exhibited substantial late gadolinium enhancement (LGE) on MRI, sparing the mid-basal septum but involving the apex (Figures 1H and I), which is a unique imaging characteristic of DD[4].

FINAL DIAGNOSIS

After reviewing the patient's gene sequencing, in conjunction with the aforementioned data, the patient's final diagnosis was DD.

TREATMENT

The patient experienced ventricular thrombosis, pulmonary thrombosis, pulmonary hypertension, and cerebral infarction in previous hospitalization, which required the administration of the cardiotonic medication digoxin and the anticoagulant warfarin. The patient and his family approved a therapeutic regimen; however, after undergoing treatment with the medications for > 1 mo, the patient's chest tightness worsened, anuria developed, and his lungs started to crackle. Additionally, paroxysmal atrial fibrillation was detected on resting electrocardiography and laboratory results showed an additional elevation in high-sensitivity cardiac troponin T (0.527 ng/mL) and NT-proBNP (84, 072.43 pg/mL) concentrations, as well as hyperkalemia (potassium level, 6.4 mmol/L). Multislice chest CT revealed serious infection in both lungs. The patient was treated with diuretics, nutritional supplementation for the myocardium, anticoagulants, and anti-infection therapy for one week. However, he did not show any significant improvement.

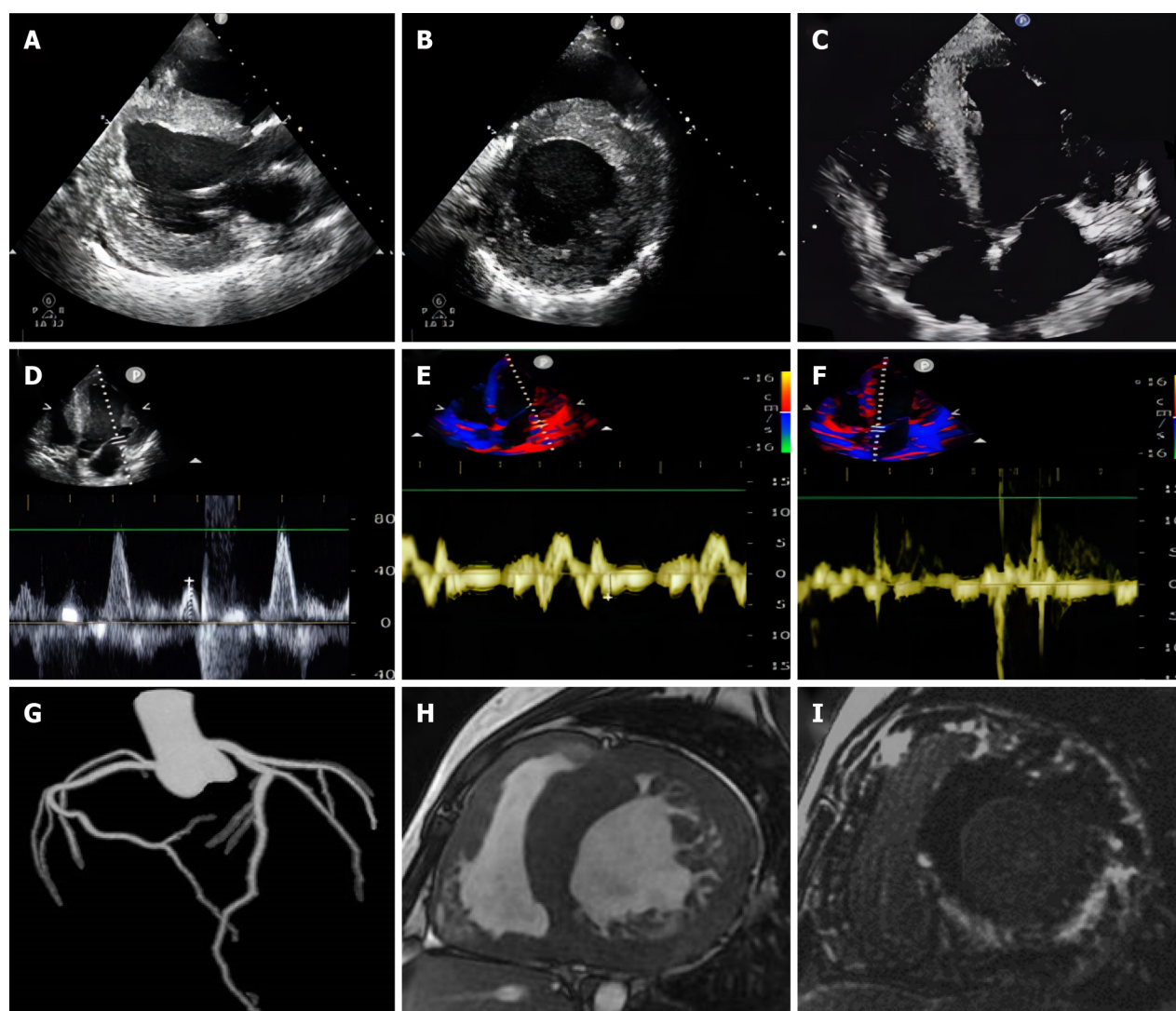
OUTCOME AND FOLLOW-UP

The patient's prognosis continued to be poor, and he subsequently exhibited signs of entering a deep coma and died, despite attempts at active resuscitation.

DISCUSSION

DD is a highly penetrant vacuolar myopathy caused by a primary deficiency in LAMP-2[5]. This condition usually involves the skeletal muscle and myocardium and can be definitively diagnosed through a biopsy. The characteristic pathological features of DD include intracytoplasmic vacuoles harboring autophagic components and glycogen[1]. The classic "trifecta," which includes cardiac enlargement, skeletal myopathy, and abnormal liver function, is used to definitively diagnose patients with suspected DD[5]. Other red flags, such as pre-excitation on resting electrocardiography, are not always present in patients with DD. Although the patient presented herein did not undergo a skeletal muscle biopsy, his decreased muscle strength, in combination with an increase in creatine kinase concentrations, indicated the presence of skeletal muscle damage.

A distinctive LGE pattern and basal septum preservation, seen on CMRI, may help distinguish DD from sarcomeric or other hypertrophic cardiomyopathy phenotypes[4,6] and strengthen a suspected diagnosis of DD. Physicians should confirm cardiac hypertrophy, impaired liver function, and a genuine pattern of progressive gadolinium enhancement on CMRI to diagnose DD. To date, CMRI findings in patients with DD have been described in only a few case reports[4]. CMRI provides accurate imaging of morphological structures and tissue characteristics, such as unusual LGE patterns, which may have practical utility in the identification and differential diagnosis of cardiomyopathy in patients with DD. Additionally, adding myocardial fibrosis to the list of indicators of DD may be appropriate. For the first time, we added feature-tracking technology to investigate cases of DD. The analysis of global and segmental longitudinal myocardial

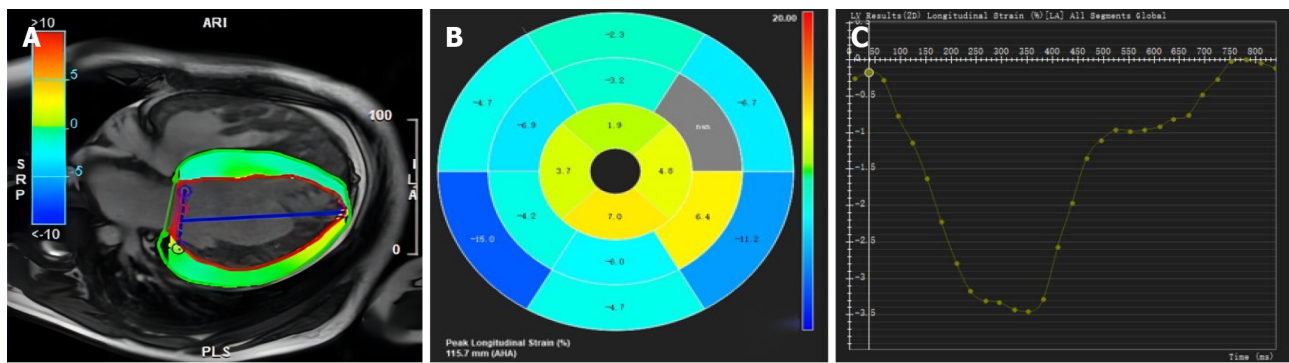


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Figure 1 Imaging features of the male patient. A: Transthoracic echocardiography shows left ventricular centripetal hypertrophy in parasternal long axis view; B: Transthoracic echocardiography shows left ventricular centripetal hypertrophy in parasternal short axis view; C: Transthoracic echocardiography shows left ventricular centripetal hypertrophy and right ventricular hypertrophy in long axis view; D: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with an E value of 70 cm/second; E: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with e' (lateral wall) value of 4 cm/second; F: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with e' (ventricular septum) value of 3 cm/second; G: The coronary tree's maximum intensity projection displays the patency of each branch lumen; H: Cardiac magnetic resonance short-axis cine shows diffuse thickening of the biventricular wall, excessive myocardial trabeculation, and pericardial effusion; I: Late gadolinium enhancement of the short axis demonstrates extensive late gadolinium enhancement of the biventricular wall, sparing only the basal segment septum.

strain using CMRI-feature tracking revealed that both were damaged; however, no other unique features were observed. We speculate that the patient presented herein was in the late stage of heart failure, although he had left ventricular non-compaction, which differs from the preservation of normal apical strain patterns described in previous reports. We hope that more patients with DD will undergo feature-tracking analysis in the future, to further characterize the unique features of cardiac strain seen in these patients.

The clinical results of treating DD depend on the severity of cardiomyopathy, which can be difficult to identify, frequently being discovered only in the presence of clinically significant symptoms. In the case presented herein, substantial myocardial injury, cardiac insufficiency, and arrhythmia were the secondary causes of numerous organ disorders that ultimately led to the patient's death. Physicians should be aware that young males exhibiting myocardial hypertrophic changes, elevated plasma creatine kinase levels, pre-excitation syndrome on electrocardiography, and/or distinctive LGE on CMRI may have DD; therefore, abnormal clinical or laboratory results and CMRI features can be used to diagnose and distinguish DD from other diseases. Furthermore, the aforementioned data allow a diagnosis to be made in a noninvasive manner, providing an alternative to the current gold standard for the diagnosis of DD – genetic testing for LAMP-2 deficiency/mutations. Although there is currently no specific gene therapy for DD, the adenovirus-mediated delivery of a functional LAMP2B transgene has been achieved in a mice model, the efficacy of which is being tested in adolescent male patients with DD.



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Figure 2 Feature Tracking strain measurements. A: Cardiac magnetic resonance feature tracking with longitudinal strain overlay on a four-chamber cine steady-state free precession image; B: Bull's-eye diagram of strain in each segment in the left ventricular myocardium of the same patient; C: The map shows the longitudinal strain values. The vertical axis shows longitudinal strain (%), and the horizontal axis shows the time in ms.

The Dalian Municipal Central Hospital Affiliated to Dalian Medical University Ethics Committee approved the present case study (No. YN2023-003-04). The patient's parents consented to the publication of anonymized case details.

CONCLUSION

In summary, the authors would like to emphasize the importance of the early diagnosis of DD, which facilitates advanced treatments, such as targeted gene therapy, cardiac transplantation, or the installation of an implantable cardioverter defibrillator. A deeper understanding of the unique clinical signs and imaging features of DD is needed, particularly with the use of CMRI. Genetic testing should also be performed as early as possible to increase diagnostic accuracy.

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Down syndrome child with multiple heart diseases: A case report

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Abstract

BACKGROUND

Down syndrome, also known as trisomy 21 syndrome, is commonly associated with congenital heart disease, and can often result in early formation of pulmonary hypertension. The development of pulmonary hypertension can result from factors such as intracardiac and macrovascular shunts, and upper airway obstruction or hypoplasia of lung tissue. Individuals with Down syndrome and congenital heart disease have a significantly lower average life expectancy, with surgical intervention being the most viable treatment option to improve longevity.

CASE SUMMARY

We report the case of a 13-year-old boy with Down syndrome presenting with atrial septal defect and patent ductus arteriosus along with severe pulmonary hypertension. The electrocardiogram shows sinus rhythm and right ventricular hypertrophy. The echocardiogram shows an atrial septal defect with interrupted echo in the interatrial septum, measuring 0.813 cm in length. The patient was initially refused to be offered surgical treatment by many hospitals due to the high surgical risk and pulmonary artery resistance. After discussing the patient's diagnosis and treatment options, we ultimately recommended surgical treatment. However, the patient and their family declined this recommendation and chose to be discharged. During the follow-up period of 6 mo, there were no significant improvements or deteriorations in the patient's condition.

CONCLUSION

In conclusion, this case highlights the challenges faced by individuals with Down syndrome and congenital heart disease complicated by severe pulmonary hypertension. Timely intervention and a multidisciplinary approach are crucial for improving prognosis and life expectancy. Further research is needed to enhance our understanding and develop effective interventions for this population.

Key Words: Down syndrome; Trisomy 21 syndrome; Atrial septal defect; Pulmonary hypertension; Review; Patent ductus arteriosus; Case report

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Core Tip: This case study presents a 13-year-old boy diagnosed with Down syndrome alongside atrial septal defect, patent ductus arteriosus, and severe pulmonary hypertension. A complex condition initially met with surgical treatment denial due to high risks, highlights the significant challenges faced by individuals with Down syndrome and congenital heart disease. This case highlights the discussion and educational value surrounding the decision to undergo surgery in complex congenital heart diseases. The educational value lies in the diagnostic and therapeutic approaches demonstrated by our team. Due to the relatively common occurrence of this case in the field of cardiology, our decision-making process holds significant value and applicability.

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INTRODUCTION

Down syndrome (DS), also known as trisomy 21 syndrome (Figure 1), is the most prevalent genetic disorder among Chinese children. The disease arises due to a mutation of the 21st pair of chromosomes, resulting in the duplication of genetic material. Common clinical manifestations include developmental abnormalities, intellectual disability, and an increased propensity for digestive tract and cardiovascular malformations[1]. Reports suggest that the incidence of congenital heart disease (CHD) in DS patients ranges from 40%-60% and can lead to heart failure, pulmonary vascular disease (PVD), and pneumonia[2,3]. Early diagnosis and surgical intervention are vital to prolong survival and enhance the quality of life of these children[4]. However, DS is a chromosomal disease impacting multiple systems, and opinions differ on the effectiveness of surgical intervention.

In the present case, the patient was refused to be offered surgical intervention by multiple hospitals due to the high risk of pulmonary arterial resistance. However, after extensive consultation, our hospital reassessed the patient's situation and proposed a promising treatment plan that ultimately gave the child a chance at life. This case may serve as a valuable reference for the management and treatment of similar cases.

CASE PRESENTATION

Chief complaints

A 13-year-old boy presented to our hospital for further evaluation and treatment.

