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ISCHEMIA trial: How to apply the results to clinical practice

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Abstract

During the last years two questions have been continuously asked in chronic coronary syndromes: (1) Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? Therefore, there was a need for a large definitive trial. This study was the ISCHEMIA trial, a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and optimal medical treatment (OMT) *vs* OMT alone in 5179 patients enrolled after a stress test. During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio for the invasive strategy as compared with the conservative strategy was 0.93 (95% confidence interval 0.80-1.08, $P = 0.34$). The ISCHEMIA trial deeply disrupted many of our prior attitudes regarding management strategies for patients with stable coronary artery disease. The findings underscore the benefits of disease-modifying OMT for stable coronary artery disease patients. The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to decision-making processes. Obviously, this changed after the trial results. The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

Key Words: Stable angina; Chronic coronary syndrome; ISCHEMIA; Stress testing; Therapy; Diagnosis

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Core Tip: During the last years two questions have been continuously asked in chronic coronary syndromes: Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

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INTRODUCTION

Since the first definition of angina by the English physician William Heberden in 1772 [1] many aspects have been discussed about this entity. Heberden described with a lot of detail a symptom, but he did not comprehend the disease. Later, in 1793, Edward Jenner detected thickened coronary arteries at an autopsy of his colleague John Hunter after sudden cardiac death due to an angina attack [2]. It took decades to get a first treatment (amyl nitrite) [3] for angina pectoris, and it was an even greater time for a valid understanding of the underlying disorder.

In 1967, Favaloro [4] used a saphenous vein and sewed it to the narrowing diseased coronary artery, making this the first coronary artery bypass grafting (CABG). Certainly, CABG showed a marked improvement of symptoms in patients with coronary artery disease (CAD). In 1979, Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty [5]; later this technique has been known as percutaneous coronary intervention (PCI) with the use of stents.

During the last years two questions have been continuously asked: (1) Do revascularization procedures (CABG or PCI) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death?

The initial enthusiasm for PCI was diminished after COURAGE trial [6], which showed no benefit of revascularization over optimal medical treatment (OMT). Nevertheless, the study was criticized due to a small proportion of the recruited patients treated in the participating centers and the use of bare metal stents. Then came the ORBITA trial [7] comparing OMT with PCI, this time using drug-eluting stents in a sham-controlled design, and the final result again was neutral. Once more, the same criticisms about small sample size were raised, and while symptoms and exercise tolerance only showed a tendency, regional wall motion was improved substantially in the stress echocardiograms [8].

Therefore, because of this uncertainty, there was a need for a large definitive trial. This study was the ISCHEMIA trial, which was presented at the American Heart Association Scientific Sessions in November 2019, and some months later it was published in the New England Journal of Medicine [9].

ISCHEMIA TRIAL

ISCHEMIA trial is a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and OMT *vs* OMT alone in 5179 patients enrolled after a stress test [9]. Related to this trial was the ISCHEMIA-CKD in patients with chronic kidney disease (CKD), which had a similar design to the ISCHEMIA trial except that the use of a computed tomography (CT) scan

was not necessary[10], and the CIAO-ISCHEMIA (Changes in Ischaemia and Angina over One year), which was a registry of patients excluded from the ISCHEMIA trial because of a negative CT scan. These latter patients represented around 14% of those initially considered for the ISCHEMIA trial and ultimately considered as ischemia with normal coronary arteries (INOCA)[11]. Moreover there was a quality of life study in the main ISCHEMIA trial, which included 4617 patients[12] that brought interesting results.

The rationale of the trial was clearly stated by the authors in the study abstract, “among patients with stable coronary disease and moderate or severe ischemia, whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain”[9].

One key element of the trial was the performance of a blinded coronary computed tomography angiography (CCTA) prior to enrolment to exclude the presence of left main CAD and the absence of obstructive CAD.

We could consider this trial as the largest comparative effectiveness trial of an invasive *vs* conservative strategy in patients with stable coronary disease. It is important to highlight a recent terminology change; these stable patients are now known as patients with chronic coronary syndromes due to a new definition of the European Society of Cardiology[13].

The ISCHEMIA study has tried to address the key limitations of previous trials, namely: Recruiting high-risk patients with at least moderate inducible ischemia at baseline, randomizing patients prior to the diagnostic coronary angiogram to reduce both selection and referral bias, incorporating the current state-of-the-art revascularization techniques that include the fractional flow reserve-guided PCI and the last generation drug-eluting stents at high-volume interventional sites who were selected for their proficiency and skill in revascularization, and employing an algorithm-based OMT and guidance for intensifying therapies in both arms of the trial.

The primary outcome of the trial was a five-component composite endpoint comprising cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, and resuscitated cardiac arrest, whereas the major secondary endpoints were time to cardiovascular death or non-fatal MI, anginal symptoms, and quality of life.

During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio (HR) for the invasive strategy as compared with the conservative strategy was 0.93 [95% confidence interval (CI) 0.80-1.08, $P = 0.34$]. There was no heterogeneity of treatment effect based on a broad range of pre-specified subgroups, including the presence of diabetes mellitus, high rate of OMT attainment, new or more frequent angina, degree of baseline ischemia, CAD severity based on 50% stenosis (*i.e.* one, two, or three vessel disease) or the presence of proximal left anterior descending coronary stenosis > 50%

There was no significant difference in total death for the invasive strategy ($n = 145$) group *vs* the conservative strategy ($n = 144$) group (HR = 1.05, 95%CI: 0.83-1.32) or in cardiovascular death (HR = 0.87, 95%CI: 0.66-1.15). There was also no significant difference in the rate of overall MI between the two treatment strategies (adjusted HR = 0.92, 95%CI: 0.76-1.11), although there were more procedural infarctions in the invasive strategy arm in early follow-up and more spontaneous myocardial infarctions in the conservative strategy arm in the late follow-up period[9].

There were significant and lasting improvements in angina control and quality of life metrics with an invasive approach in those patients who had significant angina [consider as daily/weekly (20% of ISCHEMIA patients)], but more modest improvements in patients with monthly angina (44%), while there was no improvement in patients with less frequent or no angina (35%)[12].

In the companion ISCHEMIA trial study (ISCHEMIA-CKD) of patients with CKD (defined as estimated glomerular filtration rate < 30 mL/min/body surface area)[10], with the same entry criteria and randomized treatment strategies, there was similarly no significant difference in outcome results between invasive *vs* conservative arms for the primary or secondary endpoints, however the invasive arm was associated with a higher incidence of stroke than the conservative arm (HR = 3.76, 95%CI: 1.52-9.32, $P = 0.004$) and higher incidence of death or initiation of dialysis (HR = 1.48, 95%CI: 1.04-2.11, $P = 0.03$). There were no significant or sustained benefits in relation with angina-related health status between the two arms.

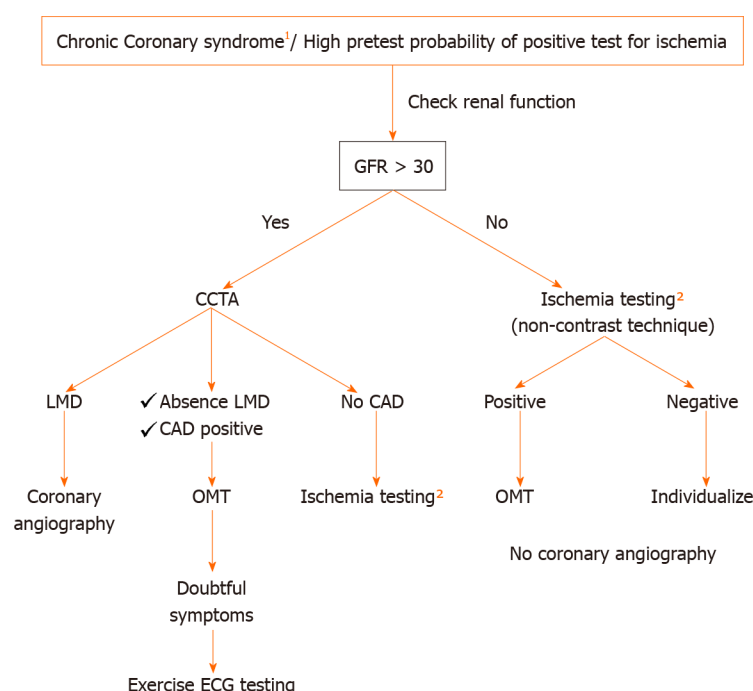


Figure 1 Algorithm for chronic coronary syndrome with high pretest probability of positive test for ischemia. ¹Previously known as stable angina. ²Stress echocardiography (non-contrast technique), single photon emission computed tomography (non-contrast technique), or magnetic resonance imaging (contrast technique). CAD: Coronary artery disease; CCTA: Coronary computed tomography angiography; GFR: Estimated Glomerular filtration rate (mL/min/1.73 m²); LMD: Left main disease; OMT: Optimal medical therapy.

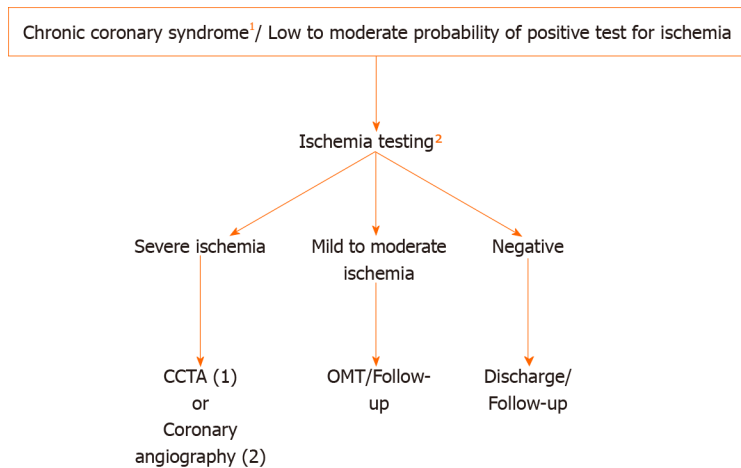
HOW TO APPLY THE RESULTS TO CLINICAL PRACTICE

The ISCHEMIA trial deeply disrupts many of our prior attitudes regarding management strategies for patients with stable CAD. The findings underscore the benefits of disease-modifying OMT for stable CAD patients, and this must be our most important focus. While revascularization will always have a crucial role in symptom relief and improving quality of life, our primary goal should be to reduce incident cardiovascular events by utilizing proven therapies that stabilize vulnerable coronary plaques and improve event-free survival.

The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to the decision-making processes. Obviously, this has changed after the trial results.

The results of this study cannot be applied to patients with a known higher risk, such as those with very severe symptoms, left ventricular dysfunction (left ventricular ejection fraction < 35%), or left main disease, since these patients were excluded from the ISCHEMIA study. The authors of the study point out, however, that the selection was near to our daily practice patients; more than half of those included were patients with severe ischemia, and also almost half of them had multivessel disease and/or CAD that included the proximal left anterior descending artery, in whom before we went to invasive management without even considering another option.

The results of ISCHEMIA and ISCHEMIA CKD might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease[13] that were based on studies published before the ISCHEMIA trial. In the next two figures we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes. **Figure 1** shows our approach for high pretest probability patients where renal function needs to be known in advance, and **Figure 2** can be applied for the low to moderate pretest probability patients. It should be pointed out that starting the work-out diagnosis by CCTA in every patient would miss a considerable number of patients with INOCA according to the combined ISCHEMIA and CIAO results (data not yet published)[11]. In addition, an initial CCTA approach would significantly increase the number of further functional tests due to unconvulsive/positive CCTAs and spurious revascularizations[14]. Another important remark for a better comprehension of our approach is that according to the ISCHEMIA-CKD results, starting ischemia testing and trying to avoid coronary intervention seems desirable for patients with kidney dysfunction.



(1) Exclude LMD as main goal

(2) Perform revascularization as main goal

Figure 2 Algorithm for chronic coronary syndrome with low to moderate pretest probability of positive test for ischemia. ¹Previously known as stable angina. ²Stress echocardiography [any glomerular filtration rate (GFR) (mL/min/1.73 m²)], single photon emission computed tomography (any GFR), or magnetic resonance imaging (only if GFR > 30). CCTA: Coronary computed tomography angiography; LMD: Left main disease; OMT: Optimal medical therapy.

CONCLUSION

To summarize our view on stable coronary disease patients after the ISCHEMIA trial, the assessment of ischemia loses priority in this scenario, symptoms evaluation gains importance, and ischemia (and not anatomy) should be the focus in certain entities like CKD or INOCA[15].

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Shortened dual antiplatelet therapy in contemporary percutaneous coronary intervention era

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Abstract

Percutaneous coronary intervention with stenting is followed by a duration of dual antiplatelet therapy (DAPT) to reduce stent thrombosis and avoid target lesion failure. The period of DAPT recommended in international guidelines following drug-eluting stent implantation is 12 mo for most patients with acute coronary syndrome, and 6 mo for patients with chronic coronary syndrome or high bleeding risk. The new generation of drug-eluting stents have metallic platforms with thinner struts, associated with significantly less stent thrombosis. Shortened DAPT has been investigated with these stents, with evidence from randomised clinical trials for some individual stents showing non-inferior safety and efficacy outcomes. This has to be balanced by the effect of DAPT on secondary prevention of systemic cardiovascular disease especially in high-risk populations. This review will outline the current evidence for individual stents with regards to DAPT duration for both acute coronary syndrome and chronic coronary syndrome and discuss further directions for research and personalised medicine in this contemporary percutaneous coronary intervention era.

Key Words: Coronary artery disease; Drug-eluting stent; Percutaneous coronary intervention; Dual antiplatelet therapy; Stent thrombosis; Target lesion revascularization

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Core Tip: The new generation of drug-eluting stents have different properties such as reduced strut thickness allowing lower level of local stent thrombosis, which may be feasible with shortened dual antiplatelet therapy (DAPT). Only a small number of

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individual stents have been validated for reduced DAPT, such as 1 mo for the BioFreedom stainless steel biolimus-eluting stent and the Onyx Resolute cobalt-chromium zotarolimus-eluting stent but in only certain populations. Future trials will compare DAPT durations within the same stent. Future research should also examine risk stratification and the parameters for patients to benefit the most from shortened DAPT.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is an interventional procedure which generally involves coronary angioplasty and stenting for individuals with coronary artery disease. Stent implantation is associated with greater lumen diameter increase in the acute period. The dimensions and the material of a stent are associated with different degrees of re-epithelialisation and risk of thrombosis. Intimal hyperplasia may cause restenosis of a vessel in bare metal stents (BMS), and metallic drug-eluting stents (DES) coated with anti-proliferative agents were developed to prevent this. However, delayed re-endothelialisation lengthens the duration of increased thrombosis risk. (Figure 1).

Dual antiplatelet therapy (DAPT), which is a combination of aspirin and an oral inhibitor of the platelet P2Y₁₂ inhibitor, is therefore recommended for a duration of time post stent implantation. Bare metal stents may only need 1 mo of DAPT, but the traditional duration for DAPT is at least 12 mo following drug-eluting stent insertion for low bleeding risk patients with acute coronary syndrome (ACS), which is Class I and Level I evidence in European Society of Cardiology and American College of Cardiology/American Heart Association Guidelines, and at least 6 mo for patients with stable coronary disease or with high bleeding risk[1,2]. High bleeding risk is defined as an increase of spontaneous bleeding during DAPT, which can be objectively calculated through risk scores such as PRECISE-DAPT[3,4].

However, the duration of this period has constantly been a subject of research, which has been influenced by the development of different P2Y₁₂ inhibitors, and evolution of drug eluting stents with different materials and anti-proliferative agent. The newer generation of stents have reduced the risk of late and very late stent thrombosis. This yields the question of whether the full period for DAPT is required and/or could it be shortened. Shortening DAPT will reduce the risk of bleeding, reduce patient noncompliance, and will be more cost effective.

This clinical review will examine the current generation of stents, and evidence for the shortened length of DAPT post stent implantation for acute coronary syndrome and stable coronary disease in the contemporary PCI era.

NEW GENERATION DES

A DES comprises 3 main components: the metallic platform, the polymer, and the anti-proliferative agent (Table 1)[5-19].

The metallic platform has a direct relationship with the dimensions of the stent. First-generation stents were constructed from stainless steel, but alloys such as cobalt-chromium, nickel-titanium, and platinum-chromium allow greater tensile strength with similar or reduced elasticity, allowing thinner struts[20]. Stainless steel stents normally have a strut of > 100 μ m, but some of the newer second-generation stents such as the Orsino stent (60 μ m), MiStent (64 μ m), and BioMime (65 μ m) are associated with 16% reduction in target lesion failure, and lower rates of any stent thrombosis in a meta-analysis of 10 trials[19]. Another meta-analysis of 69 trials comparing ultrathin (60-80 μ m), thin (81-100 μ m), intermediate (101-120 μ m), and thick (\geq 120 μ m) strut-thickness DES found that ultrathin devices had significantly less stent thrombosis (OR = 0.43, 95%CI: 0.27-0.68)[21].

Table 1 Current stents categorised by stent material, polymer, eluted drug, and shortened dual antiplatelet therapy duration validated for followed by aspirin or P2Y12 inhibitor monotherapy

Stent	Metallic platform	Polymer	Anti-proliferative agent	DAPT duration validated for	Ref.
Onyx Resolute	Cobalt-chromium (has a platinum iridium core)	Permanent	Zotarolimus	1 mo	[5,6]
BioFreedom	Stainless steel	Polymer-free	Biolimus	1 mo ¹	[7,8]
Biomatrix; Biomatrix Flex	Cobalt-chromium	Bioresorbable	Biolimus	Standard/no short DAPT	[9,10]
Nobori	Cobalt-chromium	Bioresorbable	Biolimus	6 mo	[11]
Xiience	Cobalt-chromium	Permanent	Everolimus	1-3 mo ²	[12,13]
EluNIR	Cobalt-chromium	Permanent	Ridaforolimus	Standard/no short DAPT	[14]
Ultimaster; Orsino	Cobalt-chromium	Permanent	Sirolimus	Standard/no short DAPT	[15,16]
Cre8	Cobalt-chromium	Polymer-free	Amphilimus	Standard/no short DAPT	[17]
Xposition S (self-apposing)	Nickel-titanium	Permanent	Silolimus	Standard/no short DAPT	[18]
Promus	Platinum-chromium	Bioresorbable	Everolimus	6 mo	[12]
Synergy	Platinum-chromium	Bioresorbable	Everolimus	3 mo ¹	[19]

If there was no randomised control trial or prospective trial with a paired control investigating dual antiplatelet therapy (DAPT) duration, DAPT duration validated for is put down as 'standard/no short DAPT'.

¹All trials examined both acute coronary syndrome and chronic coronary syndromes, though the EVOLVE Short DAPT study and the One-Month DAPT trial did not include patients with myocardial infarction.

²The STOPDAPT-2 trial examined 1-mo DAPT followed by P2Y12 inhibitor therapy. DAPT: Dual antiplatelet therapy.

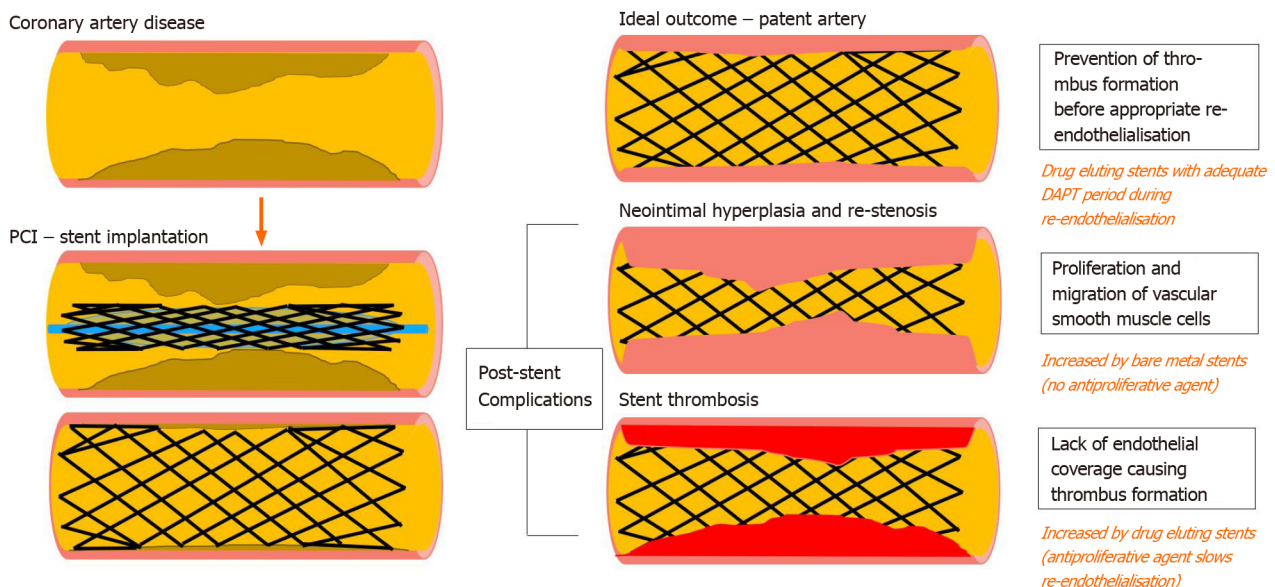


Figure 1 Percutaneous coronary intervention with stent implantation for coronary artery disease, and complications associated. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy.

Some stents have permanent or bioresorbable polymers which incorporate the anti-proliferative drug. Permanent polymers are non-biodegradable and allow continuous release of the drug. Bioresorbable polymers allow the effect of the drug to occur in the early phase of stent deployment and reverts to a bare metal stent once the polymer has become degraded, aiming to reduce very late stent thrombosis. The polymers used in first-generation stents were historically associated with delayed vascular healing and more very late stent thrombosis, but newer polymers are biocompatible. To avoid polymers entirely, some stents have the drug applied over the metallic platform of the

DES in micropores. Many network meta-analyses have found no significant difference in stent thrombosis, target lesion revascularisation, very-late stent thrombosis (defined as ≥ 1 year after implantation), or clinical outcomes between the use of different polymers independent of strut thickness and metallic platform[22,23].

The anti-proliferative drugs tend to be immunosuppressive agents, and the majority comprise sirolimus, everolimus, biolimus, and zotarolimus. Other drugs also used include amphirimus and ridaforolimus. A meta-analysis showed no difference in stent thrombosis between zotarolimus and everolimus stent[24]. However, the cobalt-chromium sirolimus stent Orsino appeared to have less stent thrombosis than the stainless-steel biolimus stent Nobori, though this may have been due to other confounding factors such as metallic platform and strut thickness, which has been previously shown to affect thrombosis[25].

Bioresorbable vascular scaffolds (BVS) are an alternative option which fully resorbs over time. However, they are less favoured in PCI currently due to association with increased risk of stent thrombosis and target lesion failure during the first 3 years after implantation and would therefore be less suitable for consideration for shortened DAPT duration[26].

As reducing strut thickness appears to be associated with less stent thrombosis, the development of the current generation of ultrathin DES with smaller strut thickness raises the question of whether shortened DAPT may be suitable in these patients.

DECREASING DAPT DURATION

The success of a PCI, stent and DAPT regimen is measured by outcomes including target lesion failure, target lesion revascularisation, major adverse cardiovascular events including stroke, myocardial infarction (MI) and cardiac death, stent thrombosis, and bleeding events measured through Thrombolysis in Myocardial Infarction (TIMI) or Bleeding Academic Research Consortium (BARC).

SHORTENED DAPT WITH NEWER GENERATION DES

A systematic review and network meta-analysis analysed 17 randomised control trials comparing at least 2 of the 3 durations of DAPT (short term < 6 mo, standard term 12 mo, and long term > 12 mo) post PCI for both ACS and chronic coronary syndrome with DES deployment, and determined that there were higher rates of major bleeding (OR = 1.78, 95%CI: 1.27-2.49) and non-cardiac death (OR = 1.63, 95%CI: 1.03-2.59) in those on long-term treatment, and higher rates of any bleeding (OR = 1.39, 95%CI: 1.01-1.92), and no significant difference in other primary endpoints[27]. Additionally, assessing the subgroup of patients with newer-second generation DES found longer term DAPT had higher bleeding events and all-cause mortality compared to short-term DAPT (OR = 1.99, 95%CI: 1.04-3.81), but had similar efficacy and safety[27].

EVIDENCE FOR SHORTENED DAPT DURATION FOR SPECIFIC STENTS

Single-arm prospective studies with paired control

It appears that shortened DAPT may be suitable for some of the new second-generation DES. The STOPDAPT single-arm study was the first prospective study to examine DAPT shorter than 6 mo for the everolimus-eluting cobalt-chromium stent (CoCr-EES). The study enrolled 1525 patients to 3 mo of DAPT followed by aspirin monotherapy after the XIENCE CoCr-EES and compared this to the CoCr-EES group in the RESET trial as a historical control, where 90% had DAPT at 12 mo. At 1 year, the primary endpoint of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and TIMI major/minor bleeding was less in the STOPDAPT than the RESET group (2.8% *vs* 4.0%, $P = 0.06$), and the incidence of stent thrombosis was lower in the STOPDAPT than in the RESET group (0% *vs* 0.3%, $P = 0.03$), suggesting that 3 mo was non-inferior to the historical control group[28].

The EVOLVE Short DAPT trial prospectively assessed the safety of 3-mo DAPT followed by aspirin monotherapy in high bleeding risk patients with the SYNERGY stent and compared this to a historical 12-mo DAPT control[19]. The primary results showed adjusted rate of death or MI in the following 3 to 15 mo was 5.6% in the 3-mo DAPT group, and 5.7% in the 12-mo control[19]. Unlike the other studies, this trial

excluded acute myocardial infarction and complex lesions.

Randomised control trials

The STOPDAPT-2 randomised clinical trial examined patients undergoing PCI with the Xience CoCr-EES and randomised them to 1-mo DAPT followed by clopidogrel against 12 mo of DAPT for 3045 patients. 1-mo DAPT was superior to 12-mo DAPT (2.36% *vs* 3.70%, hazard ratio 0.64, $P = 0.04$ for superiority), for the primary endpoint, which was a composite of cardiovascular death, myocardial infarction, stroke, definite stent thrombosis, or TIMI major/minor bleeding at 12 mo[29]. There was slightly increased stent thrombosis for 1-mo DAPT compared to 12-mo DAPT (0.3% *vs* 0.07%, $P = 0.21$ for superiority), but this was not statistically significant. 1-mo DAPT was shown to be superior with statistical significance in secondary outcomes such as TIMI major/minor bleeding and BARC 3 or 5 bleeding at 1 year.

Further studies have examined reducing this time further and using aspirin as monotherapy. The two DES with most evidence for 1-mo DAPT are the BioFreedom DES and the Resolute Onyx DES.

The LEADERS FREE I double-blinded randomised control trial examined 2466 patients with a high risk of bleeding and randomised them to the BioFreedom Biolimus polymer-free stent or the Gazelle uncoated BMS with only one month of DAPT. The BioFreedom DES was shown to be superior for the primary safety endpoint of cardiac death, myocardial infarction, or stent thrombosis, and superior for the efficacy endpoint, defined as clinically driven target-lesion revascularization[7]. This was the first time 1-mo DAPT was shown to be feasible in a DES and favourably compared to a BMS, though limitations are that BMS only has a small indication possibly in patients who need urgent surgery in < 1 mo after stenting[30].

A randomised control trial of 3020 patients compared the BioFreedom DES with short 1-mo DAPT followed by aspirin monotherapy against other DES (BioMatrix and Ultimaster) with 6-12 mo DAPT was presented at the American Heart Association Scientific Sessions 2020[8]. They examined a composite primary outcome of cardiac death, nonfatal MI, target vessel revascularisation, cerebrovascular attack, or major bleeding. There was no difference in the BioFreedom short DAPT arm compared to the contemporary DES treatment arm (5.9% *vs* 6.5%, p for noninferiority < 0.001, P for superiority 0.475). There was no statistical difference in the individual components of the composite. This included patients with and without a high bleeding risk, but did not include patients with myocardial infarction. However, an intention-to-treat analysis was used for this study, and 17% of patient remained on DAPT at 1.5 mo. Additionally, the DES that BioFreedom was compared to had not been given FDA approval for use, so the comparison group was not the current best available therapy.

The ONYX ONE Global trial randomised 1996 patients to the BioFreedom DES and the Resolute zotarolimus-eluting Onyx DES, both with 1-mo DAPT followed by single antiplatelet therapy with aspirin or P2Y12 inhibitor. Inclusion criteria were those with high bleeding risk (adjunctive oral anticoagulation to continue after PCI, age ≥ 75 , baseline haemoglobin < 110 g/L, previous intracerebral bleed, stroke in the last 12 mo, hospital admission for bleeding during the last 12 mo, nonskin cancer diagnosed or treated ≤ 3 years, planned daily NSAID or steroids for ≥ 30 d after PCI, planned surgery that would require interruption of DAPT within the next 12 mo, renal failure $\text{CrCl} < 40$ mL/min, thrombocytopenia < 100000/mm³, severe chronic liver disease, expected noncompliance to prolonged DAPT). 51% of these had acute coronary syndrome, and 32% had atrial fibrillation. They found no significant difference between Resolute and BioFreedom in primary outcomes of composite cardiac death/myocardial infarction/stent thrombosis (17.1% *vs* 16.9% $P = 0.011$ noninferiority, $P = 0.84$ superiority). The myocardial infarction rate was very high in both Resolute and BioFreedom (13.4% *vs* 14.7%), which may represent the high-risk population, but the lack of a comparison with a 3 to 6-mo DAPT regimen means this cannot be completely separated from the use of 1-mo DAPT. Additionally, BARC 2-5 bleeding was high in both groups, reflecting the high bleeding risk inclusion criteria, being slightly higher in the Resolute group but not statistically significant (15.1% *vs* 13.7%, $P = 0.4$)[5]. The Onyx One Clear Study complemented this by examining 1506 patients who had DAPT adherence and without major adverse events during the first month and found the primary endpoint of cardiac death or myocardial infarction at 1 year at be 7.0%. The Resolute Onyx DES therefore became the first 1-mo DAPT indication for high bleeding risk patients in Europe, and was FDA approved for use in the United States[6].

Observational studies

There appear to be some observational studies with evidence for shortened DAPT. The Ultimaster stent had similar rates of a composite measure of target lesion vascularisation, cardiac death, and MI for 6-mo and 12-mo DAPT in an observational study [15]. Similarly, for the Cre8 stent, an observational study showed no significant difference between patients discharged with ≤ 3 -mo DAPT due to high bleeding risk or urgent non-cardiac surgery and regular DAPT duration ≥ 6 mo for a composite endpoint of target vessel revascularisation, cardiac death, and MI [17]. Although this does show the real-world feasibility of shortened DAPT for this population of patients, the lack of a randomised control means that there is limited information for the direct comparison of DAPT duration.

Planned studies and future directions

EXCELLENT was a randomised control trial examining 6-mo DAPT compared to standard 12-mo DAPT in 1443 patients with the XIENCE/Promus everolimus stent which demonstrated non-inferiority for target vessel failure [11]. However, stent thrombosis appeared to occur more, and the study appeared underpowered for death and myocardial infarction. The XIENCE Short DAPT Program was announced in 2020, consisting of a series of 3 single-arm trials investigating 3-mo and 1-mo duration in patients undergoing PCI with XIENCE compared with historical controls [12].

Similarly, the prospective multicentre REIWA registry was announced in 2020 to investigate very short DAPT for patients with biodegradable polymer DES, such as the Synergy, Ultimaster, or Orsino. It will investigate the safety and feasibility of 1-mo DAPT followed by P2Y12 inhibitor monotherapy, much like the STOPDAPT-2 trial, but this time on bioresorbable-polymer DES rather than permanent-polymer DES [31].

Further focus could examine the use of P2Y12 inhibitor monotherapy for these stents, as this has been proved useful in the STOPDAPT-2 randomised clinical trial, or trials focusing on purely aspirin, unlike the ONYX ONE global trial. As well as clopidogrel monotherapy, ticagrelor monotherapy has also been investigated, where high-risk patients with PCI and 3-mo of DAPT continued with ticagrelor and were randomised to aspirin or placebo for one year. This showed death from any cause, MI, or stroke was 3.9% in both groups, but the 3-mo group had a lower incidence of clinically significant bleeding, warrant this as an area for further research [32]. A direct comparison of DAPT lengths between groups of 1-mo *vs* 3-mo and 6-mo DAPT can be carried out and keeping the stent type constant. Very short DAPT can be assessed in specific non-high bleeding risk patient groups to broaden the population validated for (Table 2).

DAPT DURATION DETERMINED BY SECONDARY PREVENTION OF SYSTEMIC CARDIOVASCULAR DISEASE

Although the characteristics of the newer generation of stents may be associated with the feasibility of shortened DAPT to reduce local stent thrombosis, it may be balanced out by the effect of DAPT on secondary prevention of systemic thrombosis and major adverse cardiovascular events. The PEGASUS-TIMI 54 randomised control trial examined patients ≥ 50 years old with at least one additional high-risk feature and spontaneous MI 1-3 years before enrolment. These included ≥ 65 years, diabetes mellitus, second myocardial infarction, multivessel disease, or chronic renal dysfunction. 60mg ticagrelor twice a day had marginally higher absolute benefit in terms of the primary efficacy endpoint than the absolute harm in the primary safety endpoint [33]. The DAPT trial compared 12 mo of DAPT with 30 mo of DAPT and showed an absolute risk reduction in the primary efficacy end point of the composite of death, MI, and stroke by 1.6%, and stent thrombosis by 1% [34].

A meta-analysis which included PEGASUS along with other studies with clopidogrel and prasugrel found prolonged DAPT decreased major adverse cardiac events and cardiovascular deaths compared with aspirin, but it was associated with a significant risk of bleeding, and no difference in all-cause mortality [35]. However, the efficacy may have been underestimated by PEGASUS, which allowed patients who had been off DAPT for several years to restart therapy. European and American guidelines therefore recommend consideration of prolonged DAPT in patients at low risk of bleeding with class IIb evidence [1-3].

Table 2 Summary of evidence of shortened dual antiplatelet therapy duration for specific stents from randomised control trials and single-arm prospective studies with a historical control

	Population	Study	Intervention	Control	Primary endpoint
Single-arm study	ACS (32%) and CCS (68%)	STOPDAPT [28]	1525 patients, XIENCE CoCr-EES with 3-mo DAPT followed by aspirin monotherapy	1559 patients, Endeavor CoCr-EES approximately 90% with 1-yr DAPT followed by aspirin monotherapy (RESET trial)	12-mo cardiovascular death, MI, stroke, thrombosis, bleeding; 2.8% <i>vs</i> 4.0% ($P = 0.06$)
	No acute myocardial infarction, High bleeding risk	EVOLVE Short DAPT [19]	1487 patients, SYNERGY stent with 3-mo DAPT followed by aspirin monotherapy	1493 patients, 1-year DAPT	3-15 mo death or MI; 5.6% <i>vs</i> 5.7% ($P = 0.0016$ non-inferiority)
RCT	ACS (38%) and CCS (62%)	STOPDAPT-2 [29]	1523 patients, XIENCE CoCr-EES with 1-mo DAPT followed by clopidogrel monotherapy	1522 patients, XIENCE CoCr-EES with 12-mo DAPT	12-mo Cardiovascular death, MI, stroke, thrombosis, bleeding; 2.36% <i>vs</i> 3.70% (superiority $P = 0.04$)
	ACS (42%) and CCS (58%); High bleeding risk	LEADERS FREE I [7]	1196 patients, BioFreedom DES with 1-month DAPT followed by one antiplatelet	1189 patients, Gazelle uncoated BMS with 1-month DAPT followed by one antiplatelet	390 d cardiovascular death, MI, stent thrombosis 9.4% <i>vs</i> 12.9% ($P = 0.005$ superiority)
	No acute myocardial infarction	One-month DAPT trial [8]	1507 patients, BioFreedom DES with 1-mo DAPT followed by aspirin monotherapy	1513 patients, BioMatrix and Ultimaster DES with 6-12 mo DAPT	12-mo cardiovascular death, MI, target vessel revascularisation, stroke, major bleeding; 5.9% <i>vs</i> 6.5% (noninferiority $P < 0.001$)
	ACS (62%) and CCS (38%) High bleeding risk	ONXY ONE Global [5]	1003 patients, Resolute Onyx DES with 1-mo DAPT followed by one antiplatelet	993 patients, BioFreedom DES with 1-mo DAPT followed by one antiplatelet	Cardiac death, MI, thrombosis 17.1% <i>vs</i> 16.9% ($P = 0.011$ noninferiority)

ACS: Acute coronary syndrome; DAPT: Dual antiplatelet therapy; CoCr-EES: Everolimus-eluting cobalt-chromium stent; DES: Drug-eluting stents; MI: Myocardial infarction.

PERSONALIZED ASSESSMENT OF DAPT DURATION

With the development of risk stratification and personalised medicine, DAPT duration will also be influenced by patient factors. The PRECISE-DAPT score is used at the time of stenting to determine whether the patient may benefit from 3-6 mo short DAPT or 12-24 mo standard/DAPT, and the DAPT score is used after 12 mo of DAPT to determine whether DAPT can be stopped, or if the patient should continue it to 30 mo. The PRECISE-DAPT score uses factors such as Hb, WBC, age, creatinine clearance, and prior bleeding [4]. The DAPT score uses patient factors such as age, smoking, diabetes mellitus, previous stenting or myocardial infarction, but also disease factors such as stent characteristics (diameter, paclitaxel, vein graft stent), left ventricular ejection fraction, myocardial infarction at presentation [36]. A further risk scoring model was generated from the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) registry, which calculates a risk score for both ischaemia and major bleeding at 24 mo post PCI to inform decision-making [37]. The coronary thrombotic events score used the factors of diabetes mellitus, ACS, smoking, renal function, previous PCI, and previous CABG. The bleeding events score used the factors of age, body mass index, smoking, anaemia, renal function, and triple therapy on discharge [37]. However, these have not been prospectively validated in a randomised control trial. The approval of the Onyx DES indicated for high bleeding risk patients is a step towards the personalised assessment of DAPT duration, and future research will focus on further parameters and patient stratification to identify individuals which may benefit from very short DAPT.

CONCLUSION

The period of DAPT following PCI is an area of research which has been increasingly focused on with the current cohort of contemporary DES. New stents such as the Orsino, MiStent, and BioMime are associated with thinner struts which are generally associated with less late thrombosis and may be suitable for shortened DAPT. This has been supported by a network meta-analysis which demonstrated less all-cause mortality for shortened DAPT duration (3-6 mo) compared to standard DAPT duration in the subgroup of patients with newer second-generation DES.

The STOPDAPT and STOPDAPT-2 trials directly examined the feasibility of shortened DAPT duration of less than 6 mo with CoCr-EES. STOPDAPT showed no significant difference in primary outcomes of bleeding, stent thrombosis, cardiovascular death or myocardial infarction between 3-mo DAPT followed by aspirin monotherapy against 6-12 mo DAPT, and STOPDAPT-2 showed superiority of 1-mo DAPT followed by clopidogrel monotherapy against 6-12 mo DAPT for the same composite outcome but including stroke. These are two studies which have allowed a direct comparison of DAPT timings within the same type of DES.

Some patients may benefit from shortened DAPT more due to their high bleeding risk or need to be on monotherapy by a certain point. These are patients who may have coagulation abnormalities, previous significant bleeding, recent malignancy, severe kidney or liver dysfunction, or are due to undergo timely surgical procedures. Assessing this patient subgroup for shortened DAPT trials may show greater benefit in terms of composite outcome of stent thrombosis, bleeding, cardiovascular death or myocardial infarction. The Resolute Onyx DES was tested in this population and has subsequently received a 1-mo DAPT indication in Europe and the United States. The BioFreedom DES was tested in patients both with and without a high bleeding risk. However, the limitation of these trials was the comparison against DES which were not currently licensed or standard management. Future research should focus on comparison against contemporary DES representative of current therapy, and direct comparison of DAPT duration for the same stent. There are currently registries and trials undergoing for the XIENCE, Synergy, Orsino, and Ultimaster stent, allowing direct comparison of DAPT duration in the same stent.

In addition to local effects to prevent stent thrombosis, recent evidence suggests that DAPT is useful for secondary prevention of systemic thrombosis and preventing future major adverse cardiovascular events, especially in patients with high-risk features such as diabetes mellitus, a second myocardial infarction, or multivessel disease. European Society of Cardiology and American College of Cardiology/American Heart Association guidelines support the consideration of extended DAPT for these patients.

Therefore, we are gradually moving from a “one size fits all approach” towards an era of personalised medicine where different parameters are identified to guide DAPT duration, which is reflected in current international guidelines. The development of risk scores to guide DAPT duration reflects this shift, but these remain to be clinically validated.

The contemporary PCI era brings a new generation of stents which may be beneficial, some of which are validated for shortened DAPT especially in patients with high bleeding risk. Further research is required to assess which other patient groups may benefit from this shortened DAPT approach, and balance this against the patient groups which may benefit from systemic antiplatelet therapy.

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Multimodality imaging in the diagnosis and management of prosthetic valve endocarditis: A contemporary narrative review

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Abstract

Infective endocarditis is one of the leading life-threatening infections around the world. With the exponential growth in the field of transcatheter interventions and advances in specialized surgical techniques, the number of prosthetic valves and cardiac implantable devices has significantly increased. This has led to a steep rise in the number of cases of prosthetic valve endocarditis (PVE) comprising up to 30% of all cases. Clinical guidelines rely on the use of the modified Duke criteria; however, the diagnostic sensitivity of the modified Duke criteria is reduced in the context of PVE. This is in part attributed to prosthesis related artifact which greatly affects the ability of echocardiography to detect early infective changes related to PVE in certain cases. There has been increasing recognition of the roles of complementary imaging modalities and updates in international society recommendations. Prompt diagnosis and treatment can prevent the devastating consequences of this condition. Imaging modalities such as cardiac computed tomography and ¹⁸-fluorodeoxyglucose positron emission tomography/computed tomography are diagnostic tools that provide a complementary role to echocardiography in aiding diagnosis, pre-operative planning, and treatment decision-making process in these challenging cases. Understanding the strengths and limitations of these adjuvant imaging modalities is crucial for the implementation

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of appropriate imaging modalities in clinical practice.

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Core Tip: Prosthetic valve endocarditis comprises up to 30% of all cases of infective endocarditis with a reported in-hospital mortality of 14%-22% and 1-year mortality as high as 40%. Its prompt diagnosis, although often challenging, is of critical importance to prevent deleterious consequences for patients. Advances in the field of 3-dimensional-echocardiography and the increased applications of adjuvant, complementary imaging modalities, including ¹⁸-fluorodeoxyglucose positron emission tomography/computed tomography, have enhanced the diagnostic accuracy. In the present narrative review, we discuss the epidemiology, clinical manifestations, management principles, and advantages and limitations of various imaging modalities available for the diagnosis and management of prosthetic valve endocarditis.

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INTRODUCTION

Infective endocarditis (IE) is the third most common life-threatening infection in the world with a reported in-hospital mortality as high as 14%-22% and 1-year mortality of up to 40%[1]. The volume of prosthetic valve replacement procedures has dramatically increased over the last decades[2]. This has led to an increase in the incidence of prosthetic valve endocarditis (PVE), accounting for 20% to 30% of all cases of IE[2-4]. Traditionally, the diagnosis of IE is based on the modified Duke Criteria which relies on echocardiography[5]. Initially, transthoracic echocardiography (TTE) is utilized to assess for PVE; however, due to technical limitations and acoustic shadowing, transesophageal echocardiogram (TEE) is generally mandated when it is difficult to evaluate the prosthetic structures or the clinical suspicion remains high despite an apparently unremarkable TTE, according to the contemporary guidelines from the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology guidelines (AHA/ACC)[3,5,6]. In cases where TEE yields a negative result and clinical concern persists, guidelines recommend to either repeat the study in 3-7 days or to complement the evaluation with an alternative imaging modality such as 18-fluorodeoxyglucose photon emission tomography/computed tomography (PET/CT ¹⁸F-FDG) or cardiac computed tomography (CCT)[3,5,6]. Although TEE has generally good diagnostic performance, it is limited by prosthetic material-related artifacts, and certain complications of PVE, such as abscesses and pseudoaneurysms may be missed in some cases by TEE[7].

Patients with PVE are at a higher risk of developing complications and worse outcomes when compared with native valve endocarditis (NVE) patients, even when the causative organism are similar[3,8]. Therefore, it is of uttermost importance to accurately diagnose this condition and institute prompt treatment to ameliorate its deleterious consequences. There has been increased recognition of the pivotal role of multimodality imaging in the diagnosis and treatment of PVE[9,10]. The purpose of this narrative review is to focus on the diagnosis of PVE with a special emphasis on the emerging complementary use of multimodality imaging modalities.

EPIDEMIOLOGY

The incidence of PVE ranges between 1% to 4% in the first year after surgery followed by approximately 1% per year thereafter[11]. The risk of developing PVE is higher within the first 5-years post-surgery (1.4% to 5.7%), and half of the patients with PVE develop a prosthetic valve abscess and pseudoaneurysm, which are associated with increased mortality of 30%-54%[7,12,13]. The reported incidence of PVE is heterogeneous, reflecting valve-related, patient, and geographical factors.

Valve-related factors

In a study from the Danish national registry of 18041 patients, the overall incidence of PVE was 69.8/10000 person years in patients undergoing surgical valve replacement [14]. When examined based on the anatomical location, the incidence was 65/10000 person years for mitral valve replacement (MVR), 70/10000 person years for aortic valve replacement (AVR), which increased to 89.4/10000 person years when both mitral and aortic valves were replaced[14]. Despite this difference, the cumulative incidence of PVE at 10-years was similar for both MVR and AVR (5.2%)[14].

PVE comprises 11% of all cases of tricuspid valve endocarditis and 43% of all cases of pulmonary valve endocarditis (Figure 1)[15]. In a cohort of congenital heart disease patients, 924 surgical pulmonic valve replacement were performed with 19 (2%) cases attributed to PVE, corresponding to an incidence of 333/100000 person years[16]. A large single-center cohort of 2124 adult patients (median age 41.5 years) with IE reported 24 cases of pulmonary valve endocarditis, of which 54.2% of cases occurred in the context of prosthetic valves[17].

PVE is also a feared complication in transcatheter aortic valve replacement (TAVR) [18]. In a meta-analysis by Ando *et al*[19] in 3761 patients undergoing percutaneous or surgical AVR (SAVR), the overall incidence of PVE was not significantly different between TAVR and SAVR at 1, 2 and 3.4 years follow-up[19]. Over this period of time, there was a trend towards a higher incidence of PVE in the TAVR group (0.86% to 2%) compared to the SAVR group (0.73% to 1.3%), and this was enhanced in patients with intermediate surgical risk [2.3% *vs* 1.2%; odds ratio (OR) = 1.92, 95% confidence intervals (CI): 0.99 to 3.72, *P* = 0.05]. In the Nordic Aortic Valve Intervention (NOTION) trial, 280 Low-surgical risk patients with severe aortic stenosis were randomized to TAVR (self-expanding CoreValve) or SAVR (stented bioprosthesis) [20]. This trial showed a non-significant difference in the 5 year-cumulative incidence of PVE between these two approaches (6.2% for TAVR *vs* 4.4% SAVR)[20]. Similar results were reported by Summer *et al*[21], in a pooled cohort of all patients from PARTNER I and PARTNER II trials (8530 patients, 107 cases of PVE), where the incidence over time of PVE was similar for TAVR [5.21 PVE per 1000 person-years (95% CI: 4.26–6.38)] and for SAVR [4.10 per 1000 person-years (95% CI: 2.33–7.22); incident rate ratio, 1.27 (95% CI: 0.70–2.32); *P* = 0.44][21]. Ando *et al*[19] also reported a subgroup analysis in TAVR patients which demonstrated comparable risk between balloon-expandable valves (BEV) and self-expandable valves (SEV)[19]. Similar findings were described by Regueiro *et al*[22] in a cohort of 6363 patients undergoing TAVR, where the incidence of PVE at 1-year did not significantly differ (0.95% SEV *vs* 1.25% BEV; *P* = 0.33)[22]. When other complications were analyzed, the rate of systemic stroke and embolism was higher in patients with BEV (8.7% *vs* 20.0% adjusted OR = 2.46, 95% CI: 1.04–5.82, *P* = 0.04)[22].