History of present illness

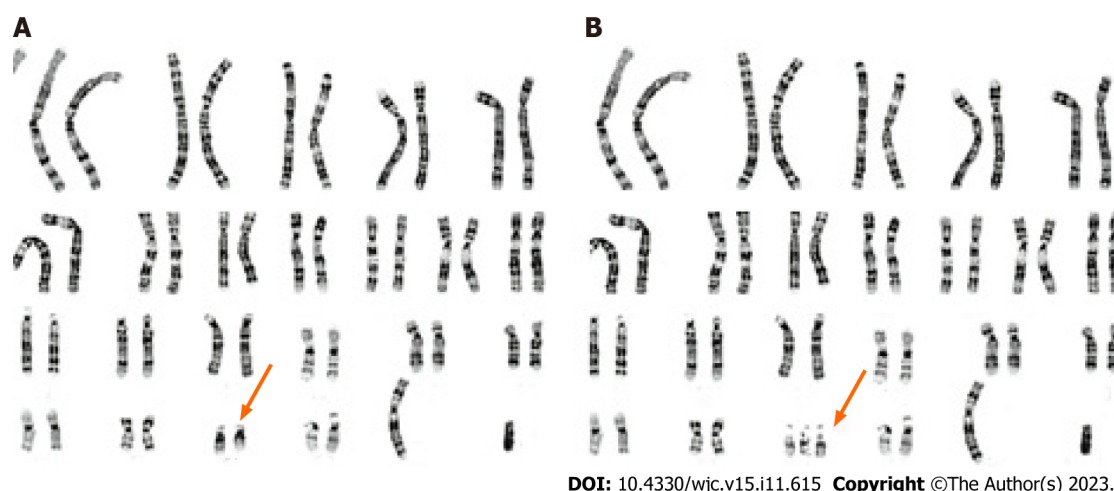
The patient was diagnosed as having DS with CHD. A patent ductus arteriosus (PDA) closure was successfully performed, but atrial septal defect (ASD) closure was withheld due to the patient's complicated pulmonary arterial hypertension. After treatment, the patient's activity tolerance improved. On July 29, 2020, the patient sought medical care at the Yan'an Hospital of Kunming City, where cardiac catheterization revealed a pulmonary artery pressure of 95/41/66 mmHg and a right ventricular pressure of 97/-10/38 mmHg. He was diagnosed with ASD complicated with severe pulmonary arterial hypertension, and continuation of oral Bosentan and Sildenafil for the management of pulmonary arterial hypertension was recommended.

History of past illness

The patient's medical history revealed that at 2 mo of age, he was diagnosed at another hospital with CHD characterized by ASD and PDA. However, no treatment was provided. In 2018, the patient developed "cyanosis of the lips and shortness of breath after exercise" and was admitted to Fuwai Hospital, where he was diagnosed with ASD and PDA, along with an enlarged heart, severe pulmonary hypertension (PH), and cardiac function Grade II.

Physical examination

Physical examination revealed a pulse rate of 95 bpm, blood pressure of 113/55 mmHg, and pale purplish lips. Cardiac percussion examination revealed leftward expansion of the heart border. Auscultation revealed regular heart rhythm with mild hyperactivity of P2, but no discernible noise.



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Figure 1 Differences between the chromosomes of normal individuals and Down syndrome patients. A: Normal human chromosome sequence; B: Down syndrome patients chromosome sequence.

Imaging examinations

Frontal and lateral chest digital radiography (DR) revealed the presence of reticular shadows in the mediastinal area indicative of postoperative changes (Figure 2). A conventional 12-lead electrocardiogram (ECG) (Figure 3) was conducted during the outpatient visit, which revealed sinus rhythm and right chamber hypertrophy. An echocardiogram was also performed, which showed an ASD (central secondary foramen) with an interrupted middle echo in the atrial septum measuring 0.813 cm. The position and functionality of the PDA interventional closing device were normal, the right atrium and ventricle show enlarged diameters and increased wall thickness in the right ventricle (Figure 4). According to subsequent reports, the patient exhibits blood flow signals indicating left-to-right shunting that can be visualized in the atrium. Additionally, a small regurgitant jet can be observed at the tricuspid valve during atrial contraction, with peak flow velocity of 398cm/s and a peak pressure gradient of 63mmHg. Following these assessments, the patient was referred to our department for the management of “ASD and associated PH”.

FINAL DIAGNOSIS

The patient was finally diagnosed with: (1) ASD (central foramen secundum type); (2) moderate PH; (3) PDA (after interventional closure); and (4) DS.

TREATMENT

For patients with inconsistent severe PH following the results of physical examination, ECG, chest DR, right cardiac catheterization, and cardiac ultrasound, it is necessary to consider the possibility of measurement instrument errors and judgment bias. We also considered the possibility of heart-lung combined transplantation. However, due to the high surgical trauma and shortage of donors, we took a conservative approach when discussing this option. Further surgical plans will be presented in the “DISCUSSION” section.

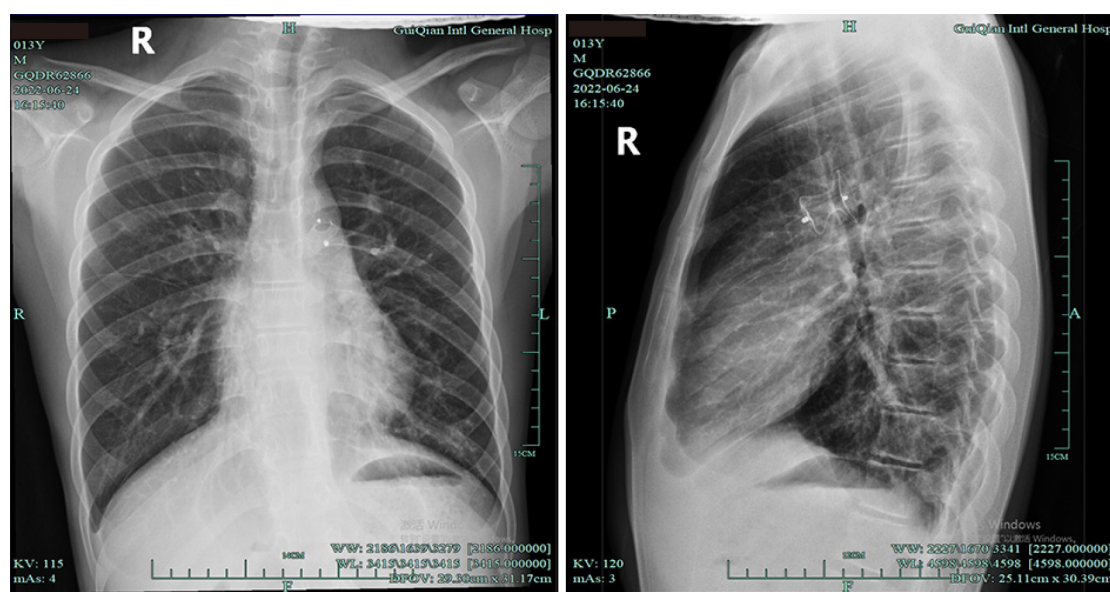
OUTCOME AND FOLLOW-UP

The patient ultimately did not accept our surgical recommendation and opted for conservative treatment (oral PH medication) before being discharged.

We conducted a 6-mo follow-up during which the patient did not show significant improvement or worsening of his condition. During the follow-up period, the patient sought medical care at two other hospitals and continued to decline surgical treatment.

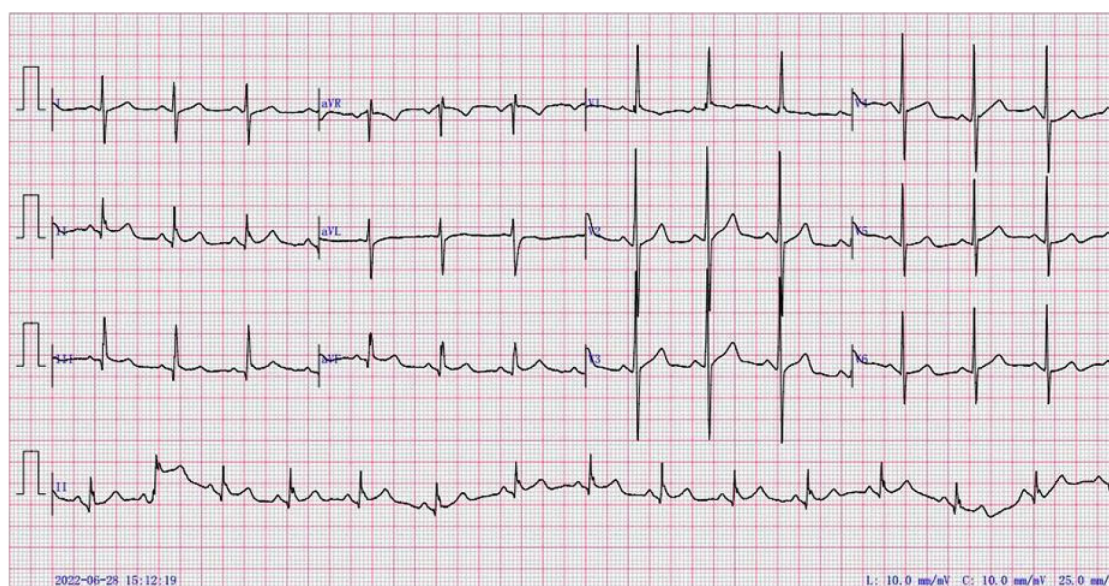
DISCUSSION

After extensive discussion by our hospital's expert group, the following findings in this case are summarized. The child had been diagnosed with DS associated with CHD. Despite a previous diagnosis by other medical facilities of severe PH



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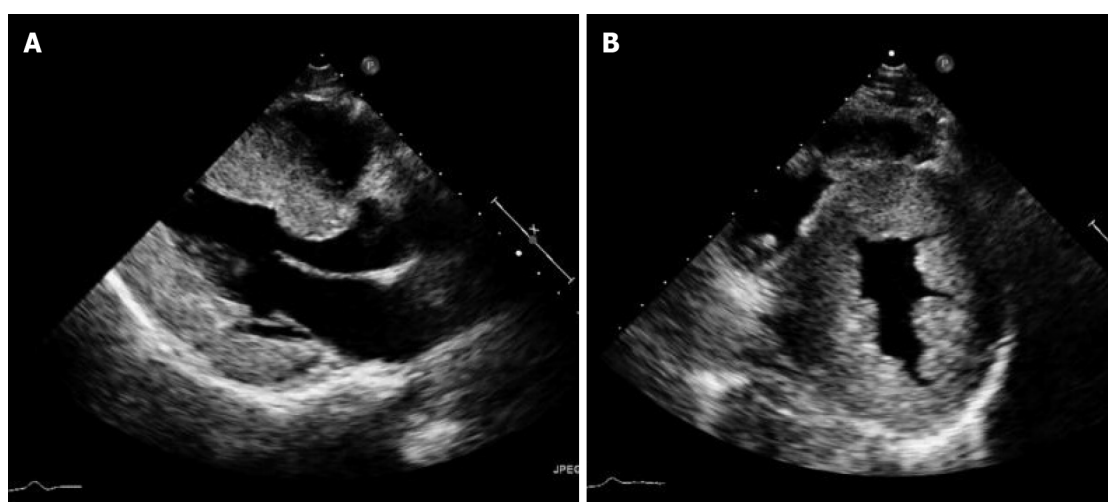
Figure 2 Anteroposterior and lateral digital radiography of the chest.



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Figure 3 Conventional 12-lead electrocardiogram.

(systolic pulmonary pressure > 70 mmHg), our physical examination only noted mild accentuated P2 heart sound, suggesting that the patient's actual PH may be mild or nonexistent, or potentially present with a two-way shunt. And the child's ECG demonstrated right ventricular high voltage without any signs of right bundle branch block, and with a low or upside-down ST-T wave, which suggests that the right ventricular hypertrophy may not have been significant. Chest DR indicated slightly expanded pulmonary artery sections without any sparse blood vessels indicative of the "no truncating phenomenon." Therefore, further evaluation was necessary *via* right-heart catheterization to obtain critical indicators for assessing the patient's pulmonary artery pressure. Further investigation was conducted to analyze the relationship between the patient's PDA and ASD. In children with PDA, blood enters the pulmonary arteries through the ASD, leading to a significant increase in pulmonary blood flow (PBF) and left ventricular overload, resulting in an increase in long-term PBF and pulmonary vascular resistance (PVR), eventually leading to PH in later stages. As PH worsens, right-to-left shunting occurs at the atrial level, known as the Eisenmenger syndrome, indicated by clinical cyanosis. However, the child's ultrasonic display did not show a significant increase in the left ventricle. This may be due to the merged ASD, which leads to an increase in the left heart load and the occurrence of left-to-right shunting at the atrial level. After interventional closure of the PDA, the left-to-right shunt in the atrium was reduced, and the systolic pulmonary pressure decreased compared to that previously, significantly improving the patient's symptoms.



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Figure 4 Echocardiography demonstrated the presence of an atrial septal defect and associated left to right shunt.

It is important to exercise caution and conduct proper communication and evaluation before considering the closure of an ASD in a child with DS combined with CHD, as the prognosis is poor, and the risks associated with anesthesia and surgery are substantial. It is also possible that, even after right heart catheterization, there still may not be any indication for interventional closure or surgery. If a patient's parents fully understand their child's medical condition, treatment plan, surgical risks and benefits, as well as prognosis, but still desire right heart catheterization and any necessary interventional therapy, it is advisable to arrange for general anesthesia appropriate for the cardiac catheterization procedure.

Unfortunately, the patient's parents were unaware of the above situation and declined the surgical recommendation. Therefore, further cardiac catheterization for examination and treatment was not performed, and he continued to take pulmonary artery pressure-lowering drugs and was discharged from the hospital for follow-up.

We also performed a review of the related literature. CHD is the most common type of malformation associated with DS and is a significant cause of mortality in DS patients. The early onset of PH resulting from cardiac defects and respiratory tract hypoplasia can lead to PVD and heart failure, further worsening the timing of surgery and prognosis. Early diagnosis and timely intervention are crucial in prolonging the survival and improving the quality of life of DS patients.

DS is frequently associated with malformations across multiple organ systems, with CHD being the most significant factor affecting patient survival. Approximately 40%-60% of DS cases are associated with CHD[5]. The specific types of CHD associated with DS and their respective composition ratios vary across different countries and regions. In North East England, atrioventricular septal defect (AVSD) is the most common (42%) type of CHD associated with DS, followed by ventricular septal defect (VSD) at 31%. Other types such as ASD, tetralogy of Fallot (TOF), and PDA account for 15%, 5%, and 4%, respectively[5]. In Mexico, ASD is the most common type, accounting for approximately 38%, while VSD and PDA make up 30% and 21%, respectively[6]. In Germany, the most frequently observed type of CHD in DS cases is AVSD (51.2%), followed by VSD (25.1%), TOF (6.7%), and ASD (8.9%)[7]. In Asia, VSD is the most common type of CHD associated with DS, accounting for 43%, followed by AVSD (15.4%), ASD (13.4%), and TOF (13.4%)[8]. The reasons for these regional differences remain unclear.

The pathogenesis of PH in patients with DS and CHD is multifaceted and may be related to both anatomical and physiological changes in the lung circulation[9]. Abnormal shunting caused by heart malformations and other factors, such as upper respiratory tract obstruction and lung tissue development in DS children, contribute to the formation of PH. Deformities in the heart structure result in abnormal shunting, with shunts flowing from left to right causing an increase in PBF[10]. This creates additional shear force on the pulmonary vascular endothelium, leading to irreversible internal cellular damage. Forward-looking studies have found that more than half of DS children show signs of PH, with AVSD often being linked to its formation. Large internal defects cause a significant amount of blood to shunt from left to right after birth, resulting in pulmonary vascular bed damage and the formation of PVD[11,12].

Furthermore, the abnormal blood shunt in the heart increases the blood flow in small arteries, leading to early reflection spasm in the pulmonary arteries and increased pulmonary circulation resistance[13]. The prolonged high flow in the pulmonary circulation leads to the main pathological change of blood vessel remodeling, eventually resulting in irreversible PVD. Studies have demonstrated that, before the age of one year, DS children show lower average PBF and average PVR levels compared to non-DS children[14,15]. Approximately 10% of DS children are diagnosed with pulmonary vascular obstructive diseases (PVOD) before the age of one year, which is not observed in non-DS children. Furthermore, compared to non-DS children with CHDs, DS children with CHDs exhibit a faster increase in PVR and an equivalent trend towards PVOD in the first year after birth[16].

Endothelial progenitor cell dysfunction is also involved in the formation of PH in children with DS. Endothelial progenitor cells maintain the stability of blood vessels and participate in the production of vascular endothelial cells[17]. Their dysfunction is mainly reflected in a reduction of cell number and physiological function, leading to damage in

Table 1 Basic characteristics of included studies evaluated not suitable for surgery

Ref.	Case	Not suitable for surgery (%)	Death without surgery (%)
Liu <i>et al</i> [22], 2015	77	17 (22.1)	5 (6.5)
Gu <i>et al</i> [5], 2016	96	38 (39.6)	4 (4.2)
Xu <i>et al</i> [23], 2019	30	0 (0)	0 (0)
Guo <i>et al</i> [24], 2015	25	0 (0)	0 (0)
Zahari <i>et al</i> [25], 2019	414	270 (65.1)	37 (9.0)
Evans <i>et al</i> [26], 2014	4231	2200 (52.4)	85 (1.9)
Baban <i>et al</i> [27], 2020	859	245 (28.5)	34 (4.0)
Aziz <i>et al</i> [28], 2020	18	6 (33.3)	-
Santos <i>et al</i> [29], 2019	139	48 (34.5)	10 (6.8)
Dias <i>et al</i> [30], 2016	102	-	3 (2.9)

maintaining the stability of blood vessels and resulting in severe or irreversible damage in the early stages of pulmonary vessel development[18]. Furthermore, several studies have indicated higher levels of various inflammatory mediators in DS children, including tumor necrosis factor- α , interleukin-6, and C-reactive protein, among others. This is also considered to impact the number of endothelial progenitor cells circulating in the blood[19].

Early onset, severe disease, and rapid progression of PH are observed in patients with DS and CHD. Therefore, early evaluation and diagnosis are critical to improving their prognosis. The assessment process involves echocardiography to determine the morphological changes in the heart and detect the presence of PH. Generally, evaluation of pulmonary arterial compression is conducted using the three-pointed reflux peak speed and Doppler ultrasonic images in combination with other ultrasonic indicators that could potentially indicate PH, such as increased pulmonary valve reflux speed, enlargement of the right heart cavity, and enlargement of the main pulmonary artery[20]. Evaluation also includes clinical manifestations, peripheral blood oxygen saturation, and other indicators to determine the level of PH.

In some cases, cardiac catheterization and acute pulmonary vascular dilation tests may be necessary to determine the level of PVD[21]. A pulmonary artery pressure of ≥ 25 mmHg under right cardiac catheterization in a static state is diagnostic for PH. Severe PH patients who cannot undergo surgery can lower their pulmonary artery pressure by taking oral diuretics and vasodilators, and partially benefit from targeted therapies[21].

Children with DS and CHD often experience repeated lung infections, weight loss, and advanced heart failure in the early stages before undergoing surgical treatment to correct cardiovascular malformations. Delayed treatment can result in an increased risk of mortality[16-18]. To investigate the status of DS with CHD over the past decade, we conducted a search of Chinese and international databases to identify cases who underwent surgical treatment. However, we found that some of these cases were deemed unsuitable for surgery (Table 1). It is important to recognize that delaying surgical treatment can increase the risk of severe complications and mortality. This highlights the need for early assessment and diagnosis to improve the prognosis of DS children with CHD.

CONCLUSION

The data in Table 1 highlight a notable discrepancy between those deemed “unsuitable for surgery” and those who passed away without undergoing surgery in various studies. This difference may be due to the various types of combined heart diseases observed in different regions or sample size differences. Nevertheless, some children are unable to receive surgical treatment and may even pass away while waiting for surgery.

FOOTNOTES

Co-first authors: Mo-Wei Kong and Yi-Jing Li.

Co-corresponding authors: Jun Li and Guo-Xiang He.

Author contributions: Kong MW and Li YJ conceived and designed the study protocol and drafted the manuscript; Li J and He GX were involved in the data collection; Pei ZY and Xie YY analyzed the data; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Kong MW and Li YJ contributed equally to this work as co-first authors. Li J and He GX contributed equally to this work as co-corresponding authors. The reasons for designating Kong MW and Li YJ as co-first authors, and Li J and He GX as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper’s quality and reliability. Second, the overall research team encompassed

authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, the co-first authors and co-corresponding authors contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors or co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Kong MW and Li YJ as co-first authors, and Li J and He GX as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Inherited arrhythmias and gene therapy: Are there any ethical considerations to take into account?

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Abstract

Interventional electrophysiology represents a relatively recent subspecialty within the field of cardiology. In the past half-century, there has been significant advancement in the development and implementation of innovative ablation treatments and approaches. However, the treatment of arrhythmias continues to be inadequate. Several arrhythmias, such as ventricular tachycardia and atrial fibrillation, pose significant challenges in terms of therapeutic efficacy, whether through interventional procedures or the administration of antiarrhythmic drugs. Cardiologists are engaged in ongoing research to explore innovative methodologies, such as genome editing, with the purpose of effectively managing arrhythmias and meeting the growing needs of patients afflicted with rhythm disturbances. The field of genome editing has significant promise and has the potential to serve as a highly effective personalized therapy for rhythm disorders in patients. However, several ethical issues must be considered.

Key Words: Arrhythmia; Sudden cardiac death; Genome editing; Long QT; Channelopathies; Mutation

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Core Tip: The use of genome editing to treat rhythm disturbances at the substrate level could provide a revolutionary treatment for disorders that the current standard of care is inadequate. Our knowledge of the disease is the only limit in identifying a perfect genome editing tool for several rhythm disturbances. As our understanding of gene vectors and transfer techniques progress, a novel therapy approach will be upon us, where cardiac muscles are altered to be impervious to rhythm disturbances, enhancing patients' quality of living and relieving the burden on healthcare organizations. Ethical issues will eventually arise, as the treatments will be expensive.

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INTRODUCTION

Inherited cardiac arrhythmias syndromes are a cluster of diverse disorders that predispose to life-threatening rhythm disturbances and abrupt cardiac death[1]. Due to inadequate penetrance and genetic variability, their detection is not invariably straightforward[2]. Additionally, current therapies are typically invasive and only preventative[1,2]. While often effective in relieving or preventing symptoms, current pharmacological or interventional treatments do not specifically address the underlying genetic defect or the key intermediary pathways implicated in the development of these disorders[3]. Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 techniques, in particular, have the ability to modify the genetic electrophysiologic substrate, hence enabling treatment for many lethal disorders[4]. So far, gene therapy has enabled the *in vitro* replication of rhythm disturbances, offering a consistent framework for variable pathogenesis, pathophysiological, and drug-testing research[1-4]. Nevertheless, *in vivo* procedures still require further investigation into the techniques' reliability, precision, and efficacy.

GENOME EDITING FOR INHERITED ARRHYTHMIAS

Inherited cardiac arrhythmia syndromes are disorders characterized by one or more genetic abnormalities that enhance the incidence of rhythm disturbance and culminate in a life-long risk of unexpected death[1]. Inherited arrhythmias can be categorized as electrophysiologic equilibrium abnormalities (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia), organic disorders linked to rhythm disturbances (hypertrophic cardiomyopathy), or a combination involving both a proclivity for rhythm disturbances and organic heart disease (arrhythmogenic cardiomyopathy)[5]. Certain compounds that modify agonists (beta-blockers) or ion channels (sodium channel blockers) have shown effectiveness in specific forms of familial rhythm disturbances, although individuals are often only partially shielded[5,6]. Several types of familial rhythm disturbances have a gradual course, and thus no presently known treatment effectively slows disease advancement[7]. Current research has suggested that genetic treatment for people with familial rhythm disturbances might be developed to prevent harmful rhythm disturbances as well as hinder disorder development by addressing core disorder processes[6-9]. These upcoming treatments have the ability to decrease adverse reactions significantly while also improving clinical results[10].

Because gene variability is widespread in channelopathies, additional genetic variants are being found and included in the prospective catalog of variations amenable to genetic analysis[1,11]. Even though both patient-dependent and patient-independent *in vitro* techniques could corroborate a variant's pathogenic potential, more compelling data and statistical validation of disorder etiology are required before they could be included in commonly utilized medical testing[1-4]. Furthermore, despite significant advances in comprehending the pathophysiology of familial rhythm disturbances, guidelines for treatment approaches, such as beta-blockers, left cardiac sympathetic denervation, or implantable cardioverter-defibrillator, have not altered in the previous 40 years[1-4]. The ability to incorporate unique disease-causing variants while maintaining the same genetic origin allows for an impartial assessment of different mutations[1-4]. This comparison research revealed that various variants in the same gene could be the result of unique genetic pathways, strengthening the viewpoint that the therapy of familial rhythm disturbances must shift toward targeted therapy and patient-specific treatments[2,12].

Precision Medicine emerged as a novel approach to disease treatment and prevention, which considers the unique interplay between an individual's genetic profile, environmental factors, and lifestyle factors[13]. The primary objective of this technique is to predict appropriate interventions and preventive measures that may yield greater efficacy for individual patients or, more feasibly, for cohorts of patients sharing common attributes[13]. The present method stands in opposition to the prevailing one-size-fits-all paradigm, wherein illness treatment and prevention strategies are formulated solely on the basis of randomized trials without taking into account individual variations[13].

While missense mutations are generally straightforward to edit using CRISPR/Cas9, addressing complex variants, including double heterozygosity, could present further barriers that must be overcome[1,2]. Furthermore, CRISPR/Cas9 has various disadvantages that have slowed the use of *in vivo* gene therapy in the management of rhythm disturbances[1,2]. The homologous recombination *cellular* mechanism, downregulated in terminally differentiated cell types such as

cardiac myocytes, reduces the odds of success[1,2]. Moreover, correcting a minor amount of molecules may result in pro-arrhythmic episodes, worsening the individuals' medical conditions[1,2].

Pro-arrhythmia is a potential concern of treatments that modify heart rhythm[2,4]. This issue is particularly significant in the context of adeno-associated viruses (AAV) genome editing, which could lead to myocardial heterogeneities due to cardiac myocytes that have and have not been transfected by AAV[2,4]. A rigorous assessment of pro-arrhythmic potential necessitates screening in bigger animals with pulse rate, anatomy, and heart physiology similar to humans[2,4].

Another field of ongoing research is the immunological reaction to genome editing[1,2]. In big animals given massive AAV loads, the intrinsic immunity mechanism was activated, culminating in a possibly deadly inflammatory process[4]. The formation of neutralizing antibodies following one AAV treatment presently precludes subsequent vector dosage, which might promote high-level transmission or increase genetic engineering longevity[4]. Even though AAV transduction of cardiac myocytes causes minor inflammation, the possibility of adverse immunity reactions must be addressed when the therapy carrier expresses a foreign protein[4].

Overall, current investigations of inherited arrhythmia disorders and gene therapy have revealed that these disorders may be effectively replicated in the laboratory, revealing deficient ion currents and enabling a suitable framework for molecular, analytical, and drug-testing research[2]. Even though immensely attractive, this technique remains in its infancy, and transitioning from the lab to the patient may require more study to increase the procedures' reliability, effectiveness, and accuracy. Future *in vivo* CRISPR/Cas9 investigation in heart channelopathies could eventually enable us to realize its promise to treat these disorders and make personalized medicine a reality[6-8].

Over the past decade, there have been significant developments in genome editing and its applicability to familial rhythm disturbances. Genome editing with AAV vectors has shown outstanding outcomes for non-cardiac disorders[1]. The obstacles for viral vector-based heart genome editing entail demonstrating effectiveness at transduction efficiencies feasible in individuals, as well as demonstrating safety at these dosages. Off-target complications, the formation of pro-arrhythmia, the durability of treatment, and the limitation of reversibility following therapy continue to pose major challenges for translation[6-8]. Creating techniques to counteract innate immunity and allow for recurrent doses will significantly increase the therapeutic value of viral vectors, increase safety, and resolve issues about treatment durability [1,2]. To render viral genome editing cost effective, the tremendous cost of medical-grade AAV development must be reduced. The discovery of technologies for effective and specific myocardial distribution for oligonucleotides and altered mRNAs would be a game changer.

CONCLUSION

The notion of a pathogenic genetic mutation within a gene that encodes a cardiac ion channel, resulting in a substrate extremely prone to arrhythmias, has emerged as the fundamental framework for understanding the pathophysiology of all these syndromes[14]. According to current guidelines, it is recommended that individuals diagnosed with hereditary cardiomyopathies and arrhythmia syndromes have genetic testing as a standard component of their medical management[15]. The use of genome editing to treat rhythm disturbances at the substrate level could provide a revolutionary treatment for disorders that the current standard of care is inadequate. Our knowledge of the disease is the only limit in identifying a perfect genome editing tool for several rhythm disturbances. As our understanding of gene vectors and transfer techniques progress, a novel therapy approach will be upon us, where cardiac muscles are altered to be impervious to rhythm disturbances, enhancing patients' quality of living and relieving the burden on healthcare organizations. Ethical issues will eventually arise, as the treatments will be expensive. Who will cover the cost? Will there be an accurate risk stratification and patient selection tool, or will existing disparities in access to healthcare interventions increase?

FOOTNOTES

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Quo vadis cardiac rehabilitation; the role of comprehensive cardiac rehabilitation in modern cardiology

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Abstract

In accordance with the guidelines established by prominent European and global cardiology associations, comprehensive cardiac rehabilitation (CR) stands as an officially endorsed and highly recommended therapeutic approach (class I recommendations; level of evidence A) for a diverse spectrum of cardiac patients. Nevertheless, it is a cause for concern to observe that fewer than 50% of eligible patients are being effectively referred for CR, whether in an outpatient or inpatient setting. Concurrently, studies reveal that a substantial proportion of individuals with atherosclerotic cardiovascular disease maintain unhealthy lifestyles and exhibit suboptimal management of modifiable cardiovascular risk factors, including hypertension, lipid levels, and diabetes. Beyond the conventional patient profile encompassing those recovering from acute coronary syndrome with or without percutaneous coronary intervention, as well as patients who have undergone coronary or valvular surgery, contemporary CR now emphasizes specialized subgroups of patients. These include frail elderly patients, the female population with its unique considerations, individuals burdened by multiple cardiovascular comorbidities, those who have developed psychological consequences due to a cardiac illness and particularly those grappling with chronic heart failure. This editorial seeks to offer a state-of-the-art assessment of the significance and role of comprehensive CR within modern cardiology.

Key Words: Cardiac rehabilitation; Chronic heart failure; Treatment of heart failure; Cardiovascular disease; Psychological disorders; Posttraumatic stress disorder

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Core Tip: Comprehensive cardiac rehabilitation (CR) is an established and endorsed therapeutic approach for a broad spectrum of cardiac patients. Nevertheless, it is concerning that fewer than 50% of eligible patients are being effectively referred for CR, whether in an outpatient or inpatient setting. This editorial aims to offer a contemporary perspective on the significance and role of comprehensive CR in modern cardiology.

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INTRODUCTION

Cardiac rehabilitation (CR) programs involve a comprehensive medical evaluation and optimization of the health status of diverse patient groups, including those recovering from acute coronary syndrome (ACS) with or without percutaneous coronary intervention (PCI), surgical myocardial revascularization coronary artery bypass grafting (CABG), valvular surgery, various endovascular procedures transcatheter aortic valve implantation, endovascular aneurysm repair (EVAR), thoracic EVAR, *etc.*, surgical management of congenital heart defects, peripheral arterial disease, and heart transplantation, among others[1].