Furthermore, percutaneous edge to edge mitral valve repair is an increasingly relevant transcatheter intervention, where post clip implantation endocarditis has been described only in case reports, remaining an extremely rare presentation[23].

In terms of the type of valve prosthesis, the Danish National Registry demonstrated in 18041 patients undergoing left-sided valve replacement that the use of bioprosthetic valves was associated with an increased risk for prosthetic infection in patient undergoing either MVR (HR = 1.91, 95% CI: 1.08–3.37) or AVR (HR = 1.70, 95% CI: 1.35–2.15) over 10 years follow-up[14]. These results were similar to those reported by Brennan *et al*[24] in a large cohort of patients undergoing SAVR (bioprosthetic = 24410; and mechanical = 14789) followed up for 12 years where the risk of PVE was higher in those patients undergoing bioprosthetic valve replacement (HR = 1.60; 95% CI: 1.31–1.94). However, a limitation of these studies was their retrospective nature [14, 24]. Conflicting evidence arises from 3 randomized clinical trials, comprising a total of 40207 patients that underwent left sided valve replacement, which showed no significant difference between bioprosthetic and mechanical prosthesis [22–24]. A major limitation of these trials is the lack of power to detect meaningful differences since IE was not specified as a major endpoint[25–27].

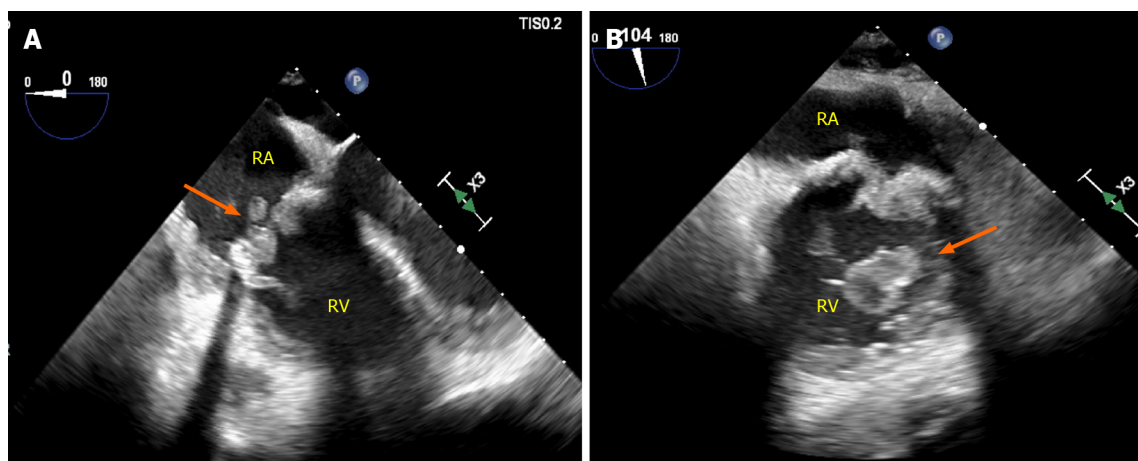


Figure 1 Prosthetic valve endocarditis complicating prior bioprosthetic tricuspid valve replacement secondary to intravenous drug abuse relapse. Thirty-two year-old male with a history of intravenous drug abuse status post bioprosthetic tricuspid valve replacement presenting with methicillin-sensitive *Staphylococcus Aureus* prosthetic valve endocarditis due to relapsed drug abuse. Images from Panel A and B demonstrate a tricuspid valve prosthesis at mid esophageal 4 chamber right ventricular focused (A) and modified bicaval views (B) with severe thickening and attached vegetations on both sides of the valve. RA: Right atrium; RV: Right ventricle.

Patient factors

There is conflicting data regarding the age group most susceptible to develop PVE. In the Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES) Database registry, which included 3120 patients with IE, patients 65-79 years old (elderly) had a significantly higher incidence of PVE compared with those < 65 years (young) and ≥ 80 years old (octogenarian) (37.3% *vs* 24.4% and 26.3%, respectively, $P < 0.001$) [28]. This observation was also demonstrated by López *et al* [29], studying a cohort of 600 Left-sided IE patients 40% of whom had PVE, showing a similar age distribution [29]. In contrast, a smaller observational study of 72 patients with IE by Menchi-Elanzi *et al* [30] demonstrated that elderly patients (65-79 years old) had a significantly lower prevalence of PVE compared to the young and octogenarians [30].

In patients with PVE, there is male predominance with 3:1 ratio across various studies [14,28-30]. This ratio changes towards 1:1 in the octogenarian group [28-30]. Interestingly, in an observational study of 621 patients with left-sided IE, mitral mechanical valve PVE was more common in women than in men [31]. The mechanism behind these findings remain unclear, and further studies are required to examine the age and gender influence on PVE.

Geographical factors

In an observational, prospective multicenter cohort of 2670 patients from 28 countries with IE, 556 patients (20.1%) had PVE [1]. The highest percentage of PVE cases was in Southern Europe, Middle East and South Africa (26.10%), and it was the lowest in South America (11.9%) [2]. In the United States, the incidence of PVE was 20.9%, with the highest source corresponding to health care associated infections (44.8%), followed by intravascular device-related infection (27.6%), non-nosocomial health care-associated PVE (21.1%), and hemodialysis (12.9%) [2].

CAUSATIVE AGENTS

The prevalence of the most common causative organisms causing PVE according to the timing and technique of valve surgery are shown in Figure 2. Within 60 days from surgical valve replacement, the most common causative organism of PVE is *Staphylococcus Aureus* (30%) followed by *Streptococcus* species (28%). Between 2 to 12 months after surgery, coagulase-negative *Staphylococci* are the most common organism (36%), and after one year, *Streptococci* predominantly viridians group, are the leading cause [2,32-35]. After TAVR, *Enterococci* and *Staphylococcus Aureus* (25% and 16%-24%, respectively) are the predominant organisms (Figure 2) [36,37].

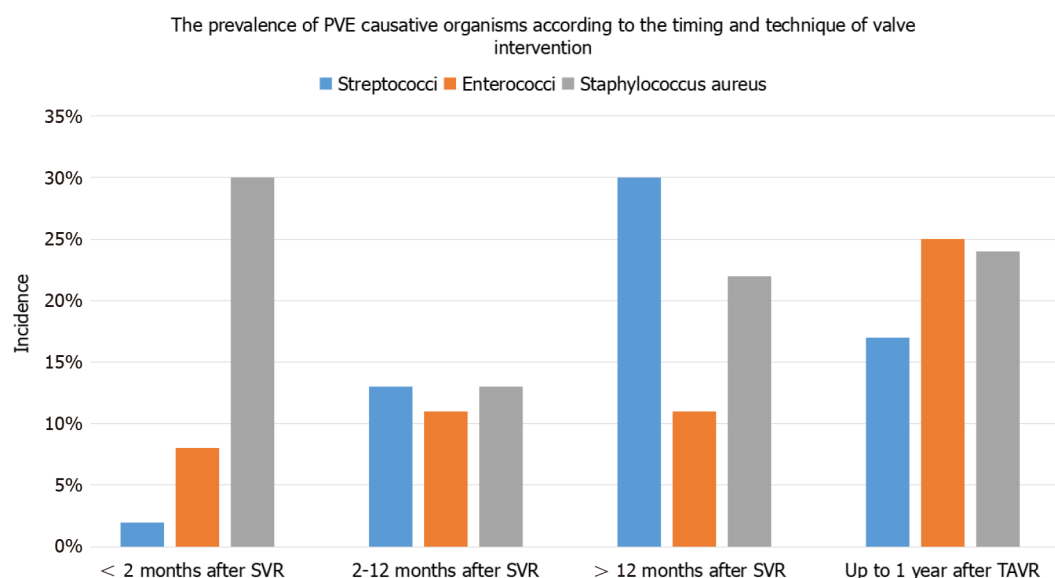


Figure 2 Prevalence of causative organisms according to timing and technique of valve intervention. The prevalence of causative organisms of prosthetic valve endocarditis in surgical left-sided valve replacement among 579 patients pooled from 5 studies[2,32-34,79] and transcatheter aortic valve replacement among 275 patients from 2 studies[35,36], categorized according to time since the index procedure. PVE: Prosthetic valve endocarditis; SVR: Surgical valve replacement; TAVR: transcatheter aortic valve replacement.

CLINICAL FEATURES

The clinical diagnosis of PVE is challenging as patients often manifest non-specific symptoms, such as fever, weakness and poor appetite in the early post-operative period[38]. Therefore, the presence of a new murmur, new or worsening congestive heart failure (CHF), conduction abnormalities and stroke should all raise suspicion for PVE[38]. Data from the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (PCS) reported the occurrence of CHF in 32.9%, intra-cardiac abscess in 29.7%, stroke in 18.2% and other systemic embolization in 14.9%, among 556 patients with PVE[2]. When comparing NVE and PVE, both had a similar incidence of CHF, stroke and persistent bacteremia; however, the incidence of systemic embolization was lower in PVE[2].

From the TAVR international registry consisting of 245 patients who developed PVE after TAVR (BEV and SEV), the most common initial symptom was fever (approximately 80%), followed by CHF (approximately 40%), and cutaneous manifestations (approximately 3%) with a median time to onset after TAVR of 5.3-5.5 months[22]. In this study, stroke was significantly higher with BEV compared to SEV (24.6% *vs* 7.8%, $P < 0.01$)[22]. The lower rate of cutaneous manifestations in PVE, such as Osler's nodes, Janeway lesions and Roth's spots could be attributed to a more acute course of the disease in PVE, compared to a more protracted course commonly seen in NVE[38]. In Reguero's cohort, patients with PVE following TAVR had no significant difference in mortality between BEV and SEV (37% *vs* 36%, respectively)[22].

In terms of mortality, Wang *et al*[2], described in-hospital mortality was significantly higher in the PVE group (127/556 patients) compared to NVE (310/1895 patients) (23% *vs* 16%, $P < 0.001$). After multivariate analysis, the key drivers of increased mortality were CHF (OR = 2.33, 95%CI: 1.62-3.34), intracardiac abscess (OR = 1.86, 95%CI: 1.10-3.15), and stroke (OR = 2.25, 95%CI: 1.25-4.03). Østergaard *et al*[14] in a cohort of 18,041 undergoing left sided valve replacement (AVR 88.8%, MVR 9.7%, and both 1.5%) demonstrated that PVE in AVR patients was associated with higher mortality than in MVR at 10 years (44% *vs* 39%, $P < 0.01$)[14]. Moreover, they also divided these results according to the prosthesis type showing a significantly higher mortality with bioprosthetic compared to mechanical valve in both AVR and MVR at 10-years. However, when both groups were matched, there was no significant difference in mortality[14].

DIAGNOSTIC IMAGING MODALITIES

Transthoracic and transesophageal echocardiography

Although acoustic shadowing and reverberation artifacts from prosthetic material hamper the imaging resolution, echocardiography remains the forefront diagnostic modality in suspected PVE[5]. Wide availability, low cost, rapid acquisition and interpretation, and a lack of radiation are some of the important qualities that make echocardiography the first-line imaging modality[6]. The echocardiographic examination should focus on identifying infection-related changes, such as vegetations, perivalvular abscess, prosthesis dysfunction or dehiscence, fistulas, or unexpected and premature structural degeneration of the valves[3] (Figure 3).

The sensitivity of TTE in PVE ranges from 17% to 36%; in comparison, it increases to 82% to 96% with TEE, suggesting the importance of TEE for better assessment of all cases of suspected PVE[39,40]. Despite the enhanced temporal and spatial resolution of multiplanar TEE, its ability to identify prosthetic valve abnormalities can be challenging[41]. Another commonly encountered limitation is an inability of echocardiography to differentiate between active and healed vegetations following antibiotic treatment. To overcome this limitation, serial studies are required to assess for size progression of the vegetation[41].

Three-dimensional (3D) echocardiography is a complementary modality which provides valuable information regarding the anatomy of the prosthetic valves and adjacent structures from different angles. Novel 3D-rendering software aid in the characterization of the vegetation size and location, destructive changes, perforations, abscess characterization, prosthetic dehiscence and associated regurgitant jets[42-44]. Chahine *et al*[45] described in 242 patients, an improved sensitivity over the recent decade for the detection of PVE (70.8% *vs* 93.7%, $P = 0.009$) with contemporary TEE technology including an increased use of 3D imaging (Figure 4)[45].

Echocardiography has been shown to predict outcomes in PVE. Wang *et al*[46] studied 115 patients with surgically proven IE (52% with bioprosthetic valves; 15.5% with metallic valves) and recognized that abscess or pseudoaneurysm detected by TEE were independently associated with increased in-hospital mortality and morbidity [OR: 3.66 (95%CI: 1.76-7.59); $P = 0.001$][46].

In cases where the clinical suspicion remains high despite an initial negative result, short-term interval follow-up is a strategy that can enhance imaging sensitivity at the expense of prolonging the time to diagnosis. This can usually be performed 3-7 days following the initial evaluation[3]. In contrast to this “watch and wait approach”, adjuvant imaging modalities play a complementary role in the diagnosis of PVE, potentially expediting patient care[7].

CCT

CCT has become an increasingly important imaging tool for the diagnosis and pre-operative planning of patients with PVE. CCT offers a number of technical advantages over echocardiography including higher spatial resolution and imaging window independence[47]. CCT has demonstrated similar diagnostic yield for the detection of perivalvular complication[7]. Feutcher *et al*[47] compared CCT with TEE in 37 patients with IE, 6 of whom had PVE. The study showed that CCT had an excellent correlation with TEE in determining vegetation size (vegetation size by TEE 7.6 ± 5.6 mm) ($r = 0.95$; $P < 0.001$). In addition, vegetation mobility was accurately diagnosed by CCT in 96% of the patients, and both modalities had similar detection rates for abscesses and pseudoaneurysms with the caveat that CCT provided more detailed anatomical location and extension[47]. Fagman *et al*[48] compared ECG-gated CT and TEE with surgical findings including abscess, vegetation, and dehiscence in 27 patients with aortic PVE. The agreement was good between surgical findings and ECG-gated CCT (kappa 0.66, 95%CI: 0.49-0.87) and TEE [0.79 (0.62-0.96)], but the combination of both TEE and ECG Gated CCT provided even better diagnostic performance [0.88 (0.74-1.0)][48]. In a more recent study by Koneru *et al*[49] in 122 patients with PVE undergoing pre-operative evaluation, the performance of high-resolution ECG synchronized 4D-CT was similar to TEE for the detection of abscess/pseudoaneurysm in prosthetic valves, independent of the type of prosthesis (70 *vs* 68 %; $P = 0.82$) and anatomical location with a synergistic effect seen when both modalities were combined (sensitivity: CT alone, 70%; TEE alone, 68%; CT + TEE, 86%)[49]. This incremental benefit of combining both modalities for PVE assessment was also described in a metaanalysis by Habets *et al*[40] who reported a pooled sensitivity/specificity of 36/93% for TEE, 86/98% for CCT, and 100/94% for both modalities together. The authors also described improved detection of peri-annular PVE complica-

CCT has also proven to be useful in surgical planning by providing additional diagnostic information regarding the anatomy of coronary arteries and aorta, and degree of calcification[3,51]. The major advantage of CCT over coronary angiography, is the ability to demonstrate coronaries and bypass graft patency non-invasively, avoiding risk of vegetation embolization during catheter manipulation[47]. It may also be valuable in the urgent evaluation of hemodynamically unstable patients who are unable to undergo TEE (Figures 5 and 6)[52].

A potential weakness of CCT is its relatively low temporal resolution, resulting in decreased sensitivity for the detection of small vegetations (< 4 mm) and leaflet perforation (< 2 mm); however, it has a comparable diagnostic performance to TEE for detecting fistulas, paravalvular leaks and prosthetic valve dehiscence[47,50] (Figure 5). Therefore, TEE remains a superior technique for the detection of small vegetations that are < 5 mm (Table 1)[53]. Some inherent technical challenges include the need for use of contrast which may exclude patients with iodine allergy or advanced kidney disease; the presence of arrhythmia that impairs the quality of image acquisition and the non-negligible amount of radiation exposure[54]. Similar to echocardiography, CCT has prognostic value in PVE. In a cohort of 155 patients with surgically proven IE, 112 (72.3%) corresponding to patients with previous valve replacement (metallic and bioprosthesis) or repair, the presence of pseudoaneurysm, abscess, and fistulas detected on CCT independently predicted mortality (HR = 3.82, 95% CI: 1.25–11.7, $P < 0.001$; and 9.84, 95% CI: 1.89–51.0, $P = 0.007$ respectively)[46].

Cardiac magnetic resonance imaging

The roles of cardiac magnetic resonance imaging (MRI) in IE, and more specifically in PVE, are currently limited, and less well defined. In general, this imaging modality offers several unique advantages such as improved 3D-visualization of cardiac structures compared to TEE, the ability to identify inflammatory changes in the myocardium and pericardium *via* delayed enhancement imaging, differentiation of vegetations from intracardiac masses, ability to diagnose infiltrative cardiomyopathies, accurate quantification of regurgitant valvular lesions and the ability to be used in patients unable to receive iodine-based contrast[54,55]. However, the role of MRI for evaluation of infective changes, especially in PVE is limited. Some of the factors that account for its limitations include incompatibility with some implantable cardiac devices, reduced availability and significant artifacts caused by metallic leaflets[53,54].

As part of the pre-operative work up, MRI does not provide as accurate information regarding the anatomy of the chest wall and its proximity to cardiac structures as does CCT, and thus is not usually favored for this purpose[56]. Nevertheless, MRI of the brain is recommended in pre-operative patients who have neurologic deficits and may also be reasonable in high-risk left-sided IE to screen for subclinical embolic events[3, 56]. The ability of brain MRI to detect subclinical cerebral lesions, which may be found in up to 70% of patients who are neurologically intact clinically, has substantial clinical implications, as presence of systemic embolization represents one minor Duke criterion[5]. This in turn may allow earlier diagnosis and the implementation of therapeutics[57,58].

PET/CT

Hybrid modalities such as leucocyte scintigraphy and ^{18}F -FDG PET/CT have also been recognized as important complementary diagnostic imaging modalities. ^{18}F -FDG PET/CT relies on the administration ^{18}F -FDG radioisotope, which is taken up by active inflammatory cells at the site of the infection. On the other hand, leucocyte scintigraphy isolates and labels granulocytes with $^{99\text{m}}\text{Tc}$ that can be localized and quantified at a specific acquisition point in time[3,59]. The steps in preparation of leucocyte scintigraphy involving the drawing and reinjection of leucocytes, makes the utilization of ^{18}F -FDG radioisotope more favorable in clinical practice[1].

The modified Duke criteria only considers echocardiography as the diagnostic imaging modality for IE. The AHA guidelines, despite acknowledging the usefulness of PET/CT for the detection of extracardiac complications, have not yet recommended its routine use for diagnosis[5]. In contrast, in the latest iteration of the ESC guidelines for the management of IE, the presence of abnormal activity of ^{18}F -FDG PET/CT or leucocyte scintigraphy SPECT/CT (> 3 months after implant) around the perivalvular region of a prosthetic valve was upgraded as a major imaging criterion for diagnosis of IE[3]. As a result, Saby *et al*[60] reported an improvement of the modified Duke criteria sensitivity from 70% to 97% without trading-off its specificity, with the use of PET/CT [60]. Although similar findings in terms of sensitivity were found by Philip *et al*[61] in 115 patients with PVE (91 definite cases and 24 rejected cases) where the sensitivity increased from 57.1% to 83.5%; there was a decrease in specificity from 95.8% to 70.8%,

Table 1 Comparison between different imaging modalities in the evaluation of prosthetic valve endocarditis

Modality	Strengths	Weaknesses	Sensitivity	Specificity
Echocardiography	Available, convenient, no radiation exposure, hemodynamic data, high temporal resolution.	Operator- and imaging window-dependent, affected by prosthesis-related artifacts.	TTE: 17%–36%; TEE: 82%–96%	TTE: 86%[39,40]; TEE: 94%[39,40,45]
Cardiac CT	Spatial resolution, defining paravalvular complications, delineating coronary-aorta anatomy, preoperative planning.	Radiation exposure, contrast exposure limits use in advanced CKD.	88%–97%	95%[47,48,50]
Cardiac MRI	Characterizing paravalvular complications, depicts inflammatory changes, assess the degree of intra-cardiac shunting.	Limited data, lower spatial resolution, incompatibility with some cardiac devices. Limited clinical applicability.	Limited data	Limited data
¹⁸ F-FDG PET/CT	Excellent diagnostic role in PVE, detection of metastatic infection foci.	Availability, cost, requires special pre-test preparation, expertise, radiation exposure.	73%–97%	80%–94%[60–62]

TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; CTA: Computed tomographic angiography; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computer tomography.

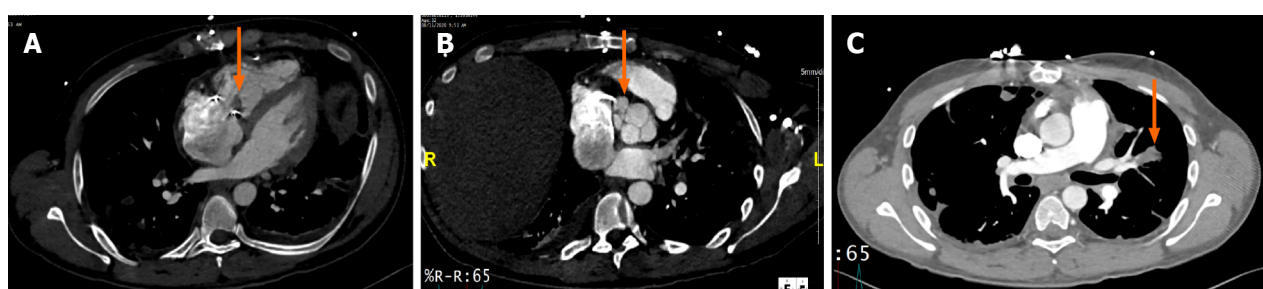


Figure 5 Cardiac computed tomography in a patient with tricuspid valve replacement endocarditis with peri-valvular extension. Thirty-two year-old male with a history of intravenous drug abuse status post bioprosthetic tricuspid valve replacement presenting with methicillin-sensitive *Staphylococcus Aureus* due to relapsed drug abuse. Cardiac computed tomography demonstrated thickening of the valve leaflets (A: Arrow) and a 2.7 cm × 1.9 cm × 1.4 cm lobulated pocket of free-flowing blood/contrast interposed between the tricuspid annulus and the aortic annulus consistent with abscess/fistula (B: Arrow). Prominent pulmonary septal embolism was also detected (C: Arrow).

with an overall improvement in accuracy from 65.2% to 80.9%. Wang *et al*[62] also reported in 333 patients with PVE an enhanced sensitivity of 86%, however, the sensitivity of the test decreased to 72% in the presence of cardiac implantable electronic devices (CIED)[62].

¹⁸F-FDG PET/CT can be utilized early in the evaluation of suspected PVE, especially if microbiologic cultures and echocardiographic imaging are unrevealing[63]. ¹⁸F-FDG PET/CT is a useful complimentary imaging modality for the diagnosis of IE that has demonstrated improving performance over time, especially in challenging cases of PVE and CIED related infections[62,64]. It has also been suggested to have a potential role in monitoring the response to antibiotic therapy[63,65]. The enhanced diagnosis of PVE with PET/CT has important clinical implications, helping to re-classify up to 90% of the “possible IE” cases by modified Duke Criteria, and providing a conclusive diagnosis (definite/rejected) in 95% of the cases[66]. It has also significantly altered the treatment plan in up to 35% of the cases by virtue of antibiotic treatment prolongation (27.5%), surgical referral (15%) and prevention of unnecessary device extraction (17.7%)[67]. This is attributed in part to its ability to detect extracardiac foci of infection, either septic emboli or other sources of infection, in around 17% of the cases with whole body PET/CT (Figure 7)[68].