CONTENT AND POSITIVE EFFECTS OF CR

CR programs stand as the most cost-effective intervention to ensure favorable outcomes across a broad spectrum of cardiovascular conditions[2]. These programs encompass physical training and counseling on future physical activity, the identification, assessment, and mitigation of various cardiovascular risk factors, optimization of medication regimens, psychosocial support, education on nutrition, weight management, the sustained benefits of regular exercise, its purpose, potential side effects, and the promotion of medication adherence. The overarching, long-term objectives of the CR program are to promote consistent unsupervised exercise, the adoption of a “healthy lifestyle”, the reintegration of employed individuals into the workforce, and the enduring reduction of major adverse cardiac events (MACEs) as well as the deceleration of the cardiovascular continuum. Some of the well-documented short-term effects of CR encompass enhancements in lipid profiles, reductions in blood pressure, the management of type 2 diabetes, decreases in inflammation high-sensitivity C-reactive protein (hsCRP), heart rate normalization, improvements in ejection fraction, mitigation of adverse left ventricular remodeling, and the alleviation of emotional stress and depression, among others[2-4].

SAFETY OF THE CR

The safety of the CR program has remained unquestionably solid. For instance, data from the French registry of complications during CR reveal an exceptionally low incidence of expected adverse events or complications, such as 1 MACE occurring in more than 8000 stress tests, 1 MACE in every 50000 h of patient exercise, and 1.3 cardiac arrests per million hours of exercise[5].

INCONSISTENCY OF RECOMMENDATIONS VS CLINICAL PRACTICE RELATED TO CR

Considering all the information presented, the European Society of Cardiology and other prominent global cardiology associations have officially acknowledged CR as a highly effective and essential component in the comprehensive treatment of all categories of cardiology patients. They have included CR in their guidelines, assigning it class I recommendations and a level of evidence A[2-4,6,7]. Despite this, it remains a matter of concern that less than half of eligible patients are actually referred for CR, whether in an outpatient or inpatient setting [2,3,7,8].

On the other hand, findings from extensive studies like Euroaspire indicate that a substantial portion of patients with established atherosclerotic cardiovascular disease (CVD) continue to maintain unhealthy lifestyles and struggle with inadequate control of modifiable cardiovascular risk factors, including elevated blood pressure, unfavorable lipid profiles, and diabetes. For instance, 55% of these patients were persistent smokers, 38% were categorized as obese (with a body mass index of ≥ 30 kg/m²), 66% engaged in physical activity for less than 30 min five times a week, 42% had blood pressure equal to or exceeding 140/90 mmHg, and 71% exhibited low-density lipoprotein cholesterol levels of 1.8 mmol/L or higher. The authors rightly emphasize that “cardiovascular prevention requires modern preventive cardiology programs delivered by interdisciplinary teams of healthcare professionals addressing all aspects of lifestyle and risk factor management, in order to reduce the risk of recurrent cardiovascular events”[9].

CENTER-BASED VS HOME-BASED CR

According to the new systematic review[10], home-based CR (HBCR) could offer a secure and practical alternative to traditional center-based CR (CBCR). Research suggests that the HBCR model may serve as an equitable intervention approach for stable patients with CVD across all risk levels for exercise-related cardiovascular complications, particularly for those who are unable to access CBCR services. Moreover, the integration of artificial intelligence, with its robust data mining and interpretation capabilities, holds substantial future promise for HBCR. Tailored HBCR programs can be implemented by harnessing artificial intelligence through wearable monitoring and personalized coaching[10].

HYBRID CR

In the current medical setting, the duration of hospital stays for patients with conditions like ACS or acute HF has notably shortened, often leaving insufficient time for comprehensive patient education regarding their medical condition. Hence, CR programs, whether in outpatient, inpatient, or hybrid formats, have become essential and ideal for ensuring the complete and long-term effectiveness of interventional, surgical, or medical treatments[11]. Particularly during the challenging period of the coronavirus disease 2019 pandemic[12], hybrid CR has gained prominence, proving to be a safe and efficient alternative to traditional rehabilitation care, offering numerous benefits for CVD patients[13,14]. Research have demonstrated the safety and effectiveness of hybrid CR exercise programs, which not only reduce the cost of delivery but also enhance patient participation[15,16]. In the latest review[16], it was revealed that hybrid CR provided similar short-term outcomes to traditional CR for patients with coronary artery disease. A recent systematic review[17] demonstrated that telerehabilitation, centered on exercise, is equally cost-effective when compared to traditional CBCR interventions. European Association of Preventive Cardiology strongly encourages the development and seamless integration of alternative digital modalities, like telerehabilitation, to offer comprehensive CR in a more refined and effective manner[12].

PATIENTS OUTCOMES AFTER CR

In a meta-analysis comprising 85 randomized controlled trials involving 23430 individuals with coronary heart disease, exercise-based CR demonstrated improved outcomes across short-term (6 to 12 mo), medium-term (> 12 to 36 mo), and long-term (> 3 years) follow-up periods. Short-term effects included reductions in myocardial infarction rates and all-cause hospitalizations, while medium and long-term effects were associated with decreased cardiovascular mortality[18]. Additionally, a recent study by Bauer *et al*[19] has affirmed that CR leads to a reduction in 2-year mortality following CABG.

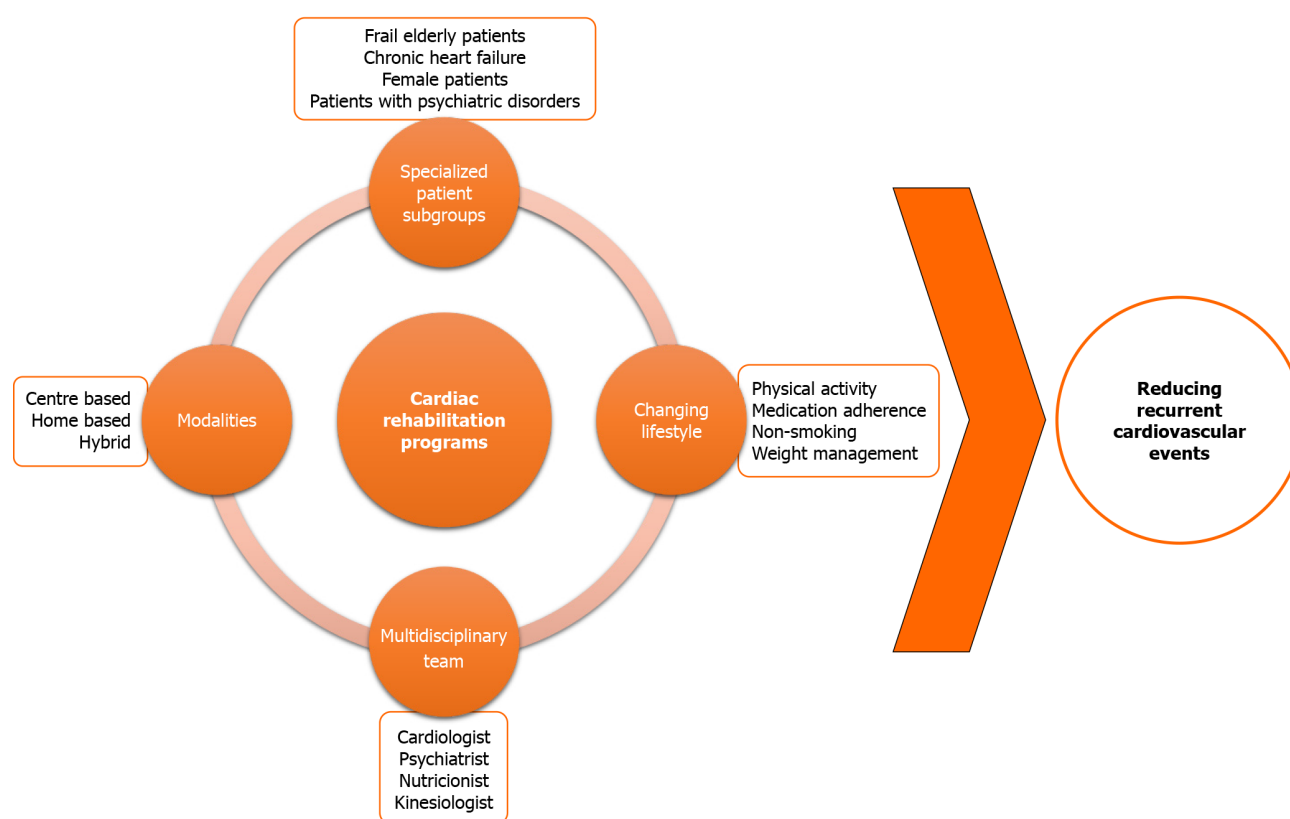
SPECIALIZED PATIENT SUBGROUPS

In addition to the conventional patient profile (comprising individuals post-ACS with or without PCI, coronary or valvular surgery), contemporary CR now places emphasis on specialized patient subgroups. These include frail elderly patients[20], the female population, with consideration for its unique characteristics (as women are less frequently referred to CR!)[21], individuals with multiple cardiovascular comorbidities, those who have undergone transcatheter implantation or valve repair, and particularly patients with chronic heart failure (HF) (CHF)[7,22,23].

Results from global survey on barriers to CR based on gender indicate that barriers to CR differ significantly between men and women across various regions, underscoring the need for region-specific, customized approaches to overcome these challenges[24]. For women, the primary barriers to enrollment encompass a lack of awareness, cost considerations, and concerns about experiencing fatigue or pain during exercise. When it comes to program adherence, women's main difficulties involve distance, transportation, and family responsibilities. Notably, non-working women experience more pronounced CR challenges. While personalized strategies aimed at addressing these challenges were highly beneficial to patients, there is a need for the implementation of automatic referral and the provision of a choice of reimbursed CR models with elements tailored to women to effectively address the primary barriers identified[24].

PATIENTS WITH CHF AND CR

Patients with CHF exhibit a significant degree of heterogeneity, forming an increasingly diverse population with a wide array of characteristics, including comorbidities, symptoms, clinical stability or instability, with preserved or varying degrees of reduced ejection fraction of the left ventricle. In patients with compensated HF with reduced ejection fraction, regular exercise has been shown to reduce both total hospitalizations and those related to HF, enhance exercise tolerance, and improve overall quality of life, including a reduction in depressive symptoms[7,22]. Taylor *et al*[7] aptly underscores in their recent publication that CR should be regarded as an essential, the fifth pillar in the treatment of HF patients, alongside pharmacological interventions such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin



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Figure 1 Comprehensive cardiac rehabilitation in modern cardiology.

receptor-neprilysin inhibitors, sodium-glucose co-transporter 2 inhibitors, and medical devices.

ADDITIONAL ADVANTAGES OF THE CR PROGRAMS

An emerging concern in recent years has been the early recognition and intervention in a wide spectrum of psychological disorders following ACS or cardiac surgery, potentially leading to post-traumatic stress disorder. These patients often go unnoticed and are known to experience a lower quality of life, an increased incidence of MACEs, and an overall poorer prognosis compared to those without such disorders[11]. Comprehensive CR, with individualized patient assessments, provides an opportune moment for recognizing and treating these psychological disorders. A multidisciplinary team approach, which actively involves psychologists and psychiatrists, is essential for comprehensive management[11,25].

CONCLUSION

Taking all the above into account, it is evident that CR programs are effective, safe, cost-effective for society, and an indispensable component of the treatment for a broad spectrum of cardiac patients. Instead of providing a traditional conclusion, we would like to conclude this editorial with a message we consistently impart to our patients: “CR cannot change a patient’s past, but it unquestionably holds the potential to enhance the future of the patient’s heart, with a high-quality life without MACEs” (Figure 1).

FOOTNOTES

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Retrospective Study

Efficacy and prognostic impact of Pericarpium Trichosanthis injection combined with nicorandil for intractable angina pectoris in elderly patients: A retrospective study

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Abstract

BACKGROUND

Coronary artery disease (CAD) is a leading cause of global cardiovascular mortality. Refractory angina pectoris, a manifestation of CAD, requires effective drug treatments. Pericarpium Trichosanthis injection, a traditional Chinese medicine, improves cardiovascular symptoms, while nicorandil alleviates spasms and angina. Both have potential in treating CAD.

AIM

To investigate the therapeutic effects of combining Pericarpium Trichosanthis injection and nicorandil in elderly patients suffering from refractory angina caused by coronary heart disease.

METHODS

A retrospective analysis was conducted on the data of 130 patients diagnosed with refractory coronary heart disease. Based on the different treatment regimens administered during hospitalization, the patients were divided into a control group (58 cases) and a study group (72 cases). The control group received conventional treatment, which included aspirin, statins, and nitrate vasodilators. In addition to the conventional medication, the study group received a combination treatment of Pericarpium Trichosanthis injection and nicorandil.

RESULTS

After treatment, the study group showed significantly higher left ventricular ejection fraction and cardiac output, and lower brain natriuretic peptide and C-reactive protein levels compared to the control group. The study group also

exhibited improvements in angina, quality of life, exercise endurance, and lipid profiles. Multivariate logistic regression analysis revealed a relationship of lipid levels and heart function with the combined treatment. Some patients in the study group experienced headaches during treatment, but no significant adverse reactions were observed. Follow-up showed that the treatment was well-tolerated, with no drug-related adverse reactions detected.

CONCLUSION

Combination of Pericarpium Trichosanthis injection and nicorandil is more effective than conventional treatment in improving symptoms and heart function in elderly patients with refractory angina pectoris.

Key Words: Pericarpium Trichosanthis injection; Coronary heart disease; Intractable angina pectoris; Nicorandil

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Core Tip: Combining Pericarpium Trichosanthis injection and nicorandil shows promise in improving symptoms and heart function in elderly patients with refractory angina caused by coronary disease, as demonstrated by a retrospective study. This combination resulted in significant improvements in left ventricular function, cardiac output, angina frequency, quality of life, exercise tolerance, and lipid profiles. The therapy was well-tolerated with minimal adverse reactions. These findings highlight the potential of this combined treatment as an effective therapeutic option for refractory angina in elderly patients.

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INTRODUCTION

Coronary artery disease (CAD) has become the leading cause of death from cardiovascular diseases worldwide, with its mortality rate only second to cancer[1]. The high prevalence of CAD is closely related to factors such as inflammation, metabolic disorders, arteriosclerosis, and thrombosis. Refractory angina pectoris is a manifestation of CAD, and refers to angina symptoms caused by coronary artery lesions that do not significantly improve or become controllable under conventional treatments (such as medication and percutaneous coronary intervention)[2]. The elderly population is a high-risk group for refractory angina, and the treatment outcomes are generally poor[2]. For refractory angina pectoris, excellent drug treatment options are crucial. Currently, drug therapy is one of the preferred methods for the treatment and prevention of cardiovascular diseases. However, many treatment options face problems such as poor efficacy and severe side effects.

Pericarpium Trichosanthis injection, a traditional Chinese medicine, is widely used in the treatment of cardio-cerebrovascular diseases[3]. Pericarpium Trichosanthis injection can improve the symptoms of cardiovascular diseases such as arteriosclerosis through its antioxidant and anti-inflammatory effects. Some studies have also found that Pericarpium Trichosanthis injection can improve blood lipids, which is beneficial for the prognosis of coronary heart disease[4]. Nicorandil relaxes coronary vascular smooth muscle by stimulating guanylyl cyclase and increasing cyclic GMP levels as well as by a second mechanism resulting in activation of K⁺ channels and hyperpolarization, that can alleviate symptoms such as coronary spasms and angina. Some studies have shown that nicorandil also has some effect in treating hypertension and heart failure[5].

In the past few decades, the combined use of Pericarpium Trichosanthis injection and nicorandil for the treatment of cardiovascular diseases has received widespread attention. However, there is currently a lack of evaluation studies for elderly patients, and it is unclear what impact this combined treatment option has on the efficacy and safety for older patients. The aim of this study was to explore the efficacy and prognostic impact of Pericarpium Trichosanthis injection combined with nicorandil in the treatment of refractory angina pectoris in elderly patients, and to provide clinical decision support for the future treatment of coronary heart disease in elderly patients.

MATERIALS AND METHODS

General information

Case data: This was a multicenter study. After screening using the inclusion and exclusion criteria, 148 patients' medical records (age 72-89 years) with coronary heart disease and refractory angina pectoris admitted to Guiqian International General Hospital and Chengdu Fifth People's Hospital between March 2021 and January 2023 were selected. After

screening and excluding cases that did not meet the criteria, a total of 130 patients were finally included in the statistical analysis, with 72 in the study group and 58 in the control group. All studies used the same method for data collection, and the screening process is shown in [Figure 1](#). There were no significant differences in general data between the two groups ($P > 0.05$) ([Table 1](#)).

Diagnostic criteria: The diagnosis of coronary heart disease was based on the diagnostic criteria established by the Chinese Medical Association for Coronary Heart Disease: (1) Confirmation of at least one major coronary artery with luminal stenosis $\geq 50\%$ through coronary angiography; (2) Auxiliary examinations such as electrocardiography, cardiac troponin, and exercise testing indicating myocardial ischemia, coronary heart disease, or acute coronary syndrome; and (3) Presence of typical angina symptoms such as chest tightness and chest pain. The diagnosis of coronary heart disease was made if it was met and at the same time or was also met. The diagnostic criteria for refractory angina pectoris mainly included: (1) Pain: Persistent angina symptoms for > 3 mo, with no obvious cause or significant improvement despite ongoing treatment; and (2) Congestive heart failure.

Inclusion criteria: (1) Applicants who met the above diagnostic criteria; (2) Inclusion criteria; and (3) The medical records were complete.

Exclusion criteria: (1) Cardiac insufficiency secondary to other diseases; (2) Acute onset of severe myocardial infarction; (3) In severe liver disease, alanine aminotransferase and aspartate aminotransferase were twice the upper limit of the reference range; (4) Malignant tumors; and (5) Surgery within 2 wk.

Methods

Treatment approach: The control group was treated according to the conventional Western Medicine Guidelines for Coronary Heart Disease (2nd edition)[6] and the recommendations of the China Coronary Heart Disease Prevention Strategy 2015[7]. This systematic and individualized medication included nitrate drugs to dilate coronary arteries and increase myocardial blood flow, statins and antiplatelet drugs, as well as calcium channel blockers and β -receptor blockers to reduce myocardial contractility and heart rate, thereby reducing myocardial oxygen consumption. For patients with underlying diseases such as hypertension and diabetes, hypoglycemic and antihypertensive treatments were given. The treatment course was 1-2 wk, and after discharge, patients were advised to take long-term secondary prevention drugs for coronary heart disease and to attend follow-up visits at 2 mo, 6 mo, and 1 year.

The treatment group, in addition to the conventional treatment of the control group, was given a combination treatment of nicorandil and Pericarpium Trichosanthis injection. Pericarpium Trichosanthis injection (Shanghai Shybio Pharmaceutical Co. Ltd.) was administered at 12 mL/dose, once daily. Nicorandil (Sihuan Kebao Pharmaceutical) was administered at 5 mg/dose, three times daily. The treatment continued for 1-2 wk. After discharge, patients were advised to take long-term secondary preventive drugs for coronary heart disease, and nicorandil, and to attend follow-up visits at 2 mo, 6 mo, and 1 year. The clinical efficacy of the two groups of patients after treatment was compared.

Efficacy evaluation: The efficacy of treatment of refractory angina pectoris in coronary heart disease was evaluated using multiple indicators, including improvement in cardiac function, frequency and duration of angina, exercise tolerance, quality of life, and cardiovascular events[8]. Specific evaluation indicators included the following: (1) Cardiac function evaluation was performed using cardiac ultrasound, including left ventricular ejection fraction (LVEF), cardiac output (CO), stroke volume, and heart rate. Data on B-type natriuretic peptide (BNP) and C-reactive protein (CRP) were collected during the treatment process; (2) Changes in the frequency and duration of angina: The Canadian Cardiovascular Society (CCS) angina scale was used to evaluate the treatment effect based on improvement in subjective symptoms and signs; (3) Changes in exercise tolerance: Maximum exercise tolerance and angina attacks before and after treatment were evaluated through a treadmill test combined with a 6-min walking test (6MWT); (4) Changes in quality of life: Changes in quality of life were evaluated using the self-acceptance questionnaire (SAQ); and (5) Occurrence of cardiovascular events: Through 2 years of follow-up, the occurrence of cardiovascular endpoints was observed, including sudden cardiac death, myocardial infarction, heart failure, and fatal arrhythmia. Sudden cardiac death was defined as sudden and unexpected death, within 1 h after the onset of cardiac-related symptoms, or no evidence other than cardiac disease was found within 24 h after the onset of symptoms. This definition was jointly established by the American Heart Association and European Society of Cardiology[9,10]. Myocardial infarction was defined based on clinical manifestations, electrocardiography, myocardial enzyme studies, and imaging examinations[11]. Heart failure was defined by clinical manifestations such as dyspnea, fatigue, and generalized edema; signs including cardiac murmurs, enlarged cardiac borders, and increased heart rate; cardiac function assessment including elevated BNP or NT-proBNP in the blood, and echocardiography and/or magnetic resonance imaging showing decreased ventricular contractile function [12]. Fatal arrhythmia was defined by clinical manifestations of syncope or sudden death, and electrocardiography showed types of arrhythmia including ventricular tachycardia, ventricular fibrillation, and long QT syndrome[13].

Assessment and measurement of blood lipids: We determined the changes in lipid levels before and after treatment in patients through medical records. The diagnostic criteria for hyperlipidemia were: (1) Serum high-density lipoprotein (HDL) < 9.0 mmol/L; (2) Total cholesterol (TC) ≥ 2.1 mmol/L; and (3) Serum triglyceride (TG) ≥ 1.70 mmol/L.

Statistical analysis

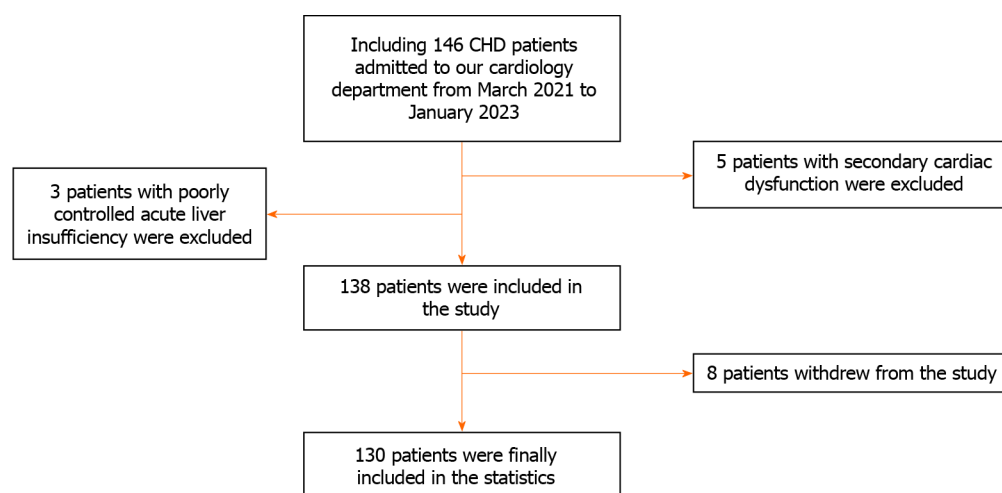
We used SPSS version 20.0 statistical software for statistical analyses. Quantitative data that conformed to a normal distribution are expressed as the mean $\pm$ SD, and single-factor analysis of variance was used for comparisons among multiple groups; least significant difference *t* test was used for pairwise comparisons; and independent sample *t* test was used for

Table 1 General data for patients (mean $\pm$ SD), *n* (%)

	Overall (<i>n</i> = 130)	Study group (<i>n</i> = 72)	Control group (<i>n</i> = 58)	<i>P</i> value
Age (yr)	73 $\pm$ 10	72 $\pm$ 11	74 $\pm$ 6	0.42
Males	78 (60)	40 (56)	38 (66)	0.09
Heart rate (bpm)	72 $\pm$ 16	71 $\pm$ 16	72 $\pm$ 17	0.01 ^a
Systolic pressure (mmHg)	114 $\pm$ 21	114 $\pm$ 20	119 $\pm$ 22	0.27
Diastolic pressure (mmHg)	73 $\pm$ 16	71 $\pm$ 9	76 $\pm$ 7	0.14
LVEF (%)	77 $\pm$ 15	77 $\pm$ 10	75 $\pm$ 11	0.47
Creatinine (mmol/L)	100 $\pm$ 52	92 $\pm$ 44	99 $\pm$ 40	0.21
Arterial high pressure	10 (8)	6 (8)	4 (7)	0.62
Diabetes mellitus	22 (17)	13 (18)	9 (16)	0.76
Dyslipidemia	44 (34)	25 (35)	19 (33)	0.22
Current smoking	50 (38)	24 (33)	26 (45)	0.62
Antithrombotics				
Aspirin	84 (65)	50 (69)	34 (59)	0.11
Clopidogrel	46 (35)	26 (36)	20 (34)	0.50
Direct oral anticoagulant	6 (5)	4 (6)	2 (3)	0.42

^a*P* < 0.05, statistically significant.

LVEF: Left ventricular ejection fraction.



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Figure 1 Screening of study subjects. CHD: Coronary heart disease.

comparisons between two groups. Categorical data are expressed as percentages, and the χ^2 test was used for comparisons. Logistic regression analysis was performed on indicators with significant differences in single-factor analysis, and *P* < 0.05 was considered statistically significant.

RESULTS

Comparison of cardiac function before and after treatment

Before treatment, there was no significant difference in LVEF, CO, BNP, CRP, or other indicators between the two groups (*P* > 0.05). After treatment, compared with the control group, the study group had higher LVEF and CO, and lower BNP and CRP, with significant differences (*P* < 0.05) (Table 2).

Table 2 Comparison of cardiac function before and after treatment in both groups (mean $\pm$ SD)

Group	LVEF, %		CO, L/min		BNP, ng/L		CRP, mg/L	
	Control group	Study group	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	43.3 $\pm$ 2.2	47.3 $\pm$ 2.2	4.8 $\pm$ 0.0	5.2 $\pm$ 0.3	724.5 $\pm$ 42.5	405.7 $\pm$ 57.4	17.4 $\pm$ 3.4	11.2 $\pm$ 1.2
Post-treatment	44.7 $\pm$ 4.1	54.5 $\pm$ 4.6	4.9 $\pm$ 0.2	5.6 $\pm$ 0.4	711.5 $\pm$ 33.4	282.6 $\pm$ 44.3	17.6 $\pm$ 3.2	8.4 $\pm$ 1.2
<i>t</i>	0.6	14.2	0.2	0.8	31.7	296.5	4.7	5.1
<i>P</i> value	0.25	0.01 ^a	0.38	0.04 ^a	0.03 ^a	0.00 ^a	0.60	0.03 ^a

^a*P* < 0.05, statistically significant.

LVEF: Left ventricular ejection fraction; CO: Cardiac output; BNP: Brain natriuretic peptide; CRP: C-reactive protein.

Evaluation of angina symptoms, quality of life, and exercise tolerance before and after treatment

Before treatment, there was no significant difference in CCS angina classification, SQA scores, or 6MWT between the groups (*P* > 0.05). After treatment, compared with the control group, the study group showed improvement in chest pain symptoms, with a significant decrease in CCS angina classification (*P* < 0.05) and a significant improvement in 6MWT (*P* < 0.05). However, the improvement in SQA scores was not significant (Table 3).

Comparison of Low-density lipoprotein, High-density lipoprotein, Total cholesterol, and Triglyceride levels before and after treatment

There was no significant difference in serum low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), or triglyceride (TG) between the two groups before treatment (*P* > 0.05). After 2 mo of treatment, the study group showed a significant decrease in TC and TG compared with the control group, while LDL and HDL did not show significant changes (*P* > 0.01) (Table 4).

Multivariate logistic regression analysis of therapeutic effects of Pericarpium Trichosanthis injection combined with nicorandil

LDL, HDL, TC, and TG (lipid indexes) as well as LVEF, CO, BNP, and CRP (cardiac function indexes) were used as independent variables, and whether to use Pericarpium Trichosanthis injection combined with nicorandil was used as the dependent variable in the multiple logistic regression. LDL, TC, TG, LVEF, CO, and BNP were significantly related to the use of the combination therapy (*P* < 0.05), and the combined treatment had an inhibitory effect on LDL, TC, TG, and BNP, and a promotive effect on LVEF and CO (Table 5).

Adverse reactions and follow-up

During the treatment period, 12 (16.7%) patients in the study group experienced headaches, with an average duration of 4 d and self-resolution. Throughout the entire treatment process, there was no impact on blood pressure, heart rate, or oxygen saturation in any of the patients. All 130 patients successfully completed the treatment, and 92 (71%) completed follow-up, with a median duration of 8.5 (3-12) mo. During follow-up, two patients in the study group and three in the control group died of respiratory failure caused by coronavirus disease 2019 at the 6-12-mo follow-up. No other related adverse reactions occurred in the patients during follow-up, and there were no deaths due to other causes.

DISCUSSION

Pericarpium Trichosanthis injection is a traditional Chinese medicine formulation that has been widely used in the treatment of cardiovascular and cerebrovascular diseases in recent years. Multiple studies have shown that Pericarpium Trichosanthis injection has significant clinical efficacy and minimal adverse reactions. A clinical study demonstrated that Pericarpium Trichosanthis injection significantly reduced the severity of angina and myocardial ischemic time, while also lowering the levels of myocardial enzymes, indicating its cardioprotective effects[14]. Another randomized controlled trial demonstrated that Pericarpium Trichosanthis injection has a significant effect in relieving symptoms and improving hemodynamic parameters in patients with angina[15]. Nicorandil has been widely used in the treatment of cardiovascular diseases such as arrhythmia and hypertension. In recent years, researchers have conducted in-depth studies on the pharmacology and clinical applications of nicorandil. A meta-analysis of nicorandil extended-release tablets found that it can significantly reduce blood pressure and heart rate, with a more pronounced effect on patients with cardiovascular diseases[16]. Another prospective study on critically ill cardiovascular disease patients using a cardiac support system demonstrated that nicorandil significantly reduced mortality and the risk of cardiovascular events. Nicorandil is also widely used in protection against myocardial ischemia. A study showed that nicorandil reduced myocardial infarct size and improved myocardial contractility through various mechanisms, such as inhibiting calcium ion influx and protecting mitochondrial membrane potential[17]. However, there is currently no relevant research on the combined use of these two drugs to improve cardiac function, and there is also a lack of research into the treatment of

Table 3 Comparison of cardiac function before and after treatment between both groups (mean ± SD)

Group	CCS angina grade (score)		SAQ grade (score)		6WMT (m)	
	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	1.6 ± 0.5	1.0 ± 0.5	66.4 ± 12.5	60.9 ± 16.0	352.4 ± 100.2	414.2 ± 84.1
Post-treatment	1.3 ± 0.7	1.8 ± 0.5	68.3 ± 10.7	63.3 ± 16.3	385.0 ± 110.1	371.2 ± 85.2
<i>t</i>	2.8	13.2	28.5	33.6	28.7	225.1
<i>P</i> value	0.76	0.02 ^a	0.36	0.53	0.85	0.01 ^a

^a*P* < 0.05, statistically significant.

CCS: Canadian Cardiovascular Society; SAQ: Self-acceptance questionnaire; 6WMT: 6-min walking test.