Cautious interpretation of ¹⁸F-FDG PET/CT results must be entertained, especially in the early postsurgical period during the first 3 months. Following the implantation of a prosthetic valve, an inflammatory response to the foreign body occurs, which is reactive in nature without necessarily implying the presence of infection[69]. Other causes of false positive results include: soft atherosclerotic plaques and active thrombi, cardiac tumors (whether primary or metastatic), and inflammatory conditions such as vasculitis and myocarditis[70,71]. Rouzet *et al*[59] described in a cohort of 39 patients with prosthetic valves and absence of clinical infection that approximately half of these patients will continue to have a homogenous uptake on ¹⁸F-FDG PET/CT in the perivalvular area that may persist years after surgery, and therefore should not be confused with infective changes[59]. On the other hand, false negative may still occur

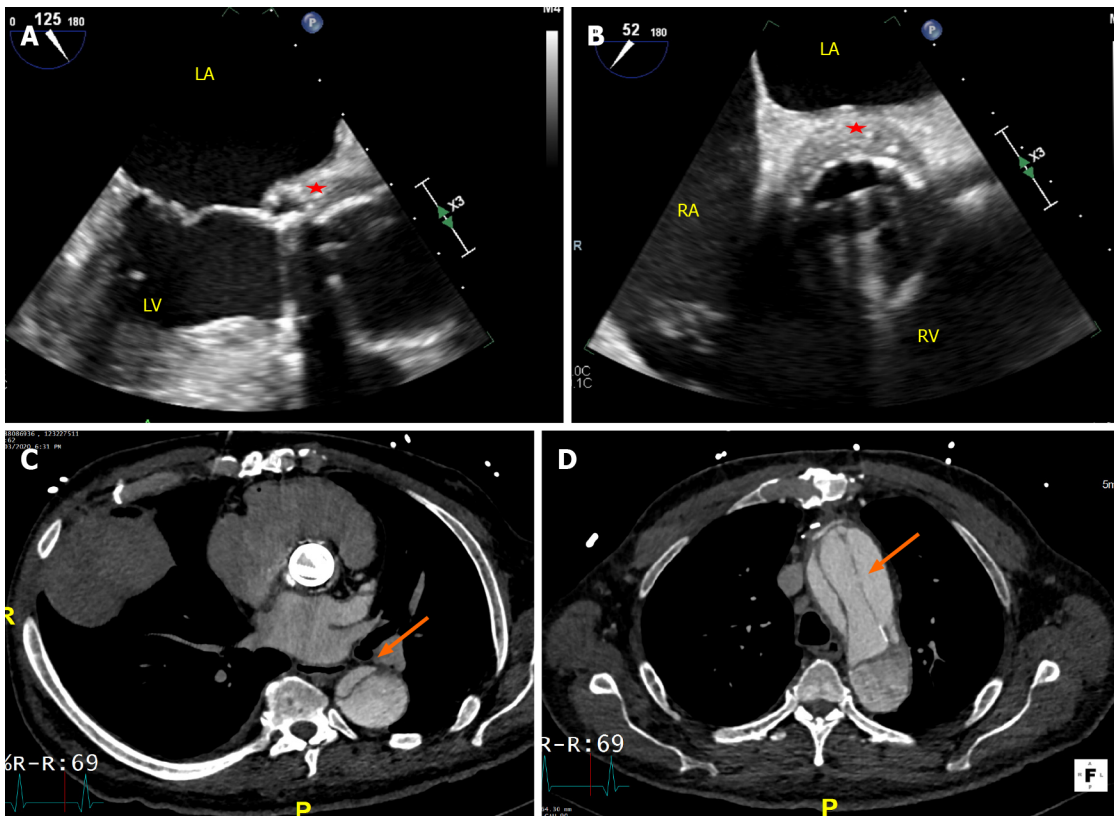


Figure 6 Transesophageal echocardiogram and cardiac computed tomography in a patient with metallic aortic valve replacement endocarditis, complicated by aortic dissection. Sixty-two year-old male with a history of type A aortic dissection status post repair with #27 CarboMedics valve conduit with reimplantation of the coronary arteries, #28 mm Hemashield bridge graft to the distal ascending aorta, presenting with PVE and extension of dissection from the distal ascending aorta to the femoral arteries. His transesophageal echocardiogram demonstrated the presence of a metallic AVR with pathological thickening of the aorto-mitral curtain and aortic root posteriorly (A and B: Star). Cardiac computed tomography axial view of the metallic aortic valve demonstrated widely open occluders and further inspection of the aorta at the level of the arch demonstrated the aortic dissection extending into the descending thoracic aorta (C and D: Arrow). RA: Right atrium; RV: Right ventricle; LA: Left atrium.

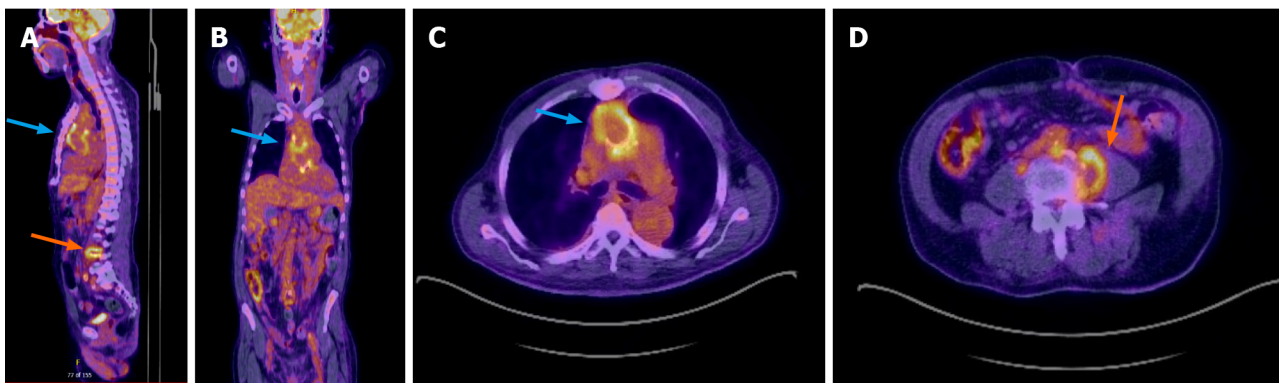


Figure 7 18-fluorodeoxyglucose photon emission tomography/computed tomography in a patient with prosthetic aortic valve endocarditis complicated by septic emboli. For details of clinical presentation, refer to Figure 6. Noted increased ^{18}F -FDG-uptake along the aortic root graft (A-C: Blue arrow) and distant septic foci at the level of L3-L4 with extension of abnormal hypermetabolism into the left psoas muscle consistent with L3-L4 discitis and left psoas muscle abscess (A and D: Orange arrow).

in the presence of small vegetations (< 5 mm), recent antibiotic administration, metastatic brain lesions and high glucose states[3,72]. Although contemporary data reported equipment availability in 70.3% of European centers and 56.3% non-ESC centers, the availability, cost, and expertise needed with this imaging modality impose additional limitations on its employment in routine clinical practice[4,73].

Real world data from the ESC-EORP EURO-ENDO (European infective endocarditis) registry in 3116 adults with IE from around the globe (2470 from Europe, 646 from non-ESC countries), identified 939 (30.1%) cases of PVE and 308 (9.9%) with

device related infection[4]. ^{18}F -FDG PET/CT was implemented in 518 cases (16.6%) and leucocyte scintigraphy in 38 (1.2%)[4]. Around 25% of the ^{18}F -FDG PET/CT were obtained in patients with PVE, and 26% in patients with device infections, which were significantly higher when compared with NVE (9.5%) ($P < 0.0001$) [4]. The test performance was superior in patients with PVE with a reported sensitivity of 66.8% (*vs* 28% for NVE and 16.3% for device infections) [4]. Extracardiac foci were observed in close to 40% of patients (34.5% in PVE, 42.3% in NVE, and 43.8% in device infections), most frequently seen in the lungs (27.1%)[4].

MANAGEMENT

In this section, a brief overview of the general management principles will be discussed; however, a detailed discussion of antimicrobial therapies and surgical techniques is beyond the scope of this article. Treatment of PVE consists of broadly surgical and/or medical management. Randomized controlled trial data comparing combined treatment to medical treatment alone are lacking. However, several large cohorts examined outcomes in surgical and medical therapy group. In a large meta-analysis by Mihos *et al*[74] of 32 studies including 2636 patients with PVE, surgical management was associated with lower 30-day mortality and higher survival at 22 months and similar rate of recurrence compared to medical therapy alone (25% *vs* 34% and 69% *vs* 58%, respectively)[74]. The limitation of this study is lack of adjustment analysis for risk factors and time from medical therapy to surgery[74]. In another large prospective study of 1025 patients with PVE, early surgery was associated with lower 1- year and in-hospital mortality compared with medical therapy alone (HR = 0.57, 95%CI: 0.49-0.67 and HR = 0.44, 95%CI: 0.38-0.52, respectively)[8]. However, this benefit with early surgery was absent after adjustment for survivor bias and clinical factors[8]. In several observational studies, the benefit of surgery was mostly seen in patients with PVE complications that carry high mortality rate such as valve regurgitation or dehiscence, paravalvular abscess or fistula, heart failure, and coagulase negative or *Staphylococcus Aureus* PVE[75-77]. In this context, a 2015 scientific statement from the AHA, 2015 ESC and 2016 American Association for Thoracic Surgery guidelines recommended as class I indication surgical intervention after weighing risks and benefits based on operative risk profile and overall outcome in the following scenarios: PVE with complications, such as new or worsening CHF, prosthetic valve dehiscence, hemodynamically significant valvular or paravalvular regurgitation, obstruction or intracardiac abscess[3,5,56]. It is reasonable to proceed with surgery as class II indication in cases of persistent bacteremia, infection-relapse despite appropriate antibiotics treatment, aggressive infection by *Staphylococcus Aureus* or fungi, non-HACEK gram negative organisms, multi-resistant organisms or in the presence of fastidious organism clustered as “culture negative” PVE[3,5,56,78]. PVE vegetations are at risk for embolization, especially when the size exceeds 10 mm, or there is increasing in size despite antibiotics[3,34,56]. In these situations, surgical intervention should be considered[3,34,56].

Antibiotic therapy should be initiated in all cases of PVE with consultation of an infectious disease specialist for guiding the antibiotic choice[3,5,38,56]. Three sets of blood cultures separated by 30-60 minutes should be obtained before antibiotic initiation and at least every 24-48 h until the blood culture is negative[3,5,38,56]. All patients should be monitored for side effects of antibiotics, clinical response and symptoms/signs that suggest PVE complications. In the latter case, an echocardiogram should be repeated. The treatment duration is generally 6 week starting from the first negative blood culture, and it can be extended for an additional 6 week if surgical specimens demonstrate a positive gram stain and culture or positive polymerase chain reaction. Antibiotic therapy should subsequently be tailored according to the culture results[3,5,38,56].

CONCLUSION

The diagnosis of PVE remains challenging due to its often non-specific clinical presentations and prosthesis-related artifacts that impair the optimal visualization of cardiac structures by echocardiography. Echocardiography continues to be the first-line imaging modality in suspected cases of PVE due to its wide availability, low cost, rapid interpretation, and safety. TEE is mandated in most PVE cases due to the reduced sensitivity of TTE in this context. The consequences of missing prosthesis-related

infections are serious, and therefore, evaluation of PVE requires the optimal complementary use of imaging modalities to achieve the best outcomes. Adjuvant imaging modalities, particularly CCT and ¹⁸F-FDG PET/CT have important niche roles. These imaging modalities improve the ability to accurately and timely diagnose PVE, contribute to the pre-operative planning of appropriate patients, and guide decision-making for therapies.

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Potential role of an athlete-focused echocardiogram in sports eligibility

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Abstract

Sudden cardiac death (SCD) of an athlete is a rare but tragic event and sport activity might play a trigger role in athletes with underlying structural or electrical heart diseases. Preparticipation screenings (PPs) have been conceived for the potential to prevent SCD in young athletes by early identification of cardiac diseases. The European Society of Cardiology protocol for PPs includes history collection, physical examination and baseline electrocardiogram, while further examinations are reserved to individuals with abnormalities at first-line evaluation. Nevertheless, transthoracic echocardiography has been hypothesized to have a primary role in the PPs. This review aims to describe how to approach an athlete-focused echocardiogram, highlighting what is crucial to focus on for the different diseases (cardiomyopathies, valvulopathies, congenital heart disease, myocarditis and pericarditis) and when is needed to pay attention to overlap

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diagnostic zone ("grey zone") with the athlete's heart. Once properly tested, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices, potentially available during first-line evaluation.

Key Words: Echocardiogram; Athletes; Sport eligibility; Pre-participation screening; Sudden cardiac death; Sport cardiology

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Core Tip: Echocardiography is a helping tool in detecting several cardiovascular (CV) conditions afflicting athletes. As physicians become more experienced with sonography, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices. This technique could help to detect some hidden CV condition and to distinguish between physiological and pathological adaptation to physical activity, assisting in sport eligibility process. In this review we aimed at describing athlete-focused echocardiogram that could be an effective time and cost-saving first line evaluation in granting sport eligibility to athletes.

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INTRODUCTION

The advantages of sport practicing in improving cardiovascular (CV) health are evident, but a concomitant raise in CV events has been seen during exercise[1]. Physical activity therefore is a double-edge sword, with both benefits and risks mostly in predisposed subjects, even if not all people are conscious about it[2].

Sudden cardiac death (SCD) of an athlete is as uncommon as shocking event[3]. Sport practice might be a trigger event of cardiac arrest in athletes with underlying heart diseases, with syncope as a frequent first manifestation[4]. Indeed, these diseases are often clinically silent and unsuspecting[5]. Athletes have an increased risk of SCD compared with their non-active counterpart, related to pathologies theoretically identifiable through pre-participation screening (PPS)[6]. Therefore, several PPSs have been developed with the aim to uncover possible hidden and fatal CV condition in athletes. There is a significative debate about the efficacy and feasibility of different kind of PPSs proposed by national and international society worldwide. While the American Heart Association has never recommended a history collection and a physical examination, opposing the routine use of electrocardiogram (ECG)[7], the European Society of Cardiology (ESC) protocol focuses on history collection, physical examination, and ECG[8] and it has been adopted by different sport committees and international federations[9]. Controversies arise regarding the sensitivity and specificity of individual tests as well as the availability of expertise and cost effectiveness[10-13].

Nevertheless, some cardiac structural diseases can be difficult to detect on physical examination and ECG, but they may definitely be recognized with further cardiac investigations. About 10% of SCD cases have been related to cardiac diseases showing structural but no electrical manifestations[14]. While in Italy an exercise stress test is mandatory before engaging in competitive sports, transthoracic echocardiography has also been hypothesized to have a role in PPS: it might be a useful, convenient and noninvasive tool to increase diagnostic power of screening evaluation[15]. Even if echocardiography is frequently adopted as a first-line screening tool for athletes[16], also by major sporting bodies such a Federation Internationale de Football Association (FIFA) or Union of European Football Association (UEFA), and mainly as a valuable second line investigation to the diagnose malignant cardiac conditions[17,18], it has never been recommended as a first-line screening tool in athletes[19,20], nor included

in recent ESC 2020 guidelines on sport cardiology[3]. Diagnostic necessity, time constraints and cost-effectiveness are probably unfavorable reasons for its use[21], even if there are only few data[22] regarding the cost-effectiveness of including an echocardiography in the PPS.

However, the use of echocardiography is highly increasing among non-cardiologist physicians and it could represent a powerful tool in the sport eligibility process by sport medicine physicians.

Therefore, the aim of the present paper is to review athlete-related echocardiographic features in order to develop a first-line screening athlete-focused echocardiogram. How should an echocardiography of the athlete be performed? What should a sport physician know about echocardiography? What would an athlete-focused echocardiogram be like?

EPIDEMIOLOGY AND ETIOLOGY OF SCD

SCD could literally be defined as “natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of symptoms”[23]. Current epidemiology of the incidence of SCD in professional athletes varies from almost 1/1000000 to 1/5000 subjects per year[24,25]. Indeed, the definition of the precise frequency of SCD is made difficult by heterogeneous study methodologies. In literature, the incidence of SCD in young athletes is fluctuating[14,26-28], with a prevalence of CV predisposing conditions of about 0.2%–0.7%[29].

Several causes of SCD in athletes are related to the age of onset. In patients from birth to adolescence, the primary cause of SCD is a congenital abnormality[30]. The great majority of young victims (age ≤ 35 years) present a concealed structural heart disease[31]. Coronary artery disease is the most frequent cause of SCD in aged athletes (35 years or older)[32]. Main causes of SCD are summarized in Table 1.

ECHOCARDIOGRAPHY IN ATHLETE'S HEART

Even if a minimum dataset is recommended for all echocardiograms[33] (Table 2), previous knowledge of some demographics data, patient's personal history and physical examination, and ECG findings will help to focus the examination and the interpretation of findings: sex, age, body mass index, ethnicity, ECG changes, symptoms, training volume, type of sport and level, and family history of unexplained cardiac death < 40 years[34]. A focused echocardiogram with real-time interpretation can considerably cut the cost and time spent performing the study, as previously demonstrated[35]. Indeed, Niederseer *et al*[21] proposed to include a double screening echocardiography in the athlete: in adolescence to rule out structural heart disease, and over the age of 30 to evaluate pathological cardiac remodeling to exercise, cardiomyopathies and wall motion anomalies. Often coronary artery disease is missed by classing screening method, so in a master athlete (> 35 years) echocardiography detection of atherosclerotic plaque[36], could represent a valid example of a focused exam.

Moreover, prolonged physical activity causes structural, functional, and electrical heart modifications that represent the physiological responses (“adaptation”) of the heart during physical effort: this series of remodeling is named as “athlete's heart”[37] and it can be appreciated both in ECG[38] and in echocardiograms. These adaptations, involving all the heart chambers[39] and strictly dependent upon on the duration, type and intensity of training, are often benign and physiological but, sometimes, may predispose to pathological conditions[40,41]. The challenges posed by athlete's heart require detailed assessment in order to distinguish between physiological adaptation and life-threatening cardiomyopathies[16,42-44], that often coexist in the so called “grey zones”.

Also, novel advanced echocardiographic techniques play an emerging role in the echocardiographic investigation of athlete[41]: Exercise stress echocardiography in the differentiation between athlete's heart and dilated cardiomyopathy, coronary artery disease and pulmonary hypertension; speckle tracking [with left ventricular (LV) global longitudinal strain] in the differentiation between athlete's heart and dilated cardiomyopathy and hypertrophic cardiomyopathy, other than the characterization of wall motion abnormalities and right ventricle description; 3D echocardiography in estimation of cardiac mass.

Table 1 Common cardiovascular diseases associated with sudden cardiac deaths in athletes (adapted from[15,21])

Type of pathology	Pathology
Cardiomyopathies	HCM
	DCM
	LVNC
	ARVC
CAD	
Myocarditis	
Congenital defects	AOCA
	BAV
Valvulopathies	MVP
Aortic diseases	Aortic dissection
	Aortic rupture
	Aortic aneurism
Kawasaki disease	
Idiopathic scarring	
Conduction defects	WPW
Channelopathies	LQTS
	Brugada syndrome
	CPVT

HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; LVNC: Left ventricle non compaction; ARVC: Arrhythmogenic right ventricle cardiomyopathy; CAD: Coronary artery disease; AOCA: Anomalous origin of coronary arteries; BAV: Bicuspid aortic valve; MVP: Mitral valve prolapse; WPW: Wolff-Parkinson-White syndrome; LQTS: Long QT syndrome; CPVT: Catecholaminergic polymorphic ventricular tachycardia.

Therefore, echocardiography has a major role in sports cardiology, and it can help physicians not only to investigate structural diseases invisible both at anamnesis and ECG, but also to rule out these physio-pathological modifications.

ATHLETE-FOCUSED ECHOCARDIOGRAM

The concept of point-of-care ultrasound is increasingly emerging in literature[45], in different body systems[46,47], including heart. Even if it is crucial to consider the ultrasound scanner and the degree of competence and knowledge of the sonographer [48], a focused protocol for point-of-care echocardiography could be developed for physicians to help screen out major CV diseases afflicting athletes in granting sport eligibility. Such protocols may gain much more attention by the fact that nowadays, portable and handheld ultrasound devices are spreading and have proven to be equally reliable and accurate in evaluating cardiac features[49,50].

Several of athlete-focused echocardiography protocols have been proposed in literature[19,51,52] by different authors[53-55], and some are reported in Table 3. Some of them are direct to rule out specific diseases, while others are designed for global viewing but only last a few minutes. Moreover, several sportive federations, such as FIFA, have their own precompetition medical assessment that includes echocardiographic examination.

We want to propose our version of first-line athlete-focused echocardiography, as seen in Table 4 and Figures 1 and 2. Some measurements are intentionally missed: visually estimated left ventricular ejection fraction and wall motion has been found to be closely related to formal quantitative methods[56,57]; valvular heart diseases can be firstly screened by color doppler[58]. We also consider a visual assessment of cardiac chambers' dimensions. All these first-line measurements, if pathological, will be eventually followed by other measurements ("second-line"), as seen in Table 5.

Table 2 Minimum dataset for transthoracic echocardiography (adapted from[33])

Echo views	Structure	Measure
PLAX	LV	IVS
		End diastolic diameter
		Posterior wall
	Mitral Valve	Wall motion
		Leaflets and annulus
		Color
	Aortic Valve	Anulus
		Valsalva Sinus
		STJ
	Ascending aorta	Color
Size		
PSAX-aortic valve	RV	RVOT
	LA	Size
	Aortic Valve	Morphology
	OCA	
	RV	RVOT
	Pulmonary valve	Color
		PW
PSAX-base	Mitral Valve	Leaflets and annulus
PSAX-mid/apex	LV	Wall motion
A4C	LV	EF
		Wall motion
		Wall thickness
		End diastolic area/ volume
	VSD	
	ASD	
	LA	LAVI
	Mitral valve	Color
		PW
		TDI
	RV	RVD1
		RVD2
		RVD3
		Wall motion
		TAPSE
TV	Color	
	CW	
	Pulmonary veins	PW
A5C	Aortic valve	Color
		CW
A2C	LV	Wall motion

Subcostal	ASD	
	Inferior vena cava	Size
		Breath collapsibility
	Pericardium	Pericardial effusion
Suprasternal	Abdominal aorta	Size
	Aortic arch	Size
		Color
		CW

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area change; LAVI: Left atrium ventricle index; LA: Left atrium; IVS: Inter ventricular septum; PW: Power doppler wave; CW: Continuous doppler wave; RA: Right atrium; STJ: Sinotubular junction; OCA: Origin of coronary arteries; PDA: Patent ductus arteriosus; COA: Aortic coarctation; ASD: Atria septum defect; VSD: Ventricular septal defect; RVD: Right ventricle diameter; TAPSE: Tricuspid annular plane excursion.

Table 3 Athlete-focused echo protocols

Ref.	Echo view (parameters assessed)	Estimated exam time
Feinstein <i>et al</i> [51]	PLAX (LV IVS, LV posterior wall, LVOT)	1-2 min
Wyman <i>et al</i> [53]	PLAX (aortic arch size, aortic valve characteristics, mitral valve characteristics, LV wall motion, LV mass); PSAX (aortic valve characteristics, aortic valve morphology, origin of coronary arteries, CW pulmonary valve, LV wall motion, LV wall thickness); A4C (tricuspid valve characteristics, mitral valve characteristics, RV size, RV wall motion, LV size); A5C (CW aortic valve)	Not specified
Weiner <i>et al</i> [52]	PLAX (aortic valve characteristics, mitral valve characteristics, CW tricuspid valve); PSAX (aortic valve characteristics, pulmonary valve characteristics, LV wall motion); A4C (RV size, RV wall motion, LV size, LV wall motion, PW mitral valve, TDI mitral valve, tricuspid valve characteristics); A5C (CW aortic valve); A2C (LV wall motion)	13 min
Yim <i>et al</i> [55]	PLAX (IVS, LV end diastolic diameter, PW, aortic arch size)	Not specified
Fishman <i>et al</i> [54]	LV IVS, LV posterior wall, LV end diastolic diameter, PW, EF, AVR, MVR aortic valve regurgitation, mitral valve regurgitation, aortic valve morphology, aortic root dimension	1 min

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; IVS: Inter ventricular septum; LVOT: Left ventricle outflow tract; LV: Left ventricle; CW: Continuous wave; RV: Right ventricle; PW: Power doppler wave; TDI: Tissue doppler imaging; EF: Ejection fraction; AVR: Aortic valve regurgitation; MVR: Mitral valve regurgitation.

Below we will describe main echo findings and grey zone in the more frequent CV conditions in athletes (Table 5), with cut off based on latest recommendations[42].

CARDIOMYOPATHIES

The diagnosis of these cardiomyopathies and their differentiation with athlete's heart still represent one of the biggest challenges of sport cardiology

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is one of the most common etiologies of SCD in athletes and represents one of the most frequent reason for denied sport eligibility according to both American and European guidelines[59-61].

Echocardiography is crucial for the diagnosis and monitoring of HCM. In the absence of another reason of hypertrophy, it can be diagnosed with a maximal end-diastolic wall thickness of ≥ 15 mm in any zone of the left ventricle; less marked hypertrophy (13-14 mm) can be diagnostic when present in relatives of a patient with HCM or along with a positive genetic test. For children, a threshold of $z > 2.5$ may be useful to identify early HCM in asymptomatic subject with no family history, while for

Table 4 Proposed echocardiographic protocol for athletes

Echo views	Structure	Measure
PLAX	LV	IVS
		End diastolic diameter
		Posterior wall
	Mitral valve	Leaflets
	Aortic valve	Color
		Valsalva sinus
PSAX-aortic valve	Ascending aorta	Color
		Size
	Aortic valve	Morphology
	OCA	
	RV	RVOT
A4C	PDA	
	LV	Trabeculations
		Wall motion
	VSD	
	ASD	
A5C	Mitral valve	Color
		PW
	TV	Color
		CW
	Aortic valve	Color
		CW
Subcostal	ASD	
	Inferior vena cava	Size
		Breath collapsibility
Suprasternal	Pericardium	Pericardial effusion
	Aortic arch	
		Size
	COA	

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; A5C: Apical 5 chambers view; A2C: Apical 2 chambers view; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area change; LAVI: Left atrium ventricle index; LA: Left atrium; IVS: Inter ventricular septum; PW: Power doppler wave; CW: Continuous doppler wave; RA: Right atrium; STJ: Sinotubular junction; OCA: Origin of coronary arteries; PDA: Patent ductus arteriosus; COA: Aortic coarctation; ASD: Atria septum defect; VSD: Ventricular septal defect; RVD: Right ventricle diameter; TAPSE: Tricuspid annular plane excursion.

children with a positive family history or a positive genetic test, a threshold of $z > 2$ could be sufficient for early diagnosis.

Measurements of LV wall thickness should be executed at end diastole, in parasternal long axis (PLAX) or in parasternal short axis (PSAX) views[15].

Grey zone: The diagnosis of HCM in competitive athletes may be difficult when LV wall thickness ranges from 13 to 16 mm[62-64]. The overlap between athlete's heart and HCM is challenging in Afro-American individuals[65]. Indeed, the extreme value of LV hypertrophy in athletes is found in male (15 mm in white and 16 mm in Afro-American athletes[66]), while lower values are found in female (11 mm in whites and 13 mm in Afro-Americans[67]). The type and the intensity of sport practiced are also important aspects to consider.

Table 5 Main echo findings of cardiovascular pathologies in athletes

Pathology	What to assess? (echo view)	Cut-off mm (mean mm)	If pathological, what to assess? (echo view)	Cut-off mm (mean mm)
HCM	LV Max end-diastolic wall thickness	M white 15 (10); M Afro-American 16 (11.5); F white 11; F Afro-American 13 (9.5); M/F adolescent 16 (12)	LV wall thickness distribution	Asymmetric (HCM)
			LV end diastolic diameter (A4C)	M 70 (55); F 66 (49); Adolescent 60 (51)
			LV mass/BSA	M 117 mm/m ² (83 mm/m ²); F 143 mm/m ² (101 mm/m ²)
			LVOT obstruction	
DCM	LV end diastolic diameter (PLAX)	M 70 (50); F 66 (49); Adolescent 60 (51)	E/A (A4C)	1.3 (1.93)
			EF (A4C)	55% (64%)
LVNC	LV trabeculation	NC/C layer ratio > 2.0 in systole	EF (A4C)	55% (64%)
			Thickness of compact layer in systole	8
			E/A (A4C)	1.3 (1.93)
ARVC	RVOT/BSA (PSAX)	> 21 mm/m ²	RV inflow (A4C)/ LV end diastolic diameter (PLAX)	> 0.9
	RVOVT/BSA (PLAX)	> 19 mm/m ²	RV wall motion abnormalities	
			RV FAC	33%
Aortic dilatation	Aortic valve max dimension (PLAX)	M 40 (32); F 34 (28)	Other congenital defects (BAV)	
	Ascending aorta dimension (PLAX)		Aortic regurgitation	
Mitral prolapse	Mitral prolapse (PLAX)	Abnormal systolic bulging of leaflets > 2 mm toward LA	Mitral regurgitation	
			PAPS (A4C)	40 mmHg (24 mmHg)
			Pulmonary veins flow	Reverse
			EF (A4C)	55% (64%)
			LV mass/BSA	M 117 mm/m ² (83 mm/m ²); F 143 mm/m ² (101 mm/m ²)
			LAVI	M 36 mm/m ² (28 mm/m ²); F 33 mm/m ² (26.5 mm/m ²)
AOCA	Coronary arteries origin (PSAX)			
BAV	Aortic morphology (PSAX)		Aortic stenosis	
			Aortic regurgitation	
			Aortic root max dimension (PLAX)	M 40 (32); F 34 (28)
			Other congenital defects (coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly or hypoplastic left heart, as well as Williams or Turner syndrome)	
ASD	ASD		RV dimension (A4C)	Basal RV: M 55 (43.5), F 49 (39); Medial RV: M 47 (34), F 43 (32); Longitudinal RV: M 109 (89), F 100 (82)
			RA area/BSA (A4C)	M 28 mm/m ² (19.5 mm/m ²); F 24 mm/m ² (15.5 mm/m ²)
			PAPS (A4C)	40 mmHg (24 mmHg)

VSD	VSD	LV mass/BSA (PLAX)	M 117 mm/m ² (83 mm/m ²); F 143 mm/m ² (101 mm/m ²)
		PAPS (A4C)	40 mmHg (24 mmHg)
		Aortic regurgitation	
		Other congenital defects (aneurysm of Valsalva sinus, ToF, TGA, DCRV)	
PDA	PDA (PSAX)	LA/Aortic root ratio	≥ 1.4
		LV mass/BSA (PLAX)	M 117 mm/m ² (83 mm/m ²); F 143 mm/m ² (101 mm/m ²)
		PAPS (A4C)	40 mmHg (24 mmHg)
		Pulmonary artery size (PSAX)	
		RV dimension (A4C)	Basal RV: M 55 (43.5), F 49 (39); Medial RV: M 47 (34), F 43 (32); Longitudinal RV: M 109 (89), F 100 (82)
		RA area/BSA (A4C)	M 28 mm/m ² (19.5 mm/m ²); F 24 mm/m ² (15.5 mm/m ²)
		Other congenital defects (COA, pulmonary atresia)	
COA	COA (PSAX)	Aortic stenosis	
		Mitral stenosis	
		LV mass/BSA (PSAX)	M 117 mm/m ² (83 mm/m ²); F 143 mm/m ² (101 mm/m ²)
		EF (A4C)	55% (64%)
		Other congenital defects (BAV, ascending aortic aneurysm)	
Myocarditis	EF (A4C)	55% (64%)	
	LV wall motion abnormalities		
	Pericardial effusion		
	Increased LV wall thickness		
Pericarditis	Pericardial effusion		
Kawasaki disease	Coronary artery abnormalities		
	EF (A4C)	55% (64%)	
	LV wall motion abnormalities		
	Mitral regurgitation		
	Aortic regurgitation		
	Pericardial effusion		

PLAX: Parasternal long axis view; PSAX: Parasternal short axis view; A4C: Apical 4 chambers view; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; LVNC: Left ventricle non compaction; ARVC: Arrhythmogenic right ventricular cardiomyopathy; BAV: Bicuspid aortic valve; AOCA: Anomalous origin of coronary arteries; ASD: Atrial septum defects; VSD: Ventricular septal defects; PDA: Patent ductus arteriosus; CoA: Aortic coarctation; M: Male; F: Female; LV: Left ventricle; BSA: Body surface area; EF: Ejection fraction; LVOT: Left ventricle outflow tract; NC/C: Non-compact/compact; RVOT: Right ventricle outflow tract; RV: Right ventricle; FAC: Fractional area change; PAPS: Pulmonary artery systolic pressure; LAVI: Left atrium ventricle index; RA: Right atrium; ToF: Tetralogy of fallot; TgA: Transposition of great arteries; DCRV: Double-chambered right ventricle.

Differential diagnosis features between HCM and athlete's heart in the gray-zone is seen in [Table 6](#). The most practical morphologic criterion is the assessment of LV cavity size and geometry, enlarged (end-diastolic diameter > 54 mm) and with an eccentric pattern only in athlete's heart[62,68]. On the other side, an asymmetric and heterogeneous pattern of LV hypertrophy represents features of HCM[62]. Further-

Table 6 Differential diagnosis between hypertrophic cardiomyopathy and athlete's heart, in the grey-zone (adapted from[42])		
HCM	Findings	Athlete's heart
Normal, reduced	LV cavity size	Enlarged, eccentric pattern
Asymmetric and heterogeneous	LV hypertrophy	Symmetric and homogeneous
Present	LVOT obstruction	Absent
Abnormal	LV diastolic function	Normal
Unchanged	LV wall thickness after detraining	Reduced

HCM: Hypertrophic cardiomyopathy; LV: Left ventricle; LVOT: Left ventricle outflow tract.

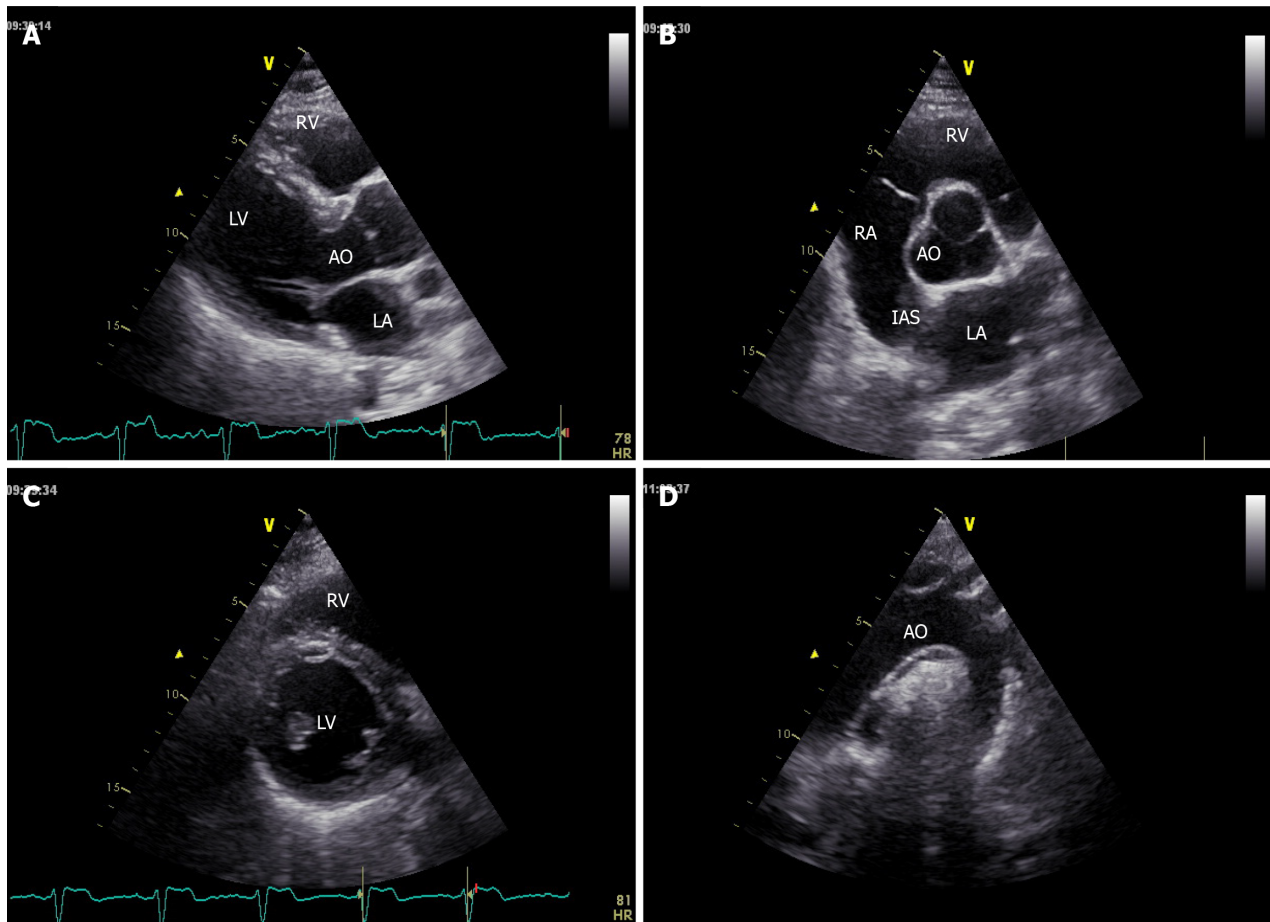


Figure 1 Parasternal long-axis, short axis and suprasternal windows showing left and right chambers and aortic valve and arch. A: Long-axis; B and C: Short axis; D: Suprasternal windows. LV: Left ventricle; LA: Left atrium; RV: Right ventricle; RA: Right atrium; AO: Aorta; IAS: Interatrial septum.

more, athletes usually show a homogeneous distribution of wall thickness and a normal diastolic function[69], besides a reduction of wall thickness after a detraining period.

What to assess? LV wall thickness. If pathological, what to assess? LV end diastolic diameter + LV mass + LV outflow tract (LVOT) obstruction + LV wall thickness distribution + LV diastolic function (E/A).

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is a not-so rare cause of SCD in athletes[70,71]. It is defined as (left) ventricular systolic dysfunction and dilatation not explained by other loading conditions. Systolic dysfunction is measured by abnormal LV ejection fraction (EF) (through biplane Simpson's rule). LV dilatation is defined by LV end-diastolic

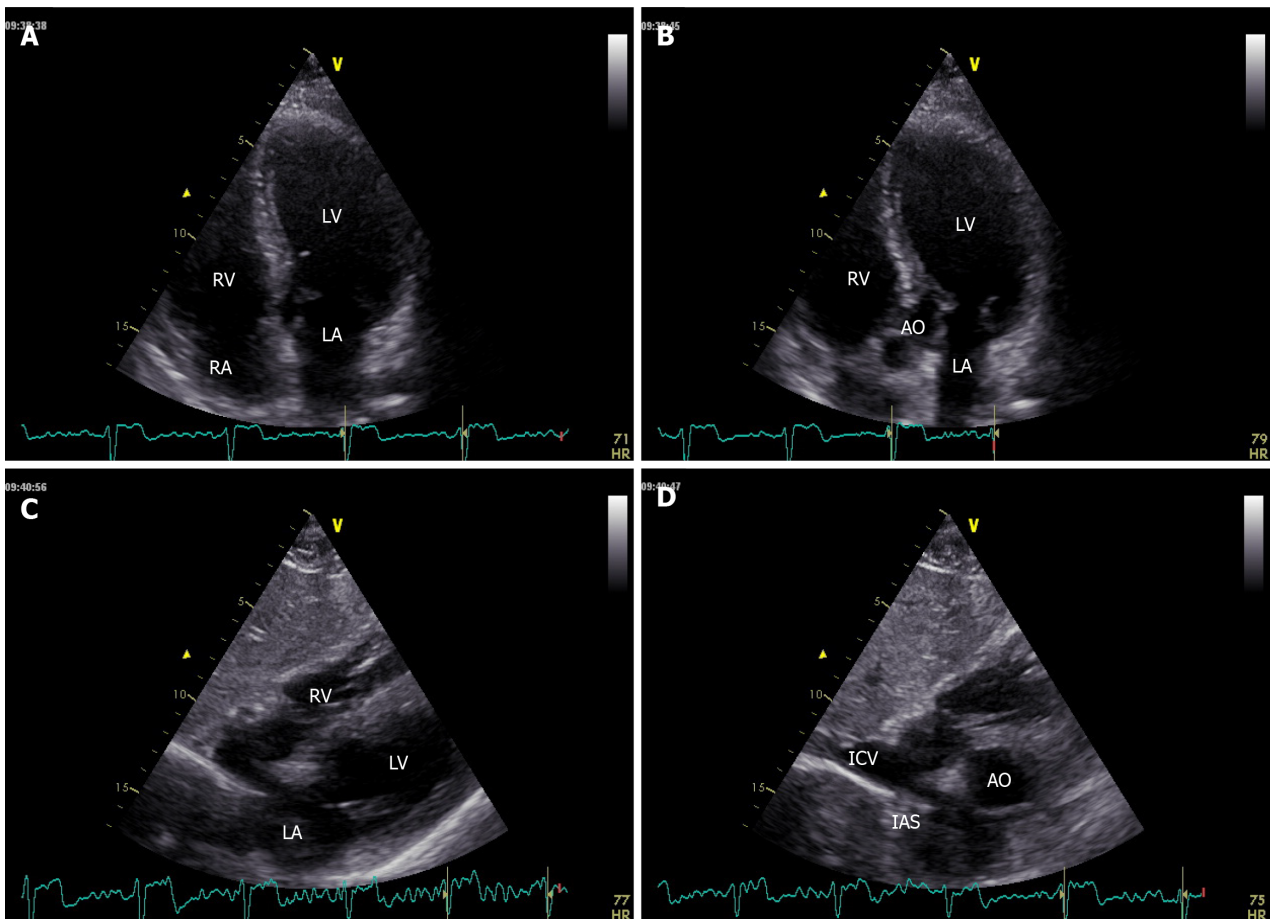


Figure 2 Apical 4-chamber, 5-chamber and subcostal windows showing left and right chambers, inferior cava vein and pericardium. A: 4-chamber; B: 5-chamber; C and D: Subcostal windows. LV: Left ventricle; LA: Left atrium; RV: Right ventricle; RA: Right atrium; AO: Aorta; IAS: Interatrial septum; ICV: Inferior cava vein.

diameters > 2 SD from normal, indexed by body surface area (BSA), age and gender. LV shape can provide additional information ("sphericity index") [72].

Grey zones: Left ventricular cavity increasing in athletes should be interpreted in the context of sport played and it is usually associated with increased wall thickness [73,74]. A significant dilation is often seen in endurance athletes. Almost 40% of athletes showed an increase of LV end diastolic diameter (> 55 mm), and almost 10% even bigger cavity (> 60 mm, with 99th percentile corresponding to 65 mm). LV dilation in athletes is frequently presented with EF $> 55\%$. Moreover, indices of diastolic function are within normal values [75]. In case of mildly reduced ejection fraction, it may be useful to perform a stress test echocardiography, along with the measure of stroke volume.

Differential diagnosis features between DCM and athlete's heart in the grey zone is showed in Table 7.

What to assess? LV end diastolic diameter. If pathological, what to assess? EF.

LEFT VENTRICLE NON COMPACTION

Left ventricle non-compaction (LVNC) is a cardiomyopathy identified by increased myocardial trabeculations and inter-trabecular recesses [76,77], ranging clinically from asymptomatic to SCD outcomes. Diagnosis is based on three proposed echocardiographic criteria, showing high non-compacted to compacted ratio within the LV myocardium [78,79].

Grey zones: About 1 in 5 athletes has LV hypertrabeculation, with about 10% complying LVNC diagnostic criteria [80,81]. This may be due to cardiac adaptation to load training. ESC guidelines on cardiovascular imaging [42] proposed the threshold for defining an LV trabeculations on echocardiography: a non-compacted to compacted (NC/C) layer ratio > 2.0 in systole [82].

Table 7 Differential diagnosis between dilated cardiomyopathy and athlete's heart (adapted from[42])

DCM	Findings	Athlete's heart
> 60 mm	LV end diastolic diameter	< 60 mm
Reduced	EF	Normal
Abnormal	Diastolic function	Normal

DCM: Dilated cardiomyopathy; LV: Left ventricle; EF: Ejection fraction.

In athletes achieving criteria for LVNC, an history of cardiac symptoms or family SCD, are suggestive of pathology. Additional echocardiography features of LVNC include low EF not improving with exercise, altered diastolic function and a thickness of compacted layer in systole < 8 mm.

Differential diagnosis features between LVNC and athlete's heart in the gray-zone is showed in [Table 8](#).

What to assess? LV trabeculation. If pathological, what to assess? FE (Simpson) + thickness of compact layer in systole + LV diastolic function (E/A).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiomyopathy characterized by progressive waste of myocytes that are substituted by fibrofatty tissue. It typically (but not only) involves the right ventricle (RV).

Diagnostic imaging criteria have been defined in 2010[83]: Disproportionate enlargement of the right ventricle outflow tract (RVOT) and RV motion abnormalities are essential characteristics of this disease[84].

Grey zones: Long-term physical activity could promote the expression of ARVC: exercise remodeling includes RV (basal) enlargement and mild reduction of global RV peak systolic longitudinal strain[15]. ESC guidelines on cardiovascular imaging[42] propose that only major dimensional criteria, indexed by BSA, should be used to define RV enlargement in athletes: specifically, RVOT > 19 mm/m² in PLAX, and/or > 21 mm/m² in PSAX. Other useful measures include the ratio of RV inflow dimension (in apical 4 chambers view (A4C))/LV end-diastolic dimension (PLAX) > 0.9[85], the RV fractional area change (FAC) < 33%[86], and a subclinical RV dysfunction with reduced RV global longitudinal strain[87]. About 50% of ARVC subjects could have regional akinesia, dyskinesia, or aneurysmal deformation.

Differential diagnosis features between ARVC and athlete's heart is seen in [Table 9](#).

What to assess? RVOT PSAX + RVOT PLAX. If pathological, what to assess? RV inflow apical/LV end diastolic PLAX + RV regional wall abnormalities + RV FAC.

AORTIC DISEASES

Aortic pathologies, such as aortic dissection or aortic aneurism, are important etiologies of SCD in athletes[88,89] and could be related to Marfan disease. Practically, aortic root diameter measurements should be performed from the PLAX view using the leading edge-to-leading edge convention (except for the measurement of the annulus, in which it is used inner edge to inner edge convention) and preferring 2D measurements[90,91]. Otherwise, in children and in subjects ≤ 25 years, aortic root dimensions should be carried out using the inner-wall-to-inner-wall technique during systole[92]. Measurements should embrace the aortic valve annulus, the sinuses of Valsalva, the sinotubular junction and the proximal ascending aorta.

Grey zone: Remodeling of the aortic root in athletes is strictly related to the overload training[93-95]. Large increases in aortic size are rare in athletes and often related to an underlying potentially fatal aortic disease[96]. The American College of Cardiology and the American Heart Association have proposed the use of z-scores to identify subjects with significant aortic root dilation[97]. If dilated aortic root dimensions are found, it is recommended to exclude the presence of associated conditions such as Marfan Syndrome of bicuspid aortic valve (BAV)[98,99]. In athletes with dilated aortic root, a periodical diagnostic assessment to monitor dimension is recommended.

Table 8 Differential diagnosis between left ventricle non compaction and athlete's heart, in the grey zone (adapted from[42])

LVNC	Findings	Athlete's heart
Reduced	LV systolic function	Normal
Reduced	Thickness of compact layer	Normal
Abnormal	Diastolic function	Normal

LVNC: Left ventricle non compaction; LV: Left ventricle.

Table 9 Differential diagnosis between arrhythmogenic right ventricular cardiomyopathy and athlete's heart, in the grey-zone (adapted from[42])

ARVC	Findings	Athlete's heart
Exceeding major criteria for ARVC	RV size	Not exceeding major criteria for ARVC
Abnormal	Regional RV wall motion	Normal
Abnormal	Global RV function	Normal

ARVC: Arrhythmogenic right ventricular cardiomyopathy; RV: Right ventricle.