Table 4 Comparison of blood lipid levels before and after treatment (mean ± SD)

Group	LDL (mmol/L)		HDL (mmol/L)		TC (mmol/L)		TG (mmol/L)	
	Control group	Study group	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	3.6 ± 1.4	1.6 ± 3.1	1.3 ± 0.0	1.2 ± 0.3	9.0 ± 3.8	7.3 ± 1.4	6.2 ± 1.6	4.6 ± 0.6
Post-treatment	3.0 ± 2.1	1.4 ± 3.7	1.2 ± 0.2	1.3 ± 0.4	8.7 ± 2.2	5.2 ± 0.9	6.5 ± 1.4	3.2 ± 0.9
<i>t</i>	0.6	4.2	0.2	1.1	1.7	3.5	4.7	3.1
<i>P</i> value	0.26	0.54	0.18	0.11	0.32	0.01 ^a	0.60	0.03 ^a

^a*P* < 0.05, statistically significant.

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride.

Table 5 Logistic regression analysis of therapeutic effects of Pericarpium Trichosanthis injection combined with nicorandil

Variable	SE	Wald χ^2	<i>P</i> value	OR (95%CI)
LDL	1.12	1.26	0.03	0.30 (0.08-0.49)
HDL	0.58	0.90	0.47	1.21 (1.02-1.87)
TG	1.87	3.60	0.05	0.57 (0.24-0.75)
TC	1.79	0.33	0.04	0.65 (0.43-0.69)
LVEF	0.05	0.70	0.01	1.16 (1.00-1.27)
CO	0.08	0.65	0.01	1.83 (1.02-2.36)
BNP	2.75	5.60	0.03	0.44 (0.10-0.64)
CRP	0.85	3.15	0.54	0.76 (0.23-0.95)

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride; LVEF: Left ventricular ejection fraction; CO: Cardiac output; BNP: Brain natriuretic peptide; CRP: C-reactive protein; OR: Odds ratio; CI: Confidence interval.

refractory angina. To fill this gap in the field, we conducted a retrospective study on 130 patients diagnosed with refractory angina admitted to our hospital.

In our study, the study group showed higher levels of LVEF and CO compared with the control group, while BNP and CRP levels were lower, with significant differences. This indicates that the combination therapy has significant advantages in improving heart function and reducing inflammatory responses. In the evaluation of angina improvement, quality of life, and exercise endurance, the study group demonstrated better CCS angina classification and 6MWT scores compared with the control group. This implies that the combination therapy not only improves cardiac function but also alleviates symptoms, improves quality of life, and enhances exercise endurance. These results are consistent with previous studies. Research has shown that Pericarpium Trichosanthis has the therapeutic effects of clearing heat, promoting diuresis, activating blood circulation, and dissolving stasis. It can improve microcirculation in the cardiovascular system, and promote the normal transportation and metabolism of calcium ions in myocardial cells, thereby improving heart function and alleviating angina[18]. Nicorandil, as a calcium channel blocker, can inhibit the influx of calcium ions into the vascular smooth muscle beneath the endocardium, reducing the tension and resistance of

coronary arteries, and improving cardiac hemodynamics[19]. However, there was no significant difference in SAQ scores between the two groups. This may be due to the wide individual variations among patients, as SAQ is a self-reported assessment. Additionally, the small sample size in this study may have limited the ability to detect significant differences.

The combined therapy showed a significant decrease in TC and TG levels compared with the control group, while LDL and HDL levels did not show significant changes. This suggests that the combination therapy of Pericarpium Trichosanthis injection and nicorandil can improve lipid metabolism, but has little effect on LDL and HDL levels[8]. Previous studies have found that Pericarpium Trichosanthis injection may affect lipid metabolism through various mechanisms, including reducing cholesterol synthesis, promoting cholesterol metabolism and excretion, and regulating fatty acid synthesis[20]. Current research indicates that the main active ingredients of Pericarpium Trichosanthis injection are cucurbitacin and cucurbitic acid, which have various pharmacological effects such as heat-clearing, detoxification, dampness-eliminating, phlegm-removing, lipid-lowering, antioxidant, and anti-inflammatory effects. Among them, cucurbitacin is believed to inhibit the activity of HMG-CoA reductase, thereby reducing cholesterol synthesis, while cucurbitic acid can promote cholesterol metabolism and excretion, and regulate fatty acid synthesis. This may be one of the mechanisms by which Pericarpium Trichosanthis injection reduces the incidence and mortality of chronic diseases such as cardiovascular and cerebrovascular diseases.

During the treatment period, 12 (16.7%) patients in the study group experienced headaches, which could potentially be related to nicorandil. Nicorandil is a calcium channel blocker that primarily acts on the heart and vascular smooth muscle, and is capable of dilating coronary arteries, peripheral vessels, and pulmonary arteries[21]. This results in a reduction in cardiac oxygen demand and blood ejection resistance, and a decrease in coronary artery contraction and spasm. However, during nicorandil treatment, adverse reactions such as headaches may occur, especially when first starting the medication. These headaches are usually mild and can resolve spontaneously, but they can sometimes affect the patient's comfort and quality of life. This might also be the reason why the study group did not outperform the control group in terms of SAQ scores in this study. After discharge, a total of 92 (71%) patients completed the follow-up, with a median duration of 8.5 (3-12) mo. During follow-up, some patients in both groups died from coronavirus disease 2019, and no drug-related adverse reactions were found. This suggests that the combined use of Pericarpium Trichosanthis injection and nicorandil is safe and does not increase the incidence of adverse reactions.

While this study achieved significant clinical results, it still had some limitations. The protocol did not exclude the use of other drugs, which could potentially have influenced the results. In addition, the study sample was small, and larger studies are needed to verify the safety and effectiveness of this combination therapy. Looking back at the development of healthcare in recent years, the concept of combining traditional Chinese and Western medicine and the deepening of related research, along with the development and practical use of new drugs, have all effectively improved the incidence of coronary heart disease and its complications. In the field of medical practice, appropriately adjusting or updating existing prevention methods, improving the homeostasis of the patient's internal environment as much as possible, and reducing or eliminating the adverse effects caused by the disease, are the focus of clinical physicians.

CONCLUSION

The combination of Pericarpium Trichosanthis injection and nicorandil is more effective than conventional treatment in improving symptoms and heart function in elderly patients with refractory angina pectoris.

ARTICLE HIGHLIGHTS

Research background

Coronary artery disease (CAD) is a global health concern that often leads to severe cardiovascular mortality. Refractory angina pectoris, a consequential manifestation of CAD, necessitates competent drug treatments. Two potential treatments include a traditional Chinese medicine known as Pericarpium Trichosanthis and a medication named nicorandil.

Research motivation

This research was driven by the need to investigate effective therapeutic procedures for elderly patients suffering from refractory angina pectoris due to CAD.

Research objectives

The primary objective for this research was to scrutinize the therapeutic impacts of a combined treatment, namely, Pericarpium Trichosanthis injection and nicorandil, on elderly patients with refractory angina pectoris caused by CAD.

Research methods

The study was performed as a retrospective study involving 130 patients diagnosed with refractory CAD; they were divided into control and intervention groups using digital randomization. While the control group received a routine treatment, the intervention group was subjected to the combined treatment of Pericarpium Trichosanthis injection and nicorandil.

Research results

The patients in the study group demonstrated significant enhancements in heart performance and lifestyle quality. Few patients experienced headaches, but no severe side-effects were observed. No drug-related adverse reactions were noted upon follow-up.

Research conclusions

The combined treatment of Pericarpium Trichosanthis injection and nicorandil substantially surpasses conventional treatment methods in managing symptoms and heart functionality among elderly patients suffering from refractory angina pectoris.

Research perspectives

The beneficial findings of the present study pave the way towards further exploring this combined treatment's potential varying application for CAD and its consequent complications, ultimately improving patient wellness and prolonging life spans. Promisingly, it may add a significant contribution to personalized treatment approaches for CAD patients.

FOOTNOTES

Author contributions: Kong MW and Xie YY confirmed the authenticity of all the raw data; Kong MW wrote the manuscript; Li J, Wang ZB, and Xu L reviewed and revised the manuscript; and all authors read and approved the final manuscript.

Institutional review board statement: The GIGH Research Ethics Committee (Guiyang, China) confirmed that the study complied with ethical requirements.

Informed consent statement: This study was conducted in compliance with the requirements of the Ethics Committee and informed consent was obtained from all participating patients. The privacy and confidentiality of the patients were strictly protected, and any identifying information was removed during the process of manuscript preparation to ensure patient anonymity. In the case of specific diagnostic images or other identifiable patient-related information, previous written consent was obtained and the current consent status has been maintained.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data used in this study was collected from the databases of Guiqian International General Hospital and Chengdu Fifth People's Hospital, both of which are publicly available. The dataset includes information on demographics, medical history, and disease outcomes. The data can be accessed from the official website of Chengdu Fifth People's Hospital (www.cd5120.com). It is important to note that the dataset contains personal and private information of patients, therefore, any use or redistribution of the data beyond the scope of this study is strictly prohibited due to privacy concerns.

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Pulmonary and tricuspid regurgitation after Tetralogy of Fallot repair: A case report

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Abstract

BACKGROUND

Tetralogy of Fallot (TOF) is one of the most common congenital heart defects, and surgery is the primary treatment. There are no precise guidelines on the treatment protocol for tricuspid regurgitation (TR) as a common complication of TOF repair. The timing for treatment in patients presenting with valve regurgitation after TOF repair is often difficult to determine. Here, we report the first case of sequential treatment of pulmonary and TR using interventional therapy.

CASE SUMMARY

We present the case of a 52-year-old female patient, who had a history of TOF repair at a young age. A few years later, the patient presented with pulmonary and tricuspid regurgitation. The symptoms persisted and TR worsened following percutaneous pulmonary valve implantation. Preoperative testing revealed that the patient's disease had advanced to an intermediate to advanced stage and that her general health was precarious. Because open-heart surgery was not an option for the patient, transcatheter tricuspid valve replacement was suggested. This procedure was successful, and the patient recovered fully without any adverse effects. This case report may serve as a useful resource for planning future treatments.

CONCLUSION

Treatment of both valves should be considered in patients with tricuspid and pulmonary regurgitations following TOF repair. The interventional strategy could be an alternative for patients with poor general health.

Key Words: Tetralogy of Fallot repair; Pulmonary regurgitation; Tricuspid regurgitation; Interventional treatment; Sequential treatment; Case report

Core Tip: Tetralogy of Fallot (TOF) is a common congenital heart disease. Complications following TOF repair, including pulmonary regurgitation, tricuspid regurgitation (TR), and cardiac arrhythmia, can have a negative impact on the prognosis. In this case, the patient had been treated with percutaneous pulmonary valve implantation after TOF repair, but developed TR progression and was treated with transcatheter tricuspid valve replacement. No standardized treatment guidelines for similar patients exist, and the timing and modalities of treatment remain controversial. Therefore, whether patients who develop both types of valve regurgitation after TOF repair should be treated simultaneously or sequentially is important. A treatment plan should be developed based on the patient's overall condition, with interventional techniques being the optimal option for patients with poor baseline conditions.

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INTRODUCTION

Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart diseases accounting for 7%-10% of all congenital heart diseases[1]. Four distinct anatomical features characterized it: Ventricular septal defect, pulmonary outflow tract obstruction, overriding aortic root, and right ventricular hypertrophy. Surgery is the primary treatment with a 30-year survival rate of patients after surgery of approximately 90%[2-4]. However, the outcomes after TOF are strongly affected by postoperative complications, including pulmonary regurgitation (PR), tricuspid regurgitation (TR), heart failure, and arrhythmias, which are closely linked to death[5,6]. These patients often undergo multiple surgeries, and percutaneous intervention is an attractive option because the procedure can be complicated by multiple sternotomies [7,8]. Challa *et al*[9] described a case of successful percutaneous insertion of a transcatheter 29 mm Edwards Sapien XT valve into the tricuspid valve in a patient who underwent TOF repair[9]. Seckeler *et al*[10] reported the case of a high-risk patient with complex adult congenital heart disease who underwent successful percutaneous tricuspid valve-in-ring placement with a SAPIEN 3 valve. Roberts *et al*[11] described 15 patients with congenital heart disease who had successful percutaneous tricuspid valve replacement with Melody valves, one of whom had TOF. Although numerous publications have described the percutaneous insertion of bioprosthetic tricuspid valves in patients with congenital heart disease, this is the first case described involving a LuX-Valve used in a patient after TOF repair and percutaneous pulmonary valve implantation (PPVI).

CASE PRESENTATION

Chief complaints

A 52-year-old female patient was admitted because of poor cardiac function and massive pleural and abdominal effusions.

History of present illness

Two years prior, she underwent PPVI with a Venus P valve device[12] at another hospital because of severe PR and TR. The patient improved immediately after treatment but soon developed recurrent right heart failure with severe TR, pulmonary hypertension, and extensive pleural effusion and ascites. In the previous year, she had been hospitalized multiple times for recurrent ascites with early cirrhotic changes on liver ultrasonography. The symptoms keep getting worse, presenting with progressive shortness of breath on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bilateral lower limb swelling. The symptoms were severe enough to make conversation difficult and limited her activities of daily life.

History of past illness

She was admitted with a 20-year TOF repair history and a 2-year history of PPVI. The patient was diagnosed with TOF at an early age and did not undergo corrective surgery until she was an adult because of her poor financial status. Postoperative complications, such as PR, TR, and right heart failure, had progressively worsened in recent years. Cardiac ultrasonography showed ventricular septum repair, despite the patient's inability to recall details of the procedure.

Personal and family history

The patient did not have a family history of congenital heart disease, heart failure, or respiratory illness.

Physical examination

A physical examination revealed reduced bilateral breathing sounds with slight tremor. Dilatation of the jugular vein and pitted edema of the lower extremities. From a cardiac perspective, the New York Heart Association functional class was IV. Comprehensive preoperative evaluation included the 6-minute walking distance of 221 meters; a Kansas City Cardiomyopathy Questionnaire result of 58 for quality of life assessment; and an The Society of Thoracic Surgeons score of 15.57% for surgical risk evaluation.

Laboratory examinations

Laboratory examinations revealed varying degrees of reduction in peripheral blood cytopenia, liver and kidney function impairment, and a significant increase in B-type natriuretic peptide (517.2 pg/mL) and N-terminal pro B-type natriuretic peptide (1490 pg/mL).

Imaging examinations

Transthoracic echocardiography (Figure 1A) indicated torrential TR (121 mL), a dilated right heart, and a preserved left ventricular ejection fraction (LVEF) of 56%. The tricuspid annular plane systolic excursion (TAPSE) was 11 mm, and the fractional area change (FAC) was 49%. Preoperative computed tomography (CT) (Figure 2A and B) showed an enlarged right heart and a widened inferior vena cava.

FINAL DIAGNOSIS

The final diagnosis was severe TR.

TREATMENT

Owing to massive pleural and abdominal effusions, the patient was admitted to the hospital and underwent closed drainage of the thorax and abdomen. Torasemide (10 mg twice daily) and sacubitril valsartan (25 mg twice daily) were administered. After one month of medication adjustment, the patient underwent transcatheter tricuspid valve intervention and replacement.

After evaluation by a multidisciplinary team, the patient was deemed unsuitable for a second surgery because of her poor physical condition and inability to withstand the trauma of traditional surgery. Based on the patient's anatomy and condition, we decided to use the LuX-Valve developed by the team for transcatheter tricuspid valve replacement (TTVR), and a size of 30-55 was chosen (Figure 2C and D). The Institutional Review Board of Changhai Hospital approved the study protocol and data publication (No. CHEC2018-136).