What to assess? aortic root dimension + ascending aortic diameter. If pathological, what to assess? BAV + aortic valve regurgitation.

VALVULOPATHIES

Mitral valve prolapse

Mitral valve prolapse (MVP) is a common valve abnormality in population that, in some case, has been associated to SCD especially in young individuals[100]. Echocardiography, ideally in PLAX view, is essential for MVP diagnosis[40]: It is literally defined by "abnormal systolic bulging of one or both leaflets toward the left atrium (LA) with displacement of coaptation point into the LA (> 2 mm beyond a line connecting the annular hinge point)". Leaflets are usually elongated and thickened: "classic" MVP is characterized by a leaflet thickness ≥ 5 mm, while "non-classic" MVP is defined by leaflet thickness < 5 mm. Furthermore, mitral annulus is usually enlarged.

Grey zone: MVP is one of the most frequent cause of mitral valve (MV) regurgitation in athletes[101]. If rare, cases of malignant arrhythmic prolapse have been reported and therefore this is a must be ruled-out condition[102-104]. Athletes usually has mild mitral regurgitation (MR), even if severe MR must be excluded (Table 10). Also pulmonary artery pressures (PAPS) and reverse flow in the pulmonary veins assessment should be performed. LV and LA dimensions must be evaluated to exclude cardiac chamber dilatation associated.

What to assess? MV prolapse. If pathological, what to assess? MR (vena contracta, CW jet area, PISA, MR flow, CW doppler, E wave) + PAPS + pulmonary vein flow + LV mass + LV function + LA dimension.

Other valvulopathies

Valvular heart disease is frequently related to degenerative processes and usually age-related[14], but may also involve younger individuals. Moreover, specific recommendations exist for athletes with valvulopathies[105]. Congenital defects are common cause of valvular heart disease in young individuals. Although cardiac magnetic resonance offers a better quality of imaging[106], these are conditions to be considered when performing an echocardiogram in athletes. Right-sided valvular pathologies and regurgitant lesions are better tolerated[107].

Valvular Stenosis

Aortic valve stenosis (AVS) counts for 5% of congenital heart defects, and is frequently caused by BAV[108]. Even if mostly asymptomatic, these subjects have a small but

Table 10 Echocardiographic criteria for the definition of severe valve regurgitation (adapted from[165])

	AVR	MVR	TVR
Vena contracta width (mm)	> 6	≥ 7	≥ 7
Other	Pressure half-time < 200 ms	TVI mitral/TVI aortic > 1.4	PISA radius > 9 mm
EROA (mm ²)	≥ 30	≥ 40	≥ 40
Regurgitant volume (mL/beat)	≥ 60	≥ 60	≥ 45

AVR: Aortic valve regurgitation; EROA: Effective regurgitant orifice area; MVR: Mitral valve regurgitation; PISA: Proximal isovelocity surface area; TVR: Tricuspid valve regurgitation; TVI: Time velocity integral.

significant risk of sudden death[109]. Echocardiography is the gold standard diagnostic tool[110] (Table 11).

Mitral valve stenosis (MVS) in young individuals can be of rheumatic origin. It results in elevated LA pressure and eventually pulmonary hypertension. An exercise-related cardiac output increase can lead to acute pulmonary edema[111]. The degree of MVS can be categorized through echocardiography (Table 8).

Tricuspid valve stenosis (TVS) can be caused by rheumatic fever and is frequently associated with MVS, rather than alone[111].

Pulmonary valve stenosis accounts for about 10% of the congenital heart syndrome [112]. It is commonly present in tetralogy of Fallot, Noonan syndrome and maternal rubella syndrome[113]. Most of these patients are asymptomatic, but rarely SCD. Evaluation of pulmonary stenosis is best evaluated with echocardiography[114,115].

Valvular regurgitation

Valvular regurgitation is a common and often harmless condition in athletes. In particular, mitral and tricuspid regurgitation are widely diffused in young subjects [116].

The more common causes of aortic valve regurgitation (AVR) include BAV, rheumatic fever, endocarditis, Marfan syndrome and aortic dissection. AVR causes LV dilatation with subsequent LV pressure and volume loading. LV dilatation should be evaluated by echocardiography. Often LV cavity dimension can be raised in healthy athletes[111]. Quantification of AVR is seen in Table 9.

There are many causes of mitral valve regurgitation (MVR), including MVP, endocarditis, rheumatic heart disease, coronary artery disease, and dilated cardiomyopathy[117]. In athletes, mitral regurgitation is mostly related to MVP. Quantification of MVR is showed in Table 9.

Tricuspid valve regurgitation (TVR) is often the result of RV dilatation. Primary TVR leads to RV volume overload and increased venous pressure. The severity of TVR can be determined by echocardiography (Table 10)[111].

CONGENITAL HEART DISEASES

A once-in-a-lifetime echocardiography allows to identify congenital heart disease in order to plan an individualized follow-up and exercise recommendation, other than screening of the athlete's family.

ANOMALOUS ORIGIN OF CORONARY ARTERIES

Anomalous origin of coronary arteries (AOCA) is a rare but recognized cause of sports related SCD[108], often missed to ECG. Identification of AOCA is not easy because these are often asymptomatic individuals and do not necessarily exhibit distinctive features on ECG stress testing. Even if echocardiography is not the gold standard for its diagnosis, this examination is the first line test recommended when there is such a suspicion also because it is the only noninvasive tool to visualize the ostia and first tracts of coronary arteries[118-120]. Each coronary artery (CA) usually originates from its respective sinus above the aortic valve leaflets, with the right CA (RCA) arising from the right sinus of Valsalva and the left main CA (LCA) arising from the left sinus of Valsalva[121]. Not all AOCA have the same prognostic impact: the most at-risk

Table 11 Echocardiographic parameters indicative of the degree of severity of different valve stenosis (adapted from[111,165])

	AVS			MVS			TVS		PVS		
	Low	Moderate	Severe	Low	Moderate	Severe	Clinically significant		Low	Moderate	Severe
V max (m/s)	2.6-2.9	3.0-3.4	≥ 4.0						< 3	3-4	≥ 4
DP mean (mmHg)	< 30	30-40	≥ 40	< 5	5-10	> 10	> 5		< 30	30-50	> 50
Valve orifice area (cm ²)	> 1.5	1.0-1.5	< 1.0	> 1.5	1.0-1.5	< 1.0					

AVS: Aortic valve stenosis; MVS: Mitral valve stenosis; TVS: Tricuspid valve stenosis; PVS: Pulmonary valve stenosis; PAP: Pulmonary artery pressure.

anomalies include an anomalous origin from a wrong aortic sinus [aortic anomalous origin of coronary arteries (AAOCA)][15]].

About the AAOCA, the ostium and proximal course of the left main and right coronary arteries can be visualized by echocardiography respectively in over 98% and 80% of subjects[122], especially from a PSAX view. The left main CA origin is approximately 4 o'clock and the RCA origin at 11 o'clock. Additional color flow mapping can help in the identification process[123]. Occasionally, clockwise rotation of the transducer in the PSAX view frequently allows the identification of the left main CA as it bifurcates into the left anterior descending branch and the left circumflex branch.

In infants and small children with good subcostal windows, the LCA origin can be seen from a coronal plane; the RCA origin is frequently best seen from a PLAX view.

What to assess? Origin of coronary arteries (PSAX). If pathological, what to assess? Additional color flow mapping of the inter-arterial space.

BICUSPID AORTIC VALVE

BAV is one of the most common congenital cardiac abnormalities[124]. Subjects with BAV may consequently have larger dimensions of the aortic sinus, ascending aorta, and aortic arch[15,89], beside possible progression to subsequent valvulopathies. The most common fusion pattern involves the right and left cusps[125]. Moreover, BAV may be associated with other diseases such as coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly, as well as Williams or Turner syndrome[126,127]. The leaflets number and fusion, and the presence of a 'raphe' can be easily evaluated in the PSAX view, while systolic doming is better seen in PLAX view. Doppler echocardiography permits assessment of valve dysfunction[110,128]

What to assess? Aortic valve morphology (PSAX). If pathological, what to assess? Aortic stenosis + aortic regurgitation + dimension of aortic root (PLAX) + other congenital defects (coarctation of the aorta, interrupted aortic arch, patent ductus arteriosus, coronary anomaly or hypoplastic left heart, as well as Williams or Turner syndrome).

ATRIAL SEPTAL DEFECTS

Atrial septal defect (ASD), the failure to close the communication between RA and LA, afflicts 1 in 4 children[129]. There are five subtypes of atrial septal defects: patent foramen ovalis, ostium secundum defect, ostium primum defect, sinus venosus defect, and coronary sinus defect[89,130]. The atrial septum can be assessed from subcostal, apical and PSAX[131,132] views, even if subcostal is the preferred one. The four-chamber view allows hemodynamic assessment of the ASD (RA and RV dilatation) RV pressure estimation (TVR jet velocity). Associated lesions include anomalous pulmonary venous connection, pulmonary valve stenosis, and mitral valve prolapse. This condition is frequent in Ebstein anomaly[89].

What to assess? ASD (subcostal). If pathological, what to assess? ASD (A4C/PSAX) + RA dimension + RV dimension + PAPS.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSD) are the most common congenital cardiac abnormality in young individuals and the second one in adults, following only BAV[133]. Four locations of the defect within the interventricular septum are possible. Multiple windows can be used to assess the ventricular septum[131], such as PSAX and A4C views. VSD is also a common component of complex anomalies, such as Tetralogy of Fallot (ToF) and transposition of the great arteries (TGA)[89]. Key findings to provide are location, number, and size of defects, severity of LV volume overload, and estimated PAPS. Double chambered right ventricle (DCRV) and sinus of Valsalva aneurysm must be ruled out[89].

What to assess? VSD (A4C). If pathological, what to assess? LV mass + PAPS + aortic regurgitation + other congenital defects (aneurysm of Valsalva sinus, ToF, TGA, DCRV).

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus (PDA) is the lasting communication between the proximal left pulmonary artery (PA) and the descending aorta, just distal to the left subclavian artery[89]. Echocardiography is choice diagnostic tool^[131]. PDA is best seen from the PSAX and suprasternal windows, where the duct can be visualized along the left border of the pulmonary artery: there is bidirectional flow across the duct, confirmed on pulsed wave doppler (PW); moreover, LA/Aortic root ratio ≥ 1.4 is suggestive of shunt[134]. A complete echocardiographic assessment should be performed to exclude pulmonary atresia or coarctation of the aorta. Furthermore, it must be assessed the degree of LV volume overload, PAPS, PA size, and right heart change.

What to assess? PDA (PSAX). If pathological, what to assess? PWPDA (PSAX) + LA/Aortic root ratio ≥ 1.4 + LV mass + PAPS + PA size + RV dimension + RA dimension.

AORTIC COARCTATION

Aortic coarctation (CoA) is considered a part of a more general arterial disease[89]: It occurs as a stenosis or as a hypoplastic aortic (arch) segment. Associated lesions include BAV ascending aortic aneurysm, aortic stenosis, mitral stenosis or complex congenital heart defects. Echocardiography provides information regarding site, structure, and extent of CoA, LV function and LVH, and aortic vessel diameters[89].

What to assess? Aortic coarctation (PSAX). If pathological, what to assess? Aortic stenosis + mitral stenosis + FE + LV mass + other congenital defects (BAV, ascending aortic aneurysm).

OTHER CONGENITAL DISEASES

Improvements in modern medicine has led to an increase in the number of adults with congenital heart disease engaging in sports activities[89,135]. Therefore, an echocardiography assessment of others various congenital heart diseases is crucial for sport eligibility.

ToF is a congenital cardiac malformation made by VSD, RVOT obstruction, override of the ventricular septum by the aortic root, and RV hypertrophy[136]. The initial presentation of ToF varies depending on the severity lung blood flow obstruction. Echocardiography has become the standard modality in its diagnosis[137]. The ventricular septal defect, the aortic override, and RV hypertrophy can be seen in PLAX view, while the pulmonary outflow tract obstruction in PSAX view[138].

Transposition of the great vessels is a group of congenital heart defects involving an abnormal spatial arrangement of any of the great vessels[139]. Congenital heart diseases involving only the primary arteries (pulmonary artery and aorta) belong to a sub-group called TGA: the aorta aligns with the RV and the pulmonary artery aligns with the LV[140]. It is the fourth most common type of major cardiac defect[141] and the second most common cyanotic lesion after ToF[140]; if not treated, it is the leading cause of SCD in neonates and infants[142]. Important echocardiographic assessments in case of TGA are position of the great arteries in PLAX or subcostal views, presence

of ASD and VSD, presence of LVOT obstruction, eventual anomalies of coronary arteries[140].

Ebstein's anomaly (EA) is a malformation of the tricuspid valve (TV) with myopathy of the RV[143]. Initial presentation of EA in adulthood is common, and natural history demonstrates decreased survival with biventricular failure[144]. Echocardiography is the imaging standard in EA and provides a platform for TV leaflet, determination of right-heart size and function and dynamic evaluation of intracardiac shunts and defects, through color doppler[143,145].

Complete atrioventricular canal, also referred to as complete atrioventricular septal defect, is characterized by an ostium primum atrial septal defect, a common atrioventricular valve and a variable deficiency of the ventricular septum inflow[146]. It is a rare congenital heart condition. Echocardiography is the key tool for its diagnosis and anatomic classification[147].

OTHER PATHOLOGIES

Even if these are acute conditions that usually manifest with other symptoms, these pathologies are often cause of sudden cardiac death in athletes and therefore need to be screened.

MYOCARDITIS

Myocarditis accounts for almost 15% of SCDs in younger populations, especially in athletes[148]. The clinical presentation varies from chest pain, exertional dyspnea and fatigue, to cardiogenic shock[148]. Some patients heal completely while other may evolve in DCM[149]. An higher incidence of sport related SCD in case of myocarditis is documented[148], for the higher rate of life-threatening ventricular arrhythmias[150]. In acute form, echocardiography may show global LV dysfunction[151], wall motion abnormalities and pericardial effusions[15,152,153], an diffuse myocardial edema (increased wall thickness)[154-157]. In healed form, echocardiographic LV systolic dysfunction is found rarely because there is often small myocardial fibrosis, with undetectable scar at echocardiography[158]: Its evaluation still represent one of the bigger challenges of sport cardiology.

What to assess? EF; LV wall motion abnormalities; pericardial effusion; increased LV wall thickness.

PERICARDITIS

In athletes presenting with chest pain, the diagnosis of pericarditis should always be taken in consideration[159], particularly in younger ones[160]. Pericarditis and myocarditis may coexist in 20%-30% of patients[135]. Specific sport recommendations exist for patients with this disease[135]. Echocardiography is the diagnostic test of choice. The presence of pericardial fluid is recorded as an echo-free space between the posterior pericardium and left ventricular epicardium (in case of small effusion) or anterior right ventricular epicardium (in case of larger effusion)[159]. It can be assessed mostly in subcostal view.

What to assess? Pericardial effusion.

KAWASAKI DISEASE

Kawasaki disease (KD) is an acute vasculitis affecting young children, resulting in coronary artery abnormalities in case of delayed diagnosis[161,162].

Echocardiography is the imaging modality of choice for its detection: LV function and wall motion, of valvar regurgitation (particularly the mitral and aortic valves), and pericardial effusion should be assessed[163,164].

What to assess? Coronary artery abnormalities (PSAX/PLAX); EF; LV wall motion abnormalities; mitral regurgitation; aortic regurgitation; pericardial effusion.

CONCLUSION

Echocardiography is a valuable tool helping in detecting several CV conditions afflicting athletes. As physicians become more experienced with sonography, focused echocardiography by sports medicine physicians may become standard practice in larger screening practices. This technique could help to detect some hidden CV condition and to distinguish between physiological and pathological adaptation to physical activity, assisting in sport eligibility process. Even if we admit that a good manual skill, a training period and echocardiography experience should be required to perform it, our athlete-focused echocardiography could be an effective time-saving first line evaluation tool in sport eligibility process, eventually followed by a carefully exam. As such, a focused cardiac ultrasound examination may optimize cost-effectiveness: early detection of asymptomatic structural heart conditions could have important prognostic implications, with a relative less expensive cost than a complete echocardiogram. Nevertheless, further clinical trials should investigate its efficacy, accuracy, and applicability.

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In-depth review of cardiopulmonary support in COVID-19 patients with heart failure

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Abstract

Coronavirus disease 2019 infection has spread worldwide and causing massive burden to our healthcare system. Recent studies show multiorgan involvement during infection, with direct insult to the heart. Worsening of the heart function serves as a predictor of an adverse outcome. This finding raises a particular concern in high risk population, such as those with history of preexisting heart failure with or without implantable device. Lower baseline and different clinical characteristic might raise some challenge in managing either exacerbation or new onset heart failure that might occur as a consequence of the infection. A close look of the inflammatory markers gives an invaluable clue in managing this condition. Rapid deterioration might occur anytime in this setting and the need of cardiopulmonary support seems inevitable. However, the use of cardiopulmonary support in this patient is not without risk. Severe inflammatory response triggered by the infection in combination with the preexisting condition of the worsening heart and implantable device might cause a hypercoagulability state that should not be overlooked. Moreover, careful selection and consideration have to be met before selecting cardiopulmonary support as a last resort due to limited resource and personnel. By knowing the nature of the disease, the interaction between the inflammatory response and different baseline profile in heart failure patient might help clinician to salvage and preserve the remaining function of the heart.

Key Words: COVID-19; Heart failure; Cardiopulmonary support; Extracorporeal membranous oxygenation; Ventricular assist device; Coagulopathy

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Core Tip: Coronavirus disease 2019 (COVID-19) infection might cause severe respiratory distress and demonstrates an extrapulmonary involvement. Recent evidence shows direct involvement of COVID-19 and deterioration of the heart function. Severe infection is commonly found in high risk population, indicates a complex interaction between host inflammatory response and the infection itself, signifies the use of cardiopulmonary support and associated with high mortality. There are relatively scarce information regarding the use of ventricular assist device and extracorporeal membrane oxygenation and here we will be discussing the possible mechanism of how cardiopulmonary support may improve COVID-19 infection outcome.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging viral infection which has caused global pandemic with resulting both high global economic burden and mortality rate [1,2]. It also caused an alteration and restructuration in our healthcare system, especially in treating patients with infection and chronic disease [3]. Patients with both condition of COVID-19 and prior cardiovascular disease have an increased risk of cardiovascular complications which severely affect the mortality rate.

COVID-19 is also associated with higher incidence of cardiovascular complication in compare to previous coronavirus outbreaks [4,5]. Deterioration of the cardiac function is prominent in COVID-19 and those with lower baseline function are prone to further decline in cardiac function. A study demonstrate the preexistence of chronic heart failure (CHF) and high cardiac biomarkers is associated with worse outcome [6]. Recent study also shows that patient with heart failure (HF) is associated with an increased risk of mechanical ventilation and overall mortality regardless of left ventricular ejection fraction (LVEF) [7].

The use of cardiopulmonary support in COVID-19 shares the same prominent role in managing severe conditions such as severe respiratory distress and heart failure [3, 8]. However, there are several distinct clinical characteristics of HF patients which may differ from non-pre-existing HF patients. These factors have to be considered before choosing cardiopulmonary support as a treatment of choice. Another challenging issue is the highly selective inclusion and exclusion criteria before a patient is eligible for the use of extracorporeal membranous oxygenation (ECMO). Therefore, the management of both HF and COVID-19 has to be tailored since the concept of one treatment fits all might not suitable in these patients.

HEART FAILURE AND COVID-19

The mechanism of cardiac function disturbance in COVID-19 is poorly understood and it is thought to be an interaction between several mechanisms including direct myocardial injury, cytokine release, prothrombotic state causing microvascular thrombosis and exacerbation of underlying cardiovascular disease [3,9-13]. In the context of COVID-19, CHF patients are vulnerable to acute exacerbation. These patients are at risk because of their lower baseline status which unable to cope with the increasing metabolic demand in systemic inflammation triggered by the infection [14]. In the settings of advanced HF with left ventricular assisted device (LVAD) support, functional capacity of the lung has already impaired and contributes even more to the decrease of the cardiopulmonary reserve [15,16].

Several studies have demonstrated more severe infections and higher mortality rate in patients with preexisting cardiovascular disease [6,7,14,17]. Older age along with other comorbid such as obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease and frailty are seems to

be more prevalent in the HF group and might contribute to an increased rate of mortality and morbidity[7,18]. Moreover, these patients generally have a reduced immunity, general frailty, and tend to be in an inflammatory state[14,19].

A lower pulmonary function is commonly found in HF patients and is contributed mainly by chronic obstructive pulmonary disease (COPD)[20]. Combination of underlying parenchymal disease and elevated left ventricular filling pressure leads to the development of pulmonary hypertension[21]. In COVID-19 infection, respiratory failure and acute respiratory distress syndrome (ARDS) further exacerbates pulmonary vasoconstriction and interstitial edema. This condition is further worsened by pre-existing biventricular failure and ARDS that eventually lead to right ventricular function impairment.

Recent studies have shown that COVID-19 is associated with acute myocardial involvement which described as an acute cardiac injury[3,12,13]. A suspicion of cardiac involvement in COVID-19 is best described by an elevation in cardiac biomarker [high-sensitivity troponin (hs-TnI)] above 99th percentile upper reference limit[13,22]. Early reports had been analyzed, with notable findings suggest an increased level of cardiac troponin was associated with admission to intensive care and higher in hospital mortality[12,23-26]. A careful observation of endomyocardial biopsy in COVID-19 patients has revealed an evidence of acute myocardial inflammation through the presence of viral particles and a diffuse myocardial edema on cardiac magnetic resonance, therefore raising the suspicion of direct viral myocardial invasion[27]. Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV2) binds with angiotensin-converting enzyme 2 (ACE2) receptor and with the help of transmembrane protease serine 2 (TMPRSS2), facilitates viral entry through the cell[28,29]. ACE2 and TMPRSS2 are widely expressed in various tissue, including the heart, and might explain the involvement of heart during the course of infection[29]. Viral inclusion bodies were found from the biopsy of myocardial tissue along with identification of SARS-CoV2 genomic RNA in patients with suspected COVID-19 myocarditis, therefore raising the possibility of direct viral invasion to the myocardium[30-33]. Although there was a high viral load which is associated with higher proinflammatory cytokine expression in the cardiac tissue, these findings were not accompanied with an elevated inflammatory cell infiltrates[34]. The exact proportion of myocarditis is still hard to be determined, mainly because of the lack of definitive diagnostic procedure done in the patients[13,27]. However, myocarditis is important to be considered as it may cause abnormal electrical conductance in the myocardium[10].

Myocardial infarction plays a significant role in the development of acute HF in COVID-19 infection. Both Type I and II myocardial infarction might occur in patient with COVID-19, worsening the function in an already impaired baseline function[3]. This may leads to worse outcome in patient with a history of HF[3].

Cardiac arrhythmia is a major concerning issue in the context of HF and COVID-19 infection. Careful observation of the heart rate and rhythm are vitals in the clinical settings. Atrioventricular block, atrial fibrillation, polymorphic ventricular tachycardia and pulseless electrical activity have been closely associated with COVID-19 despite of the unknown mechanism of how these rhythms abnormalities may develop[22,35]. QT prolongation is constantly a threat, considering that QT prolongation is an independent risk factor of adverse outcome in advanced heart failure[36]. Even though the use of hydroxychloroquine and azithromycin is no longer recommended due to the lack of evidence to reduce mortality and severity, patients with HF are often already have underlying structural abnormalities. These abnormalities are related to the delay of ventricular repolarization which is manifested on electrocardiogram (ECG) as prolonged QT interval[37-39]. The use of another agents such as loop diuretic, may promote electrolyte imbalance and increase the risk of developing malignant arrhythmia. Sepsis is a known risk factor for QT prolongation that has to be considered in these patients[40]. The proposed mechanism of cardiac function deterioration is depicted in Figure 1.

ROLE OF INFLAMMATORY RESPONSE IN HEART FAILURE PATIENTS WITH COVID-19

Profound cytokine release in the setting of severe COVID-19 infection is commonly found. The release of proinflammatory cytokines, increased metabolic demand and coagulation disorder in sepsis may contribute to the development of new onset HF and decompensation episodes in CHF[41]. Cytokine storm is observed in viral induced infection such as influenzae and COVID-19 and in the setting of graft-versus-host

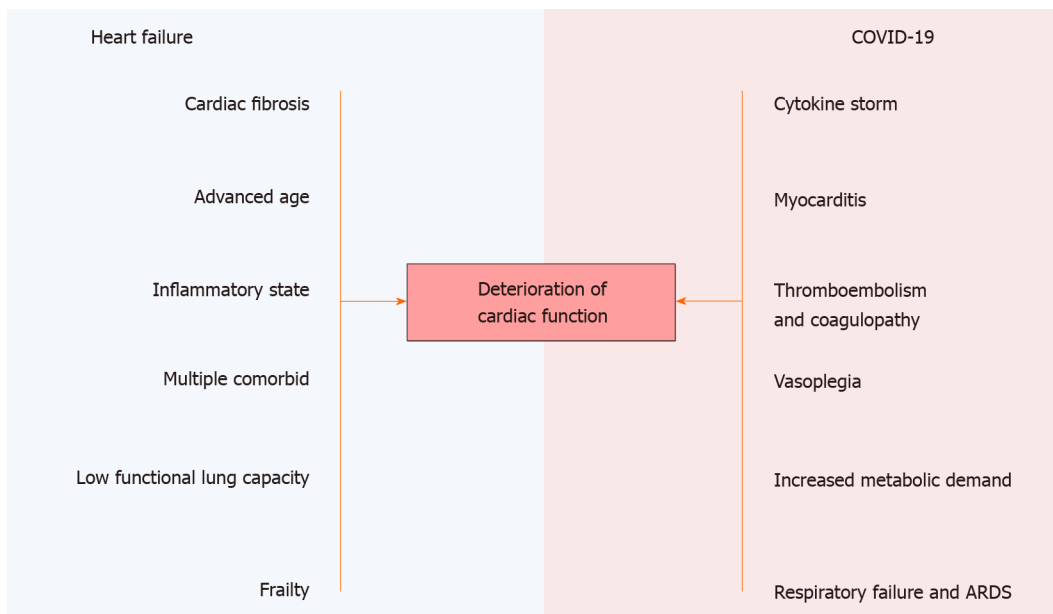


Figure 1 Proposed mechanism of deterioration of cardiac function in preexisting chronic Heart failure patient with coronavirus disease 2019 infection. CHF: Chronic Heart failure; COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome.

disease. Lymphopenia, C-reactive protein, lactate dehydrogenase, ferritin, D-dimer and troponin are among the biomarkers that reflect the severity of the hyperinflammatory state[42,43]. In HF, the inflammation happened as a response to the myocardial stressors. Multiple preexisting comorbidities that might further contribute to the profound inflammatory response are coronary artery disease, hypertension, arrhythmia, diabetes, and obesity. Increased level of inflammatory cytokine directly linked to the deterioration of the heart function[44,45]. The increased level of several cytokines such as tumor necrosis-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6) and galectin-3 may predict worse outcome in HF patients[46,47]. Interestingly, an elevation of IL-6 Level is also seems to be correlated with mortality in COVID-19 infection[48]. Moreover, the systemic hyperinflammation state that might occur in the setting of COVID-19 has extrapulmonary involvement and causing additional burden to the heart. The effect of hyperinflammation is well reflected by an elevation of cardiac biomarkers such as troponin and N-terminal pro B-type natriuretic peptide [43]. In this stage, vasoplegia and myocarditis might also occur[43].

Pro-inflammatory response which is induced by the infection might worsen hypoxia which in turn causing more stress to the damaged heart[42]. Hypoxia serves as a risk factor of survival in COVID-19 patients and should not be overlooked since it has deleterious effect in patients with HF and COVID-19[49]. Acute respiratory distress syndrome and exaggerated inflammatory response contributes to the development of hypoxia which may cause cardiac lesion and further exacerbates HF[50-53].

COAGULOPATHY IN THE WORSENING HEART DURING COVID-19

Coagulopathy is a common disorder found in COVID-19 infection. It is thought that the interaction between host defense mechanism and coagulation system during COVID-19 infection may lead to hypercoagulability and a high prevalence of thrombotic events[54-56]. This finding is reinforced by an elevated D-dimer level which is often present in the setting of COVID-19 infection[5,55]. The combination of endothelial dysfunction, inflammatory state, oxidative stress and platelet activation are thought to be responsible for a hypercoagulable state[1,5,55]. The true nature of the course is remain unknown to date, however the role of endothelial activation cannot be overlooked. It is thought that ACE2 receptor that serves as an entry point for the SARS-CoV-2 into the cell, plays an important role[57,58]. The presence of ACE2 receptors on the endothelial cells as well as antithrombin (AT), heparin and other anticoagulation might play an important role in regulating the inflammatory response [57]. AT interacts with heparin-like glycosaminoglycan (GAG) on endothelial surface and therefore involved in the release of prostacyclin which will inhibit leukocyte

activation by decreasing IL-6 Level[57,59]. The hypercoagulability state is also involved in the development of both micro- and macrovascular thrombus and may also plug the extracorporeal circuits[5,55]. Grave consequence of thrombosis may occur in COVID-19 patients as it may present as pulmonary venous thrombosis leading to right heart failure and or microvascular thrombosis may leads to myocardial dysfunction, worsening the heart function[5,55,60-62].

Patients with a preexisting history of heart failure are already in an increased risk for developing thromboembolism due to venous stasis, endothelial injury, ischemic cardiomyopathy and atrial fibrosis[63,64]. This condition might be worsened by the presence of COVID-19 infection which may trigger coagulopathy and the presence of implantable device which also may trigger thrombosis[65,66]. The pre-existing cardiopulmonary support such as left ventricular assisted device (LVAD) alone might increase the risk of developing pump thrombosis, although the risk of stroke with co-existing COVID-19 infection has not been assessed yet[3,67].

CARDIOPULMONARY SUPPORT IN COVID-19 PATIENTS WITH HEART FAILURE

Patient with COVID-19 might require mechanical circulatory support as a consequence of COVID-19 induced cytokine release syndrome or cytokine storm[3]. Hypoxemic respiratory failure may cause circulatory collapse in a small subset of patients and the need of lung-protective ventilation (LPV) in these patients is evident [68,69]. The use of extracorporeal life supports (ECLS) is reserved for patients with refractory hypoxemia or hypercarbia, right ventricular failure as a consequence of hypercarbia and acidemia, and hypoxic pulmonary vasoconstriction. These patients might have benefit from the use of venovenous (V-V) ECMO while those who suffer from refractory cardiogenic shock might consider the use of venoarterial (V-A) ECMO which might improve cardiac condition by pronounced LV unloading[70-72].

However, the use of these devices is remain in question since significant resources such as specialized equipment and trained personnel are needed to plant and maintain the device[4,42]. The decision of implanting the device might be considered for patients with ARDS and or cardiogenic shock refractory to traditional management with favorable outcome with the use of the device[68]. Close monitoring is also essential and health care workers exposure is also needed to be looked closely[42]. Still, despite the use of cardiopulmonary support, management of patients with HF and COVID-19 infection remain difficult due to complex interaction between the volume status and the biventricular dynamics[42]. There are also strict criterias have to be met before implanting ECMO in COVID-19 patient. While there are no difference for indication of ECMO between COVID-19 and non-COVID-19 patient, there are several things to be remembered[68]. First, careful selection is needed as patients with advanced age and significant comorbidities might not have much benefit from the use of ECMO. Also, patient with underlying CHF tend to be older, have multiple existing comorbidities and often fall into profound clinical status in the natural course of COVID-19 infection[6,7,14]. Therefore, the use of ECMO should be restricted in these patients unless there are a reasonable chance of recovery[5]. The use of ECMO should be carefully taken, considering that the hospital capacities and resources are limited in most settings and the possible outcome that the patient might achieve[5,42,68].

There are some small subset of patient who may choose another options in regard to the treatment of advanced HF. Patients who are not eligible for the heart transplant might use the left ventricular assist device (LVAD). However, the use of this device is not without risk, especially in the context of COVID-19 infection. These patients are known to have different types of HF that may produce different inflammatory profile in response to the implanted device[47]. To the best of our knowledge, until now there are no specific indication of when to implant ventricular assist device (VAD) in the context of severe COVID-19. First reported case of VAD implantation in patient with COVID-19 infection demonstrate the possibility of VAD as an alternative in a setting of prolonged cardiogenic shock and hemodynamical instability with modest chance of VA ECMO weaning[65]. Careful consideration and assessment of patient's clinical status has to be put in top priority in determining when to implant the device. The indications and contraindications for ECMO in COVID-19 is described in Table 1.

The presence of hardware in the body and prolonged support such as LVAD may cause immune dysregulation, increase the risk of infection and cellular immunity impairment as prior studies had already demonstrated[47,66,73,74]. In COVID-19, severe inflammatory response might induce profound patient's clinical status and

Table 1 Indications and contraindications for Extracorporeal membranous oxygenation in coronavirus disease 2019

Indications for ECMO	Contraindications for ECMO
V-V ECMO; PaO ₂ /FiO ₂ < 60 mmHg for > 6 h < 50 mmHg for > 3 h; pH < 7.2 with PaCO ₂ > 80 mmHg for > 6 h	Relative contraindications; Age ≥ 65 yr old; Body mass index ≥ 40; Immunocompromised status; No legal medical decision maker available; Advanced chronic underlying systolic heart failure; High dose vasopressor requirement (and not under consideration for VA or V-VA ECMO); Absolute contraindications; Advanced age; Clinical frailty scale category ≥ 3; Mechanical ventilation > 10 d; Significant comorbidities: Chronic kidney disease ≥ III; Cirrhosis; Dementia; Baseline neurological disease which might prohibit rehabilitation potential; Disseminated malignancy;
V-A ECMO; Refractory cardiogenic shock; Persistent tissue hypoperfusion; Systolic blood pressure < 90 mmHg; Cardiac index < 2.2 L/min/m ² while receiving noradrenaline > 0.5 mcg/kg/min; Dobutamine > 20 mcg/kg/min or equivalent	Advanced lung disease; Uncontrolled diabetes with chronic end-organ dysfunction; Severe deconditioning; Protein-energy malnutrition; Severe peripheral vascular disease; Other preexisting life-limiting medical condition; Nonambulatory or unable to perform activities; Severe multiple organ failure; Severe acute neurologic injury (example: anoxic, stroke); Uncontrolled bleeding; Contraindications to anticoagulation; Inability to accept blood products; Ongoing cardiopulmonary resuscitation

ECMO: Extracorporeal membranous oxygenation; V-V: Veno-venous; V-VA: Veno-Venoarterial; V-A: Veno-arterial.

worse outcome. The pre-existing LVAD in severe COVID-19 infection may raise some concerns in the context of management. The risk of pump thrombosis has to be kept in mind, as hypercoagulability state in COVID-19 infection and the pump itself may induce thrombosis[65]. Despite of severe hypoxemia might improve by prone position, there is a specific concern of the outflow graft compression, driveline damage and elevated pressure in the right ventricle with subsequent right ventricular failure[66, 67]. Moreover, additional load to the right ventricle may predispose to right heart failure which is well known as a potential etiology of hypotension in the setting of LVAD use and inflammatory surge[66,67]. However, prone position in patients with LVADs is not contraindicated in the management of hypoxemic respiratory failure although more data are needed[3].

Anticoagulant use in LVAD patient has to be closely monitored due to a high risk of thrombosis in this population[3,14]. More interestingly, patient with COVID-19 infection may often shows a hypercoagulability state despite therapeutic dose of anticoagulation and to overcome this state, requires an increase dose which will carry the risk of life-threatening bleeding[75]. Still, thromboembolism carries a significant risk of adverse outcome and the use of closely monitored anticoagulation might have a beneficial role[55].

Several biomarkers that reflect the severity of hyperinflammation in COVID-19 might be obtained before the infection and serves as a baseline markers in patient with LVAD. Baseline lactate dehydrogenase (LDH), absolute lymphocyte count, troponin and natriuretic peptide that are taken prior the infection might bring an important information that should not be overlooked[42]. These indicators are valuable in following LVAD patients with COVID-19 infection[42]. The role of cardiopulmonary support in COVID-19 infection is illustrated in Figure 2.

CONCLUSION

As discussed above, COVID-19 infection has deleterious effect on the heart function. In addition, exaggerated inflammatory response in severe COVID-19 infection in combination with preexisting impairment of the heart function and multiple comorbid as seen in the HF patients may severely affect the outcome. Cardiac function in patient with HF should not be overlooked as deterioration of the heart function may occur rapidly as a consequence of the infection. Therefore prompt diagnosis and early monitoring of the heart function are critical in the management. Careful monitoring of inflammatory marker during the course of the disease might also play an important role, as patient with advanced HF often have their baseline checked regularly. Any elevation of the inflammatory marker might serve as a clue of worsening inflammation and the heart function.

Another thing needs to be considered is the use of anticoagulation in severe COVID-19 patients with heart failure might have beneficial effect. Hypercoagulability state is often found in the patient, it is possibly because of the inflammatory response and the implanted device that may induce coagulation. However the risk of bleeding has to be kept in mind since fluctuant international normalized ratio and overt bleeding is not uncommon[55,76-78].

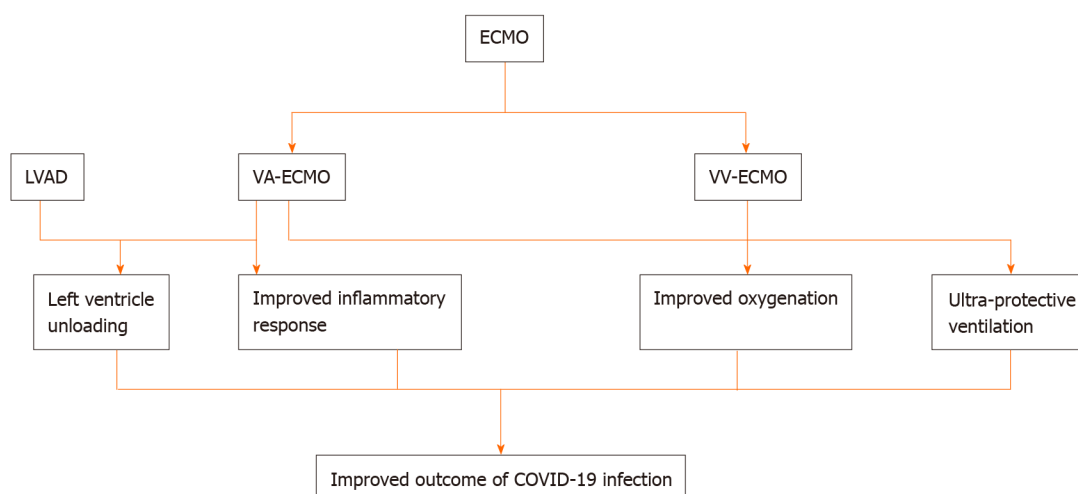


Figure 2 Proposed role of cardiopulmonary support in coronavirus disease 2019 infection. ECMO: Extracorporeal membranous oxygenation; LVAD: Left ventricular assist device; VV: Venovenous; VA: Venoarterial; COVID-19: Coronavirus disease 2019.

The use of cardiopulmonary support in this patient remains an issue. A small subset of patients with implanted LVAD also need to be concerned as unfamiliarity of the healthcare personnel to the device and the possible manipulation of the patient's position such as prone position might increase the right ventricular pressure and might lead to hypotension[66]. The use of ECMO and COVID-19 is very challenging due to its highly selective criteria and contraindicated in most patient with COVID-19 due to multiorgan dysfunction, significant comorbidities and the risk of bleeding[5,8].

Currently, supportive treatment remain the mainstay of treatment for COVID-19 infection. Focus is now directed on primary prevention and vaccination program. High burden and mortality rate was found in patient with preexisting cardiovascular disease, therefore American college of cardiology recommends to prioritize vaccination program in this high risk group[79].

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Surgical strategies for severely atherosclerotic (porcelain) aorta during coronary artery bypass grafting

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Abstract

Porcelain aorta (PA) is an asymptomatic atherosclerotic disease, characterized by circumferential calcification throughout the whole perimeter of the aorta. It is seen in 2% to 9.3% of patients undergoing elective coronary artery bypass grafting (CABG) and makes manipulation of the ascending aorta impossible. It has been clearly shown that most emboli seen and detected during the CABG procedure occur during aortic cross-clamping and aortic side-clamping. Manipulation of porcelain or a severely atherosclerotic aorta increases the risk of perioperative stroke. The incidence of stroke after CABG is between 0.48% and 2.9%, and the risk is correlated with the extent and severity of the atherosclerotic disease. A conventional CABG procedure involves successive steps that include cannulation of the ascending aorta, application of a cross-clamp to the aorta, and partial clamping of the aorta to create the proximal anastomosis. Therefore in procedures that involve cannulation, clamping, or proximal anastomosis, and where aortic manipulation is inevitable, preassessment of the atherosclerotic aortic plaques is crucial. Although many surgeons still rely on intraoperative manual aortic palpation, this approach has very low sensitivity and underestimates the severity of the atherosclerotic illness. Imaging methods including preoperative computed tomography or intraoperative epiaortic ultrasonography enable modification of the surgical technique according to the severity of atherosclerosis. Various surgical techniques have been described to reduce the risk of atheroembolism that may lead to cerebrovascular events in patients with severely atherosclerotic ascending aorta. Anaortic or "no-touch" techniques that do not utilize aortic manipulation may significantly decrease the development of neurological complications by avoiding aortic maneuvers known to cause emboli. In cases where severe atherosclerotic disease or other factors preclude safe use of the ascending aorta, modifications in the surgical techniques, such as switching to different cannulation sites including the axillary/subclavian, femoral and innominate arteries, or using hypothermic ventricular fibrillation and in-situ

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pedicled arterial grafts, or performing proximal anastomoses at alternative anatomical locations will enable CABG operations to be performed safely with low morbidity and mortality rates in patients with porcelain aortas.

Key Words: Coronary artery bypass grafting; Cardiopulmonary bypass; Severe atherosclerotic aorta; Porcelain aorta; Stroke; Mortality

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Core Tip: Porcelain aorta (PA) is a serious atherosclerotic disease that prevents manipulation of the aorta, and it is seen in 2% to 9.3% of the patients undergoing elective coronary artery bypass grafting (CABG). Although various mechanisms have been proposed to explain the development of stroke in cardiac surgery, embolic events resulting from manipulation of the ascending aorta are the main cause of stroke. Perioperative stroke is still among the most crucial complications of CABG surgery with its high patient morbidity and mortality. The best approach to prevent embolic events is the use of alternative surgical techniques which aim to minimize or eliminate the manipulation of a severely atherosclerotic or completely calcified aorta. Here, surgical strategies which are used for the management of patients with PA are summarized.

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INTRODUCTION

Coronary artery bypass grafting (CABG) remains the standard of management for the multi-vessel and left main coronary disease, however it is associated with an increased risk of postoperative complications. Severe circumferential calcification of the aorta is defined as porcelain aorta (PA) and its frequency has been reported as 2% to 9.3% in patients who are undergoing elective CABG[1-4]. PA is a serious atherosclerotic disease that, due to increased risk of perioperative embolic stroke, precludes manipulation of the aorta during CABG operations. It is expected that cardiac surgeons will encounter more patients with PA, due to the gradual aging of the world population, the increase in life expectancy, and the increase in the number of co-morbid diseases such as diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, and peripheral artery diseases.

A conventional CABG procedure involves cannulation of the ascending aorta, two-stage cannulation of the right atrium, insertion of antegrade cardioplegia cannula for cardiac arrest, application of a cross-clamp (CC) to the aorta, partial clamping of the aorta to create the proximal anastomosis, and finally removing these cannulas in a certain order. Although various mechanisms have been defined in the development of stroke in patients undergoing CABG surgery, embolic events caused by intraoperative aortic manipulations remain the main cause of stroke[5-7]. Embolic signals that are monitored by intraoperative transcranial Doppler (TCD) ultrasonography have demonstrated that most of the emboli in CABG procedures emerge during cross-clamping and side-clamping[5-8]. Perioperative stroke is still one of the most important complications of CABG surgery and causes an increase in economic costs, due to excessive consumption of resources in addition to high patient morbidity and mortality. Stroke after CABG is seen in approximately 0.48%-2.9%[3,9-11] of the operations, and stroke risk increases with the presence and prevalence of the atherosclerotic disease[4,12,13]. Some preoperative variables such as advanced age, peripheral vascular disease, and diabetes have been stated as risk factors for the development of postoperative stroke[4,10,11].

Clamping the aorta during CABG increases the risk of postoperative stroke regardless of the severity of aortic disease[6,14]. The best approach to prevent cerebral embolic complications is to modify the surgical techniques to minimize or eliminate

the manipulation of a severely atherosclerotic or fully calcified aorta. To safely perform CABG operations with low morbidity and mortality rates, various methods including the use of axillary/subclavian artery[15-17], femoral artery (FA)[4,18], or innominate artery (IA)[15,19] for cannulation, utilization of aortic “no-touch” or anaortic off-pump CABG surgery[4,20-23], use of in-situ pedicle arterial grafts[24-26], hypothermic ventricular fibrillation[4,21,26,27] and carrying out the proximal anastomoses in different anatomic locations[28-30], have been suggested. This review examines the relevant studies on patients who have a severe atherosclerotic disease of the ascending aorta or PA, and who need to undergo CABG surgery. The surgical strategies for the prevention of perioperative atheroembolic events and management of severe aortic atherosclerotic disease or PA are summarized in detail.

DEFINITION OF PA

PA is an asymptomatic atherosclerotic disease that is characterized by circumferential calcification of the aorta and which renders manipulation of the ascending aorta impossible (Figure 1). It is detected incidentally in patients evaluated for cardiovascular or pulmonary diseases. The use of different diagnostic methods and differences in the definition makes it difficult to determine the true prevalence of PA[31]. Severe atherosclerosis of the ascending aorta is reported to be present in 2.0% of CABG patients[32]. Studies have shown that atherosclerotic disease most frequently affects the distal part of the ascending aorta, and calcified plaques are significantly more common than complex plaques[12,13]. This may be associated with a large number of patients (75%) treated with lipid-lowering drugs, which can lead to increased calcification of the atherosclerotic plaques.

Hangler *et al*[3] found that atherosclerosis in the ascending aorta was normal or mild in 151 patients (42.9%), moderate in 167 patients (47.5%), and severe in 34 patients (9.6%). Also, by using epiaortic ultrasound (EU) before manipulating the aorta, Daniel *et al*[2] graded atherosclerotic disease within the ascending aorta using an ordinal variable (grade 1–5), according to the presence and thickness of mobile atheroma. Grade 1: normal (< 2 mm thickness); Grade-2: minimal disease (2–3 mm); Grade-3: moderate disease (3–5 mm); Grade-4: severe disease (> 5 mm); and Grade-5: the presence of a mobile plaque within any part of the ascending aorta. Grade 1-2 aortic disease was detected in 450 (85.7%) patients and grade 3–5 disease in 75 (14.3%) patients. In another study, it was observed that 22% of patients had simple intraluminal atheroma and 2% of them had complex intraluminal atheroma[7].

Amorim *et al*[1] divided aortic calcifications into two types; Type 1 (circumferential calcification of the ascending aorta) and Type 2 (calcification of the descending aorta including the aortic arch, and no involvement in the ascending aorta). Also, Type I has been divided into two subgroups as Type Ia (the type in which calcified aorta is not likely to be clamped) and Type Ib (calcified aorta with possible clamping).

DIAGNOSIS: PREOPERATIVE AND INTRAOPERATIVE EVALUATION

The presence of an aortic plate thicker than 4 mm is associated with a significant risk of stroke[33,34]. Therefore, a preassessment of atherosclerotic aortic plaques should be performed before procedures such as cannulation, clamping, or proximal anastomosis during which aortic manipulation is unavoidable[13]. Calcification of the arch the ascending aorta may be visible on chest x-ray or fluoroscopy during coronary angiography, however, these are not adequate for evaluating the degree and extent of the disease. Frequently used diagnostic methods are computed tomography (CT), intraoperative epiaortic ultrasonography (EU), and transesophageal echocardiography (TEE).