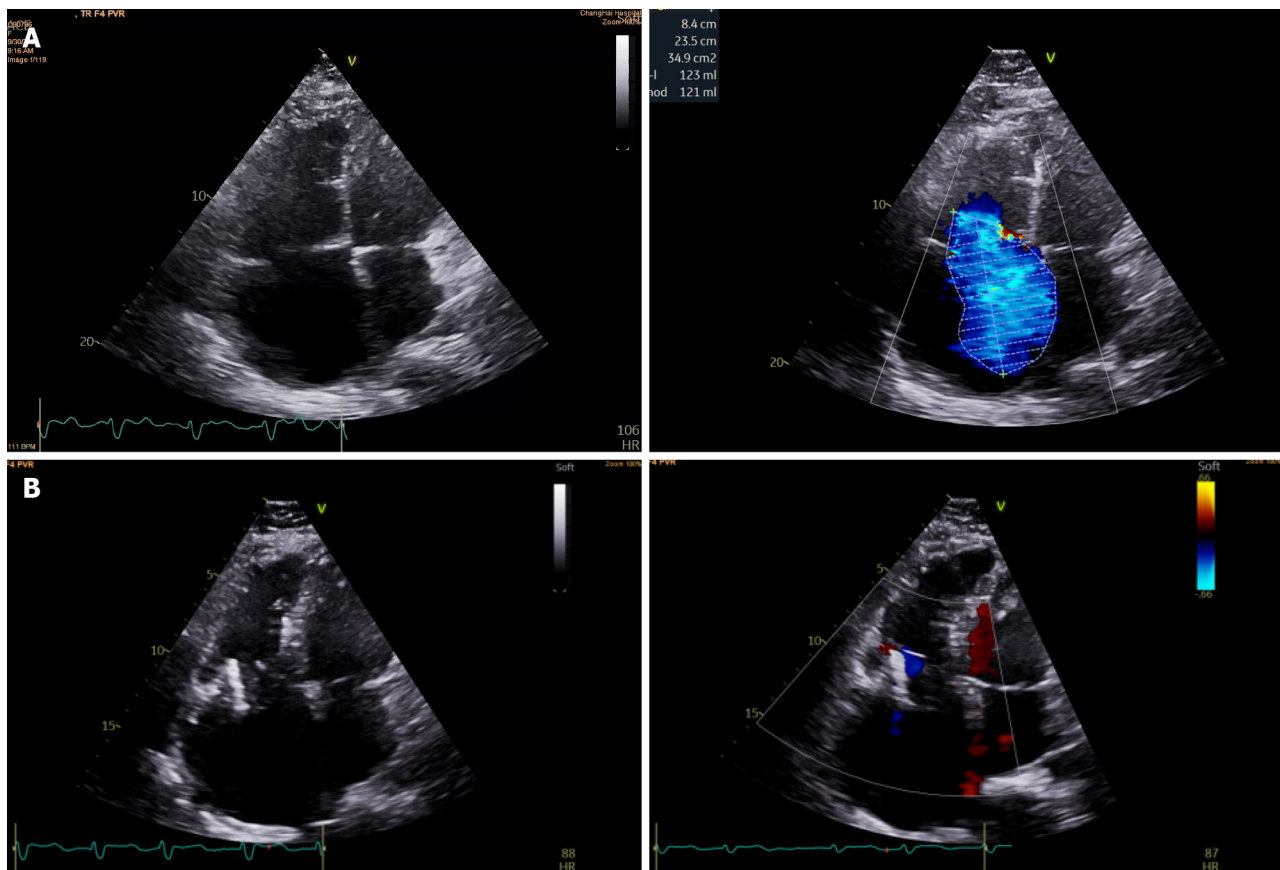
The procedure was performed in the digital subtraction angiography operating room under transesophageal echocardiography and X-ray fluoroscopy guidance. We chose a minimally invasive right-fifth intercostal thoracotomy to create the delivery channel. Following angiography to determine the TR volume, the delivery system was sent to the right heart until it reached the tricuspid valve. The valve delivery system was gently retracted, and the prosthesis was released to capture the anterior leaflet. The delivery system was adjusted to ensure the graspers were in good contact with the valve leaflet and released into the right atrial disc. Finally, the anchor was secured to the ventricular septum until the valve was adjusted to minimize perivalvular leakage. The delivery system was removed, and angiography showed satisfactory valve function with no regurgitation or paravalvular leakage (Figure 2E and F). The pressure in the right atrium immediately decreased from 41 mmHg to 34 mmHg (Videos 1 and 2).

OUTCOME AND FOLLOW-UP

Transthoracic echocardiography 1 mo after the operation showed that the valve was in position with no obvious regurgitation or paravalvular leakage, with an LVEF of 57% (Figure 1B), and the enlargement of the right atrium was significantly improved (from 327 mL to 253 mL). The TAPSE and FAC became 13mm and 38%, respectively. The mean abdominal circumference reduced from 916.51 mm to 810 mm.

DISCUSSION

PR, a common complication of TOF repair, is a major cause of distant cardiac insufficiency and death[7]. Up to 36% of patients who undergo early TOF repair require pulmonary valve replacement within 30 years of surgery[13]. Compensatory cardiac mechanisms can maintain early homeostasis after TOF repair. However, with disease progression, prolonged exposure to PR and chronic right heart volume overload can lead to right heart dysfunction, progressive right ventricular dilatation, an enlarged tricuspid annulus, and worsening TR[14,15]. The incidence of moderate-to-severe TR after TOF repair is 32%[16]. Owing to delayed treatment for PR, although patients with combined TR improve immediately after pulmonary valve replacement, TR worsens and even leads to arrhythmias and sudden death in more



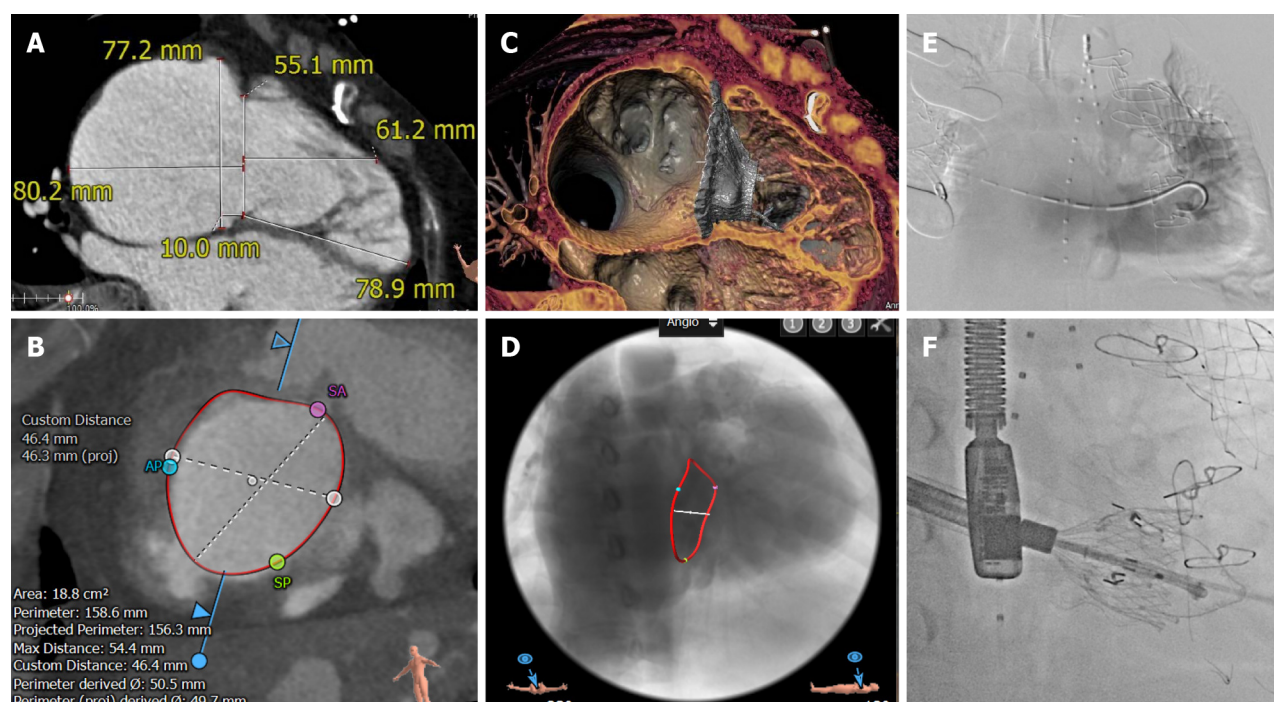
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Figure 1 Transthoracic echocardiography images. A: Preoperative transthoracic echocardiography showed an enlarged right heart and massive tricuspid regurgitation; B: Postoperative transthoracic echocardiography 1 mo showed the valve in place with no obvious regurgitation or paravalvular leakage.

than 15% of patients during long-term follow-up[17]. Numerous studies have discussed the type of treatment that is more beneficial for patients who have undergone TOF repair and subsequently develop pulmonary and tricuspid valve lesions. Most authors believe that tricuspid valve repair should be performed concurrently with pulmonary valve replacement in patients with combined moderate-to-severe TR. In the first multicenter study, the Surgical Correction of Tricuspid Insufficiency in Adult Congenital Patients requiring Pulmonary Valve Replacement (SCOTIA-PVR) and concurrent tricuspid valve intervention was shown to be safe and to improve early tricuspid valve function more than pulmonary valve replacement alone in patients with significant TR after TOF[18]. However, some studies concluded that the long-term results of pulmonary valve replacement with simultaneous tricuspid valve repair are controversial. Studies have shown no statistical difference at 6 mo between patients who underwent concurrent tricuspid valve repair and those who underwent pulmonary valve replacement alone[19]. Our patient underwent PPVI after TOF repair when she developed PR and TR. However, the patient's symptoms did not improve significantly, and right heart failure continued to progress after treatment. The reasons are as follows: (1) Although we could not obtain information about her past treatment, we speculated that the repair resulted in adhesion between the tricuspid valve and the ventricular patch. Therefore, treatment with PR does not make any sense for TR; (2) As described previously, pulmonary valve replacement alone may not improve TR, and treatment is still required. This finding indicates that both PR and TR should be considered after TOF repair; and (3) Infective endocarditis. Several studies have reported endocarditis after valve placement. Patel *et al*[20] described 4 cases of endocarditis after transcatheter pulmonary valve replacement. This may have been caused by the eccentric turbulence and thrombogenesis. Butera *et al*[21] also reported 2 cases of endocarditis following valve placement. Valve implantation is a risk factor for the development of infective endocarditis, making early monitoring and anti-infective therapy after the interventions indispensable[22].

Lesions after TOF repair are often amenable to transcatheter intervention. In selected cases, PR can be treated with transcatheter valve insertion[23]. Regarding sequential or concurrent therapy that should be used in managing PR and TR, ongoing monitoring of RV function is an important part of clinical assessment. Meanwhile, multicenter large-scale clinical studies or randomized controlled studies may help clarify whether concurrent tricuspid valve repair can improve patient prognosis.

The LuX-Valve is a novel radial-force-independent TTVR device that we previously designed. Its skirt-shaped, self-expandable, nitinol-valved stent can adapt well to an enlarged annulus and effectively prevent perivalvular leakage. The radial force-independent anchoring concept can minimize damage to the conduction bundle and reduce the occurrence of an atrioventricular block. Pre-clinical and early clinical trials[24-26] have shown that the LuX-Valve is a relatively safe and effective treatment for patients with severe TR *via* right atrial access. Patients who reach an advanced stage of the



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Figure 2 Preoperative computed tomography and intraoperative digital subtraction angiography images. A and B: Computed tomography of the right ventricle revealed an enlarged right heart and tricuspid annulus; C and D: Simulating the morphology of the prosthetic tricuspid valve after placement; E: The guide wire passed through the tricuspid valve into the right ventricle and angiography indicated massive tricuspid regurgitation; F: Release of the artificial tricuspid valve.

disease are in poor general condition and cannot tolerate conventional open heart surgery. Based on our experience, interventional treatment may be a preferable option and should be considered when managing patients with TOF with advanced disease and a challenging clinical status.

CONCLUSION

Attention should be paid to the treatment of patients with postoperative complications of TOF. Multiple clinical studies are meaningful, and the formulation of relevant guidelines is helpful for the diagnosis and treatment of the disease.

FOOTNOTES

Co-first authors: Jing-Yi Cao and Xiao-Ping Ning.

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R-I subtype single right coronary artery with congenital absence of left coronary system: A case report

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Abstract

BACKGROUND

Isolated single coronary artery is a rare congenital anomaly. R-I subtype single coronary artery is even rarer. In this subtype, a very large right coronary artery extends in the coronary sulcus to the anterior base of the heart where it produces the left anterior descending coronary artery. Currently, only a few case reports are available in the literature for this anomaly.

CASE SUMMARY

Here, we report the case of a 62-year-old woman who presented to the cardiology clinic with decreased exercise tolerance and poor blood pressure control. The patient underwent coronary angiography (CAG) and emission computed tomography (ECT). CAG images revealed a single gigantic right coronary artery (R-I type) arising from the right coronary sinus with branches supplying the left coronary territory. The ECT results confirmed myocardial ischemia at the location of the absent left coronary artery. The ECT findings confirmed that ischemia was consistent with the vascular loss location in CAG images. In such anomalies, there is a compensatory widening of the coronary artery lumen. Medical treatment was administered, and the patient was discharged.

CONCLUSION

Isolated single coronary arteries are associated with ischemia and potentially fatal acute coronary events. Hence, controlling risk factors is critical.

Key Words: Single coronary artery; R-I type; Congenital anomaly; Emission computed

tomography; Coronary angiography; Case report

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Core Tip: We present the rare case of an elderly woman with an isolated single right coronary artery (R-I subtype) detected by coronary angiography and myocardial ischemia confirmed by emission computed tomography. Since such an anomaly may be fatal in these patients, providing appropriate medical treatment promptly has a positive effect on their prognosis.

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INTRODUCTION

An isolated single coronary artery is a rare congenital anomaly in which only one coronary artery arises from the aortic trunk and supplies the entire heart *via* a single coronary ostium[1]. Such an anomaly occurs in approximately 0.024%-0.044% of the population[2]. The R-I subtype single coronary artery is even rarer, with a reported incidence of 0.0008%[3]. In the R-I variant, a single large right coronary artery (RCA) extends to the anterior base of the heart and produces the left anterior descending coronary artery, which supplies blood flow to the left side of the heart.

According to our literature review, a single RCA is exceedingly rare, and only a few cases have been reported. Saglam *et al*[4] described a 72-year-old woman with a single coronary artery anomaly who was admitted with atypical chest pain and may be a new subtype of the Lipton R-I subtype. Siddiqui *et al*[5] presented a single RCA arising from the right sinus of Valsalva in the absence of an equivalent left coronary artery system branches and associated mitral valve prolapse. Yoldaş *et al*[6] reported an extremely rare case of a 14-month-old girl who was diagnosed with a single RCA, a coronary artery fistula communicating with the right ventricle, and congenital absence of a left coronary artery. In these reports, coronary angiography (CAG) and multidetector computed tomography CAG findings were shared. However, we did not find any case reports that further verified the presence of myocardial ischemia. Herein, we presented the case of a 62-year-old woman with an R-I subtype single coronary artery and verified that myocardial ischemia was consistent with the area of vascular loss observed in emission computed tomography (ECT) images.

CASE PRESENTATION

Chief complaints

A 62-year-old female with many cardiovascular risk factors such as diabetes, hyperlipidemia, and hypertension presented to our cardiology clinic with decreased exercise tolerance and poor blood pressure (BP) control.

History of present illness

The patient reported that the symptoms began 2 wk before presentation.

History of past illness

In addition to the cardiovascular risk factors mentioned above, the patient's history of past illnesses was not significantly different.