Chatzikonstantinou *et al*[35] advocated that conventional CT angiography, with efficacy proven to be superior to TEE, should be the reference method for imaging the ascending aorta. Similarly, Park *et al*[36] stated that CT angiography significantly affected the perioperative management or follow-up plan of the patients, and they recommended the use of preoperative CT angiography as a routine test unless contraindicated. Park *et al*[36] obtained a multislice CT scan before CABG in 284 patients and found severely atherosclerotic aorta in 36 patients (12.7%) and severe left subclavian artery stenosis in 18 patients (6.3%) that would alter the conduit selection or grafting strategy. CT accurately diagnoses PA and provides information on the location and extent of aortic calcification. Also, it provides detailed information about the distribution of the disease through 3-dimensional images of the aortic wall[1,31].

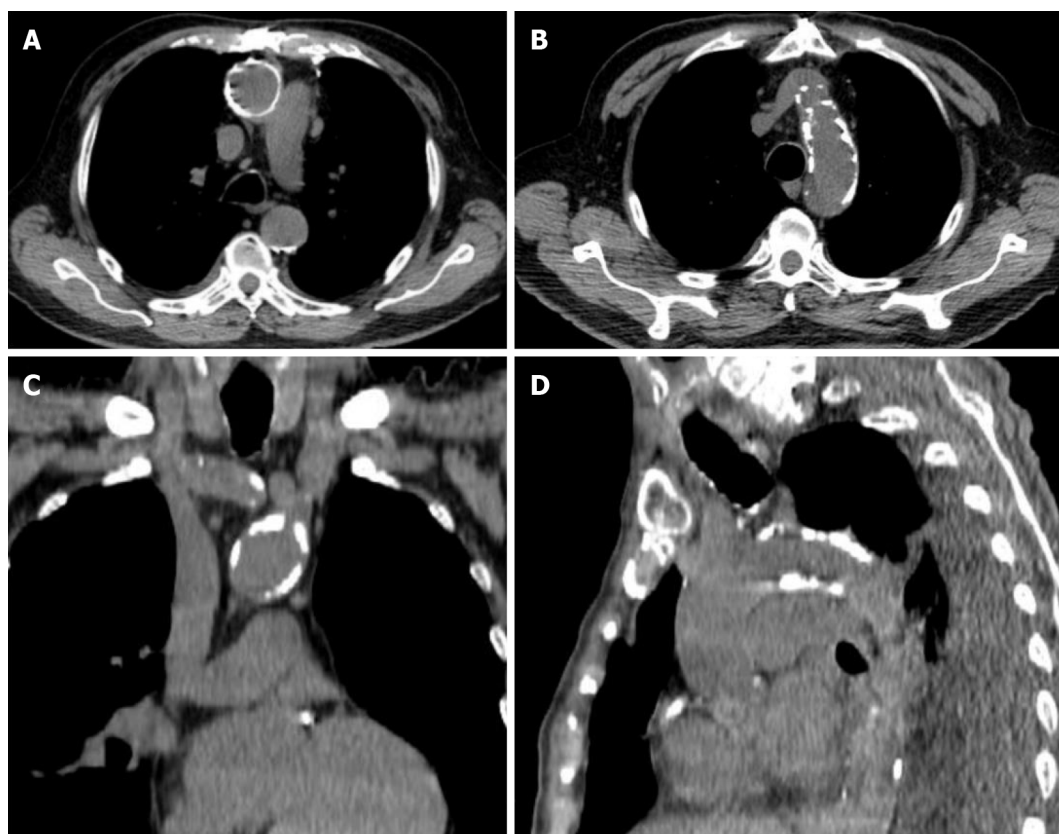


Figure 1 Porcelain aorta. Computed tomography reconstructions demonstrate circumferential calcification of the ascending aorta (A) and severe calcification of aortic arch (B-D).

There is evidence that EU is superior to manual palpation of the aorta and TEE in the detection of atherosclerotic disease of the ascending aorta and the aortic arch[37-39]. TEE evaluation of the distal ascending aorta, especially the CC and cannulation sites, is limited because the interposition of the left main bronchus between the esophagus and the aorta obstructs the vision[40]. Although many surgeons still rely on manual aortic palpation, this approach has a very low sensitivity and underestimates the severity[41]. EU is a simple and reliable solution to accurately scan the entire ascending aorta for the presence of intraluminal atheroma and has a sensitivity superior to both TEE and palpation[2,42,43].

INTRAOPERATIVE EPIAORTIC ULTRASONOGRAPHY

EU scanning is a fast, non-invasive and sensitive technique that provides information about the ascending aorta. Its use is limited because it does not allow preoperative planning, provides intraoperative information after the surgical incision has been made, extends the duration of surgery, needs special equipment, and requires trained personnel for both uses of the device and interpretation of the acquired data[7,44].

To determine any potential effect on intraoperative surgical decision-making, 6051 consecutive patients, who underwent EU of the aorta during cardiac operations have been analyzed retrospectively by Rosenberger *et al*[44]. The overall effect of the EU on surgical decision-making is 4.1%. This effect was stated as 0.6% for off-pump CABG requirement, 0.5% for the avoidance of aortic CC, 0.2% for change in arterial cannulation area, or avoidance of aortic cannulation. In patients whose surgical plans changed, aortic atheroma was more common in the anterior aspect of the aorta than the posterior. The overall stroke rate is lower in patients in whom intraoperative EU was used, compared to all patients undergoing the surgical procedures[44]. Shapeton *et al*[7] prospectively evaluated the impact of EU on surgical cannulation strategy and cerebrovascular events, as well as its use in cardiac surgery. EU was performed by the surgeon using a high frequency (> 7 MHz) ultrasound transducer, and two-dimensional images of the ascending aorta were obtained in multiple planes before aortic cannulation and CC application. Aortic cannulation or CC strategy were altered based

on EU findings in 7% (19/269) of the cases. No difference was found between patients with and without EU in terms of stroke (1.9% *vs* 1.2% $P = 0.523$).

Hangler *et al*[3] performed EU screening in 352 patients who underwent primary CABG and modified the applied surgical strategy according to the severity of atherosclerosis. In the presence of moderate atherosclerosis (maximum aortic wall thickness between 3 and 5 mm), single aortic CC is preferred first, while in severe atherosclerosis (maximum aortic wall thickness > 5 mm) no-touch techniques (aortic no-touch techniques on the beating heart) were used. The surgical technique was modified in 31% of patients with moderate aortic atherosclerosis and 91% of patients with severe aortic sclerosis. While there was no perioperative mortality for mild disease, mortality rates were 3% for moderate disease and 9% for severe disease ($P = 0.005$). Stroke rates were 2.0%, 2.4% and 2.9%, respectively ($P = 0.935$). Similarly, Djaiani *et al*[45] showed that the use of EU led to changes in intraoperative surgical management in patients undergoing CABG surgery [16 (29%) of 55 patients in the EU group and 7 (12%) of 58 patients in the control group]. However, they showed that the use of EU did not lead to a decrease in the number of cerebral emboli detected by TCD before or during cardiopulmonary bypass (CPB). Bolotin *et al*[38] also showed that the EU led to a change in the surgical procedure in 28% of 105 patients undergoing CABG procedures.

In a retrospective study involving 2292 patients who underwent isolated off-pump coronary artery bypass (OPCAB), patients were divided into two groups [the non-EU group with OPCAB under intraoperative TEE only ($n = 1019$) and the EU group with OPCAB under the EU ($n = 1273$)]. In both groups, OPCAB was performed with or without a partial aortic clamp. There was no statistically significant difference in the incidence of early stroke between the groups with and without EU (non-EU 1.7% (17/1019) *vs* EU 0.8% (10/1273); $P = 0.052$). However, in subgroups of patients with partial aortic clamps, the incidence of early stroke was significantly lower in the EU group (2.8% (9/317) *vs* 0.7% (2/301) $P = 0.041$)[39].

Konstadt *et al*[46] reported 100% sensitivity and 60% specificity for TEE in the assessment of the ascending aorta for atherosclerotic disease. A TEE study showed that negative findings for an atherosclerotic plaque suggested that the presence of a significant plaque is not high, whereas when the TEE study showed positive findings the possibility of having a significant disease in the ascending aorta was 34%. Therefore, they stated that the EU should be considered in cases where an atherosclerotic plaque is detected by TEE. On the other hand, it has been reported that routine intraoperative TEE identifies patients with the severe atherosclerotic aortic disease [47], and EU may be required when the insertion of a TEE probe is difficult or contraindicated[48].

CANNULATION STRATEGIES

The standard cannulation site in conventional CABG is the ascending aorta[27,32,49-51]. If the ascending aorta cannot be used safely because of severe atherosclerotic disease or other reasons, alternative cannulation sites may be used. The most preferred sites for the arterial inflow in CPB are the femoral arteries, axillary/subclavian arteries, and IA[51]. When choosing the arterial cannulation area, the risk profiles and benefit/cost ratios of the patients should be evaluated separately.

Femoral artery cannulation

FA cannulation is routinely used for extracorporeal circulation and constitutes the most common alternative to ascending aorta cannulation. The coexistence of severe atherosclerosis in the abdominal aorta or iliofemoral arteries limits its use[27,49,50]. The main disadvantages are the risk of cerebral atheroembolism and retrograde dissection caused by retrograde perfusion[17,27,51]. Grossi *et al*[47] showed that retrograde perfusion had no significant effect on the incidence of stroke in patients under 50 years of age, but it was an important risk factor for the occurrence of neurologic events in high-risk patients with aortic disease. Intraoperative malperfusion, arterial dissection, vascular injury, or limb ischemia are complications that are associated with cannulation. Femoral cannulation-related local wound complications occurred in only 1% of the patients, while the stroke rate was found to be 2%[18].

Axillary/subclavian artery cannulation

The axillary artery (AA) is a safe and effective path to maintain adequate arterial flow during CPB[17,27,51]. Because they are less affected by the atherosclerotic disease process, the axillary/subclavian arteries are safe access places, even in patients with

the severe atherosclerotic disease[51]. However, critical stenosis of the axillary, subclavian, or innominate arteries[52], inadequate AA diameter, AA dissection, and morbid obesity limit its usage[53]. AA cannulation is a safe method that offers shorter mean operative times, shorter average lengths of stay in the intensive care unit and hospital. Minor complications of axillary cannulation include seroma, hematoma, chronic pain, and pectoralis major muscle atrophy[53]. Brachial plexus injury, arterial dissection[16,54], and AA thrombosis requiring thrombectomy[51] are other complications.

The AA can be cannulated either directly or using a side graft[16,55-57]. Sabik *et al* [16] investigated whether the use of side grafts reduced morbidity in patients with 399 AA cannulations. In more than half of the patients (212 patients, 53%) the AA had been cannulated directly, and the remainder (187 patients / 47%) were cannulated using a side graft. Complications related to cannulation were brachial plexus injury in 7 (1.8%), AA injury in 7 (1.8%), aortic dissection in 3 (0.8%), and arm ischemia in 3 (0.8%) patients. These complications were statistically lower in the side graft group (2.1% *vs* 7.0%, $P = 0.03$). Carino *et al*[55] recommend the open Seldinger-guided approach for axillary cannulation (52/404, 13%) because of its safety, efficacy, speed, and simplicity.

Axillary inflow using a lateral graft reduces stroke and is a preferred method for complicated cardiac operations requiring circulatory arrest[57]. No superiority of AA cannulation over IA cannulation concerning perioperative outcomes in thoracic aortic surgery has been demonstrated[58]. In a study where they compared the early and late postoperative outcomes of patients who underwent axillary ($n = 107$) and FA($n = 198$) cannulation during the repair of acute Type A aortic dissection, Stamou *et al*[59] found that operative mortality was not affected by the cannulation site (16% for axillary cannulation *vs* 19% for femoral cannulation, $P = 0.64$) and that stroke rates were similar between the two techniques. On the contrary, Etz *et al*[60] reported on their 10-year experience with over 869 patients who were surgically treated for complicated aortic pathology. They compared aortic cannulation ($n = 157$) with femoral ($n = 261$), and direct right axillary ($n = 451$) cannulation. The right axillary cannulation was found to be superior regarding the rates of stroke and mortality. Similarly, Svensson *et al*[57] found a higher mortality risk in the femoral cannulated group compared to the group that was cannulated using a side graft to the AA.

Innominate artery cannulation

IA cannulation is an easy-to-apply technique that is used as an alternative to AA cannulation and enables selective antegrade cerebral perfusion. Its important advantages are the absence of a need for an extra incision in contrast to femoral and axillary cannulations, and the wide diameter which enables ideal flow without high pump pressures during CPB. Its large diameter is also a safe and advantageous technique for complex aortic repair, allowing faster cooling and rewarming in patients requiring circulatory arrest[15]. Other advantages of IA cannulation include the presence of the cannulation site within the same surgical field, ease of application in obese patients, lack of risk of brachial plexus injury or arm ischemia, prevention of malperfusion and retrograde cerebral atheroembolism associated with femoral cannulation, and the possibility of antegrade cerebral perfusion[15,19]. It can be cannulated either directly[61] as in AA cannulation or using a side graft[19,62].

In a retrospective study evaluating the surgical results of 206 patients with complex aortic pathology, axillary and IA cannulations accounted for 37% ($n = 77$) and 67% ($n = 129$) of the cases, respectively. Shorter times for CPB (189 *vs* 150 min, $P < 0.001$) and circulatory arrest (22.5 *vs* 11 min, $P < 0.001$) were found in the group which underwent IA cannulation. Blood transfusion rates were also found to be lower compared to the AA group[15]. Harky *et al*[58] reported shorter CPB times (173.12 \pm 51.85 min for AA cannulation and 167.45 \pm 54.67 min for IA cannulation, $P = 0.004$) in patients who underwent AA and IA cannulation. However, they did not find a significant difference between the two patient groups in terms of mean deep hypothermic circulatory arrest (DHCA) durations (29.14 \pm 23.55 min for right AA cannulation and 38.48 \pm 31.32 min for IA cannulation; $P = 0.06$). It was observed that axillary and IA cannulation were responsible for 3.5% and 4.48% of permanent neurological deficits and 3% and 9.70% of transient neurological deficits, respectively, and there was no significant difference detected between the two groups concerning cannulation-related complications ($P > 0.05$).

In IA cannulations using side grafts, Preventza *et al*[19] reported neurological complication rates of 4.4% and mortality rates of 1.5%, while Huang *et al*[62] reported transient neurological dysfunction in 5 (10.9%) of 46 patients. Di Eusanio *et al*[54] also reported that their patients who underwent IA cannulation (44 patients) had no morbidity due to cannulation, and neurologic complication and hospital mortality

rates in these patients were 6.8%. IA cannulation is a safe and effective alternative to femoral or axillary cannulation for arterial flow in proximal aortic surgery[19]. However, there are no high-quality data to prove that it is superior to AA cannulation in providing cerebral protection[57].

Other cannulation areas

The arch of the aorta[4,63,64], carotid artery[52,65], and brachial artery[66,67] are reported as alternative cannulation sites. Carotid artery cannulation was first performed by Urbanski *et al*[52] for acute aortic dissection surgery and has become the standard approach for surgical interventions requiring circulatory arrest. It has been noted as a fast, safe, and effective method of arterial cannulation, even in very obese patients.

AORTIC MANIPULATION AND CLAMP RELATED NEUROLOGIC COMPLICATIONS IN PATIENTS UNDERGOING CONVENTIONAL CABG AND OPCAB

It has been demonstrated that most emboli detected during CABG operations occur during the manipulation of the aorta[5,8]. Barbut *et al*[68] studied the formation of transient microembolisms during different maneuvers in on pump-CABG. They found that, in addition to a much smaller number of microembolisms during clamp application, CC and side-biting clamp removal was responsible for 58% of the total cerebral microembolic load (34% and 24%, respectively). In another study, 39% of the total microembolisms occurred during side-biting clamp application, and 46% during clamp removal[5]. Lev-Ran *et al*[69] compared 429 patients who underwent the aortic no-touch technique with 271 patients who underwent PC, they found a significantly lower incidence of stroke in the no-touch group and identified PC as an independent predictor of stroke.

In a meta-analysis comparing the results of different CABG techniques; (anaortic off-pump, off-pump with the clampless Heartstring device, off-pump with a PC, traditional on-pump CABG with aortic CC) the anaortic off-pump is an effective treatment method to reduce the risk of postoperative stroke, mortality, renal failure, bleeding complications, atrial fibrillation and to shorten the length of stay in intensive care unit[6]. The degree of EU, postoperative stroke score, operative approach, and aortic clamping were independently associated with an increase in postoperative stroke compared to the no-touch technique. Also, the observed-expected stroke rate increased as the degree of aortic manipulation increased[14].

In a study investigating the effect of different clamping strategies on postoperative stroke incidence during CABG; the double clamp (CC + PC) on-pump strategy showed a 2.5-fold increase in the risk of postoperative stroke compared to the single CC technique. In the OPCAB group, no difference was found between PC and no-clamping. The authors stated that the rate of clamp use generally decreased over the years, nonclamped techniques were used in 93.3% of patients with grade 3–5, and none of these patients developed postoperative stroke. Also, surgery year and surgeon identity were not found to be associated with postoperative stroke risk[2].

Avoiding aortic manipulation may reduce the risk of postoperative stroke, especially in patients at high risk of stroke[6]. In these patients, OPCAB, which is a less invasive method, may be preferred to reduce mortality and morbidity. Motallebzadeh *et al*[70] randomized a total of 212 patients [on-pump (104 patients) and off-pump (108 patients)] undergoing CABG, and assessed embolic signals from the middle cerebral artery by bilateral TCD ultrasonography. A better neurocognitive score ($P = 0.01$) and decreased cerebral embolism rates were observed in patients in the off-pump group at discharge, and they found no significant difference in the neurocognitive score at the sixth week and sixth month. Also, age ($P = 0.02$), length of education ($P = 0.03$), and on-pump status ($P = 0.006$) were found to be independent predictors of pre-discharge neurocognitive score. In another study, no significant difference was found between off-pump and on-pump CABG in the 30-day composite result ratio (7.0% and 5.6%, respectively; $P = 0.19$), the ratio of patients who ended up with less number of completed grafts than previously planned was higher in off-pump patients compared to on-pump CABG (17.8% vs 11.1%, $P < 0.001$). Follow-up angiograms revealed a lower overall graft patency rate in the off-pump group compared to the on-pump group (82.6% vs 87.8%, $P < 0.01$)[71]. In contrast, in their study where they shared the results of patients who underwent OPCAB (13 889 patients) and on-pump CABG

surgery (35 941 patients), Hannan *et al*[72] showed that OPCAB patients had a significantly lower 30-day mortality (adjusted OR 0.81, 95% confidence interval [CI] 0.68 to 0.97) and a lower incidence of postoperative stroke (adjusted OR 0.70, 95%CI 0.57 to 0.86). While there was no difference in three-year mortality between the groups (hazard ratio 1.08, 95%CI 0.96 to 1.22), higher rates of subsequent revascularization (hazard ratio 1.55, 95%CI 1.33 to 1.80) were found in OPCAB patients.

In another report; Emmert *et al*[73] similarly reported that the mortality and stroke rates were significantly lower in patients who underwent OPCAB compared to on-pump CABG. A meta-analysis of seven observational studies comparing unclamped OPCAB with conventional CABG and OPCAB regarding the use of partial clamp avoidance during OPCAB, the conventional CABG (0.38 *vs* 1.87% RR 0.27; 95%CI 0.14-0.58; $P < 0.0001$) rate showed a significant reduction in stroke risk compared to OPCAB using partial clamps (0.31 *vs* 1.35%; RR 0.34; CI 95% 0.18-0.65; $P = 0.001$)[74]. A similar meta-analysis comparing neurologic complications in off-pump surgery with and without aortic manipulation showed that post-surgical neurologic complications were reduced by half in anaortic OPCAB grafting cases (OR 0.46; 95 CI, 0.29-0.72; $P = 0.008$)[22]. Another study compared the patients who underwent CABG without aortic manipulation (1201/1758, 68%) with those who underwent a minimum of one proximal anastomosis using a side-biting aortic clamp or no-clamp proximal anastomotic device (557/1758, 32%). In the anaortic group, the incidence of perioperative neurologic deficits was lower than in the aortic manipulation group (0.25% *vs* 1.1%, $P = 0.037$). It was also found that advanced age is associated with peri-operative neurologic injury (OR 1.1, 95%CI 1.01-1.20, $P = 0.017$)[75].

Douglas and Spaniol[76] emphasized the role of unclamped OPCAB as an important tool in the prevention of postoperative stroke and also reported that assistive techniques (such as anastomotic assist devices) may be an important factor in reducing stroke occurrence for patients with significant atherosclerosis. On the other hand, large randomized controlled trials have reported similar neurologic results after on-pump and off-pump CABG[71,77,78].

PA AND CABG

Various techniques have been described and implemented in patients with atherosclerotic ascending aorta to reduce the risk of atheroembolism that may cause cerebrovascular events. The “no-touch” technique avoids all types of clamps in the aorta. Also when using this technique, no cardioplegia is applied, no grafts are anastomosed to the aorta, and deep hypothermia is not necessary[20,21]. Anaortic or no-touch techniques without aortic manipulation can significantly improve the development of neurologic complications by avoiding aortic maneuvers known to cause embolism[22, 23]. Halbersma *et al*[24] compared the 4-year results with those in the surgical arm of the SYNTAX trial in 400 consecutive non-touch total arterial OPCAB patients without touch, and there was a clear trend towards a reduction in stroke rate in the no-touch group (0.8%) compared to the surgical arm of the SYNTAX trial (2.2%). Also, there was no significant difference in the stroke rates between the non-touch OPCAB group and the PCI arm of the SYNTAX trials. Based on these results, they recommended off-pump in situ grafting as “standard care” to reduce neurologic complications. OPCAB no-touch with total arterial Y-graft and composite graft revascularization is an effective method for preventing thromboembolic events[23-25].

The internal mammary artery (IMA) can be used as an inflow site for saphenous vein (SV) grafts as in the total arterial T, or Y-shaped graft technique[28,32]. Mills *et al* [32] reported the frequency of severe atherosclerosis of the ascending aorta as 2.0% for patients undergoing CABG, and by using the “no-touch” technique they anastomosed the SV to the IMA in an end-to-side-fashion in 26 patients. They did not encounter any recurrence of angina in the patients. The “no-touch” technique has been used in 18 patients with heavily calcified and atherosclerotic ascending aorta who had myocardial revascularization. With this technique, 37 pedicled arterial grafts (22 IMA and 15 gastroepiploic arteries) were anastomosed proximally to the internal thoracic artery. Fifty-two distal anastomoses were performed using 15 free grafts, and no patients had neurologic complications[20]. However, accompanying subclavian artery stenosis may limit the use of these grafts both in situ and as Y-grafts. In this situation, the pre-operative diagnosis becomes even more crucial, and preoperative subclavian artery stenting may be required, as in the cases of Adesanya and Kilic[79].

One of the methods used to achieve optimal coronary revascularization is hypothermic ventricular fibrillation or hypothermic fibrillatory arrest[4,21]. The hypo-

thermic fibrillatory arrest also allows easy proximal anastomosis to a disease-free area of the ascending aorta in patients with a high risk of cerebral embolic complications and significant ascending aortic disease[21,27]. Gaudino *et al*[4] could not find a difference between hypothermic ventricular fibrillation and beating heart in terms of the overall in-hospital mortality rate. To achieve optimal coronary revascularization and minimize cerebrovascular events, Akpınar *et al*[80] also used the moderate degree hypothermic fibrillatory arrest technique with pedicled arterial grafts (internal mammary and gastroepiploic artery) in 21 patients with severe calcification of the ascending aorta, and they did not encounter any neurologic complications. However, the hypothermic ventricular fibrillation technique was associated with a greater incidence of neurologic complications (stroke and transient ischemic attack), renal insufficiency, and stay in the intensive care unit and hospital[4].

In conventional and OPCAB, the standard proximal anastomosis site or location is the ascending aorta itself. In advanced stages, the presence of PA makes it difficult to perform proximal anastomoses, and when in situ grafts cannot be used due to limited graft flow