Personal and family history

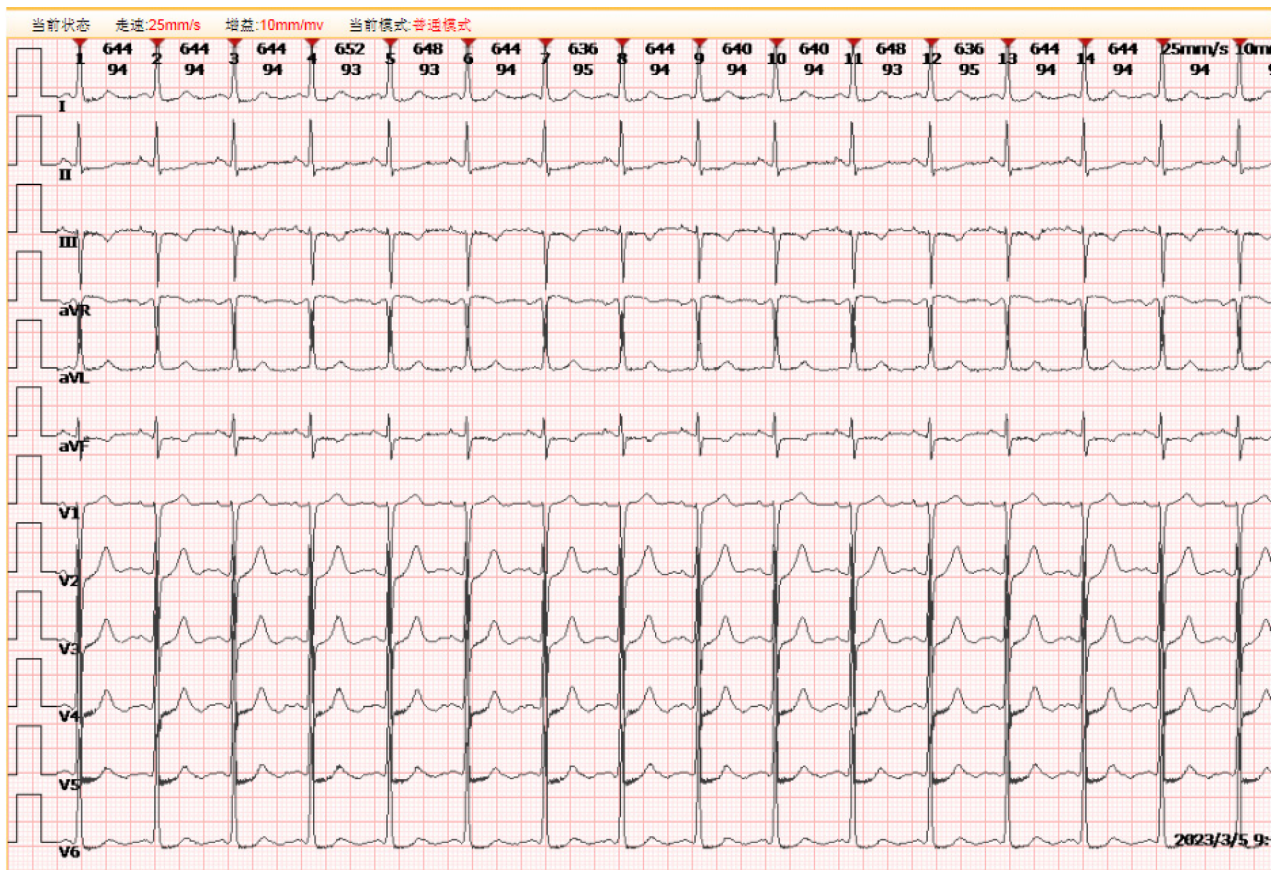
The patient denied having a history of decreased tolerance to exercise. However, within her family, her father has a history of hypertension.

Physical examination

On physical examination, the vital signs were as follows: body temperature of 37.3 °C; heart rate of 92 beats per min; BP of 151/86 mmHg; and body mass index of 23.4 kg/m². Dyspnea, heart murmurs, and other signs of heart failure were not observed.

Laboratory examinations

Cardiac troponin I levels were negative. The lipid profile revealed low-density lipoprotein, high-density lipoprotein, and total cholesterol levels of 3.16, 1.19, and 4.96 mmol/L, respectively. Fasting blood glucose was 9.49 mmol/L, and 2 h after a meal the blood glucose level rose to 22.54 mmol/L. Glycosylated hemoglobin A1c was 7.51%. Electrocardiography



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Figure 1 Electrocardiogram of the patient. A normal sinus rhythm with ST-T wave changes in leads I, II, III, aVF, and V4-V6.

showed a normal sinus rhythm with ST-T wave slight depressions in leads I, II, III, aVF, and V4-V6 (Figure 1). The echocardiography of the heart revealed no regional wall motion abnormalities and good left ventricular systolic function.

Imaging examinations

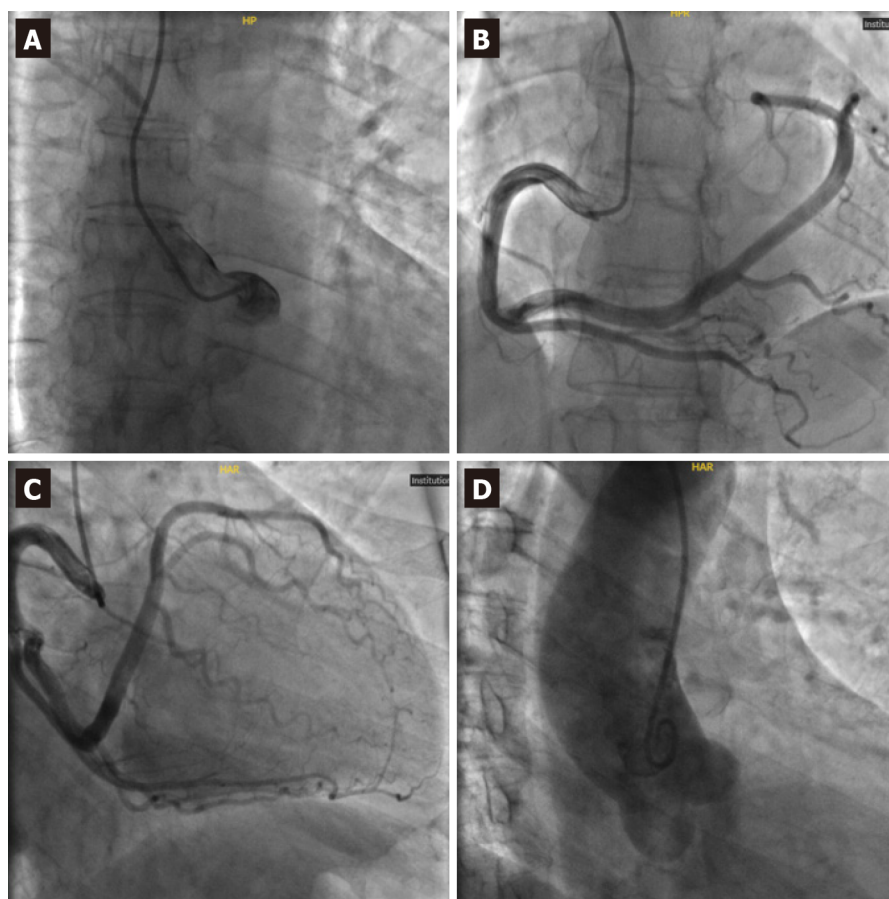
During CAG, selective cannulation of the left coronary artery (LCA) was not possible, and nonselective injection revealed the absence of a coronary artery arising from the left coronary sinus. Aortography showed the absence of the LCA, with no other vessels arising from the left or non-coronary cusps. We could not locate the left anterior descending artery or left circumflex artery (Figure 2, Videos 1, 2, 3 and 4). After selective injection into the right coronary sinus, a single ostium was visualized (Figure 2B). The RCA is a large vessel without significant atheromatous occlusive stenosis. The RCA passed within the right coronary sulcus before continuing through the crux of the heart to the left part of the coronary sulcus and terminating anteriorly in a small vessel supplying the territory of the left anterior descending coronary artery (Figure 2C). The ECT results showed that the inferior wall basal segment, inferior lateral wall basal segment, inferior septal wall middle segment, and basal segment of the left ventricle had a small-to-medium range of moderate myocardial blood flow perfusion reduction, considering the presence of myocardial ischemia (Figure 3A). Overall, left ventricular systolic function was normal without abnormal wall motion. However, the resting left ventricular ejection fraction value of the left ventricle was normal, and the load left ventricular ejection fraction value did not increase, indicating a decrease in the left ventricular systolic reserve function (Figure 3B).

FINAL DIAGNOSIS

Combined with the patient's previous medical history and the CAG and ECT imaging findings, the final diagnosis was a single RCA of the R-I type without significant coronary atherosclerosis. Myocardial ischemia was consistent with the area of vascular loss.

TREATMENT

The patient was managed with a β blocker, angiotensin receptor enkephalin enzyme inhibitor, nitrate for hypertension, statin for hyperlipidemia, biguanides, α -glucosidase inhibitor, and sulfonylurea for diabetes. Since the patient had high



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Figure 2 Results of coronary angiography. A: Coronary angiography in multiple projections showed no coronary artery arising from the left coronary sinus; B: A single and large right coronary artery originated from the right sinus continues in the coronary sulcus; C: Right coronary artery extended to the anterior base of the heart, where it gave rise to the left anterior descending coronary artery; D: No left coronary artery was found on nonselective injection of the aortic root.

risk factors such as hypertension, diabetes, and hyperlipidemia with a single RCA, we administered aspirin (100 mg once daily) for the primary prevention of coronary heart disease and trimetazidine (35 mg twice daily) to improve myocardial hypoxia. The patient was discharged on postoperative day 3, with blood glucose and blood pressure controlled smoothly, and the symptoms disappeared.

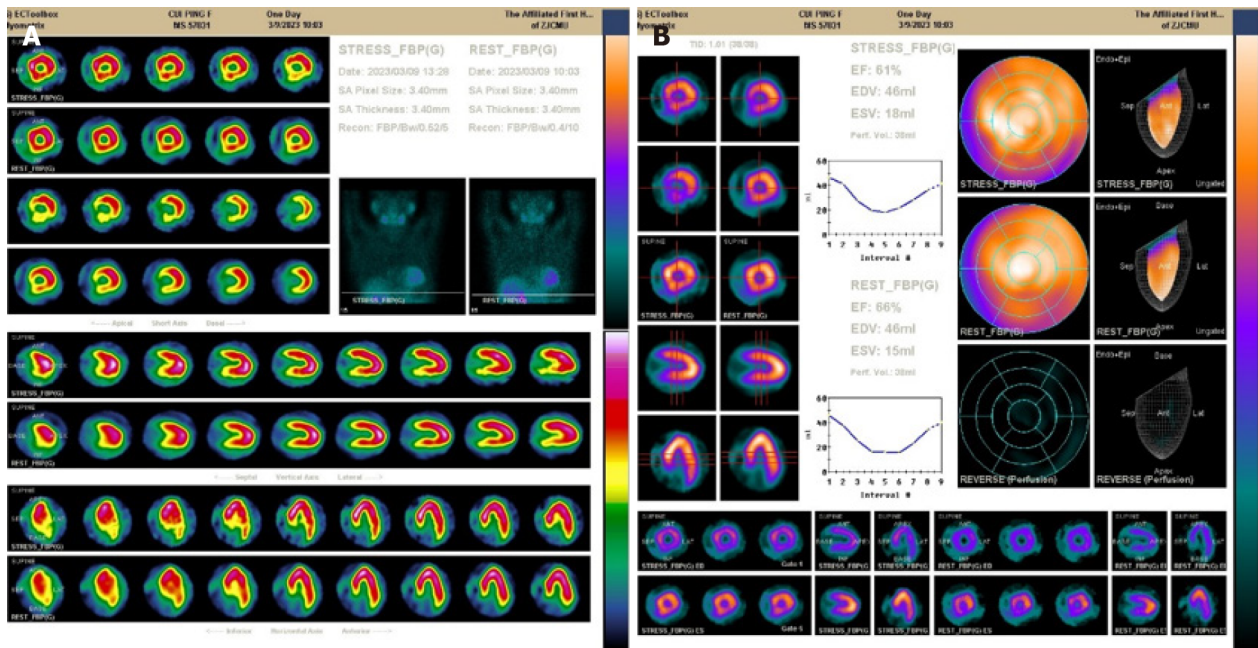
OUTCOME AND FOLLOW-UP

At the last follow-up (6 mo postoperatively), the patient felt better with no recurrence of symptoms.

DISCUSSION

The presence of a right single coronary artery with congenital absence of the LCA (type R-I, the anomaly in the present case) is the least common type of single coronary artery, with a reported incidence of 0.0008% [3]. R-I subtype single RCA with congenital absence of left coronary system has been reported only a few times. The first reported case of a single RCA was described in 1867 [7]. In a 31-year angiographic study by Villa *et al* [8], which examined the incidence of congenital coronary artery abnormalities in adults, only one R-I subtype single coronary artery was found in 13500 coronary angiography cases. Even though Desmet *et al* [9] examined 50000 coronary angiographies and Lipton *et al* [10] examined 4382 coronary angiographies, neither of them reported any cases of R-I type single coronary artery.

R-I subtype single coronary artery typically presents with a benign clinical course of disease, and the diagnosis is usually an incidental finding on noninvasive imaging. Invasive CAG can be used to diagnose symptomatic patients. Upadhyaya *et al* [11] presented the case of a young male patient with non-ST-elevated myocardial infarction. The patient was found to have a single coronary artery by employing invasive CAG. The few cases of R-I subtype detected by arteriography and autopsy have a co-compensatory mechanism of an enlarged aortic opening of regional citrate anticoagulation and an enormous dilation of the blood vessel itself with a sharp increase in lumen diameter, which can allow for perfusion of the entire heart through a single blood vessel [12,13].



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Figure 3 Results of emission computed tomography. A: The inferior wall basal segment, inferior lateral wall basal segment, inferior septal wall middle segment, and basal segment of the left ventricle had a small-to-medium range of moderate myocardial blood flow perfusion reduction; B: Normal left ventricular systolic function without abnormal wall motion with a left ventricular ejection fraction of 66%. The load left ventricular ejection fraction was 61%.

In our case, because the patient had decreased exercise tolerance and many risk factors, she underwent CAG directly, which confirmed a single, gigantic, and hyperdominant RCA arising from the right coronary sinus with branches supplying the left coronary territory. However, this discovery was accidental. With the development of minimally invasive cardiac surgery, the number of clinically significant incidental findings detected using computed tomography has increased to 18.7% [14]. The patient was discharged on postoperative day 3 without having to undergo diagnostic computed tomography angiography. This is a limitation of the present study.

The main purpose of ECT is to observe myocardial blood perfusion and metabolism, and it is usually employed to diagnose patients with myocardial ischemia and coronary heart disease. To further confirm the presence of myocardial ischemia and the relationship between ischemia and the coronary artery-deficient area of the heart, the patient underwent ECT. The results of ECT showed that the RCA was insufficient for perfusion of the entire heart, whether at rest or after an increased cardiac load. We observed ischemia in the myocardium, where blood vessels were absent. In patients with a single coronary artery, the effect of coronary artery stenosis or occlusion may be catastrophic. Therefore, active preventive treatment is important for improving patient prognosis.

CONCLUSION

CAG revealed a congenital vascular anomaly. The presence of myocardial ischemia was confirmed by ECT. Through a literature search, we found that this is the first case report of a patient with a single RCA R-I subtype who underwent ECT to verify myocardial ischemia. Although we discovered this abnormality serendipitously in our clinical practice, acute coronary events can be fatal in these patients. Therefore, once this variant is identified, active treatment and control of risk factors are necessary to improve patient prognosis.

FOOTNOTES

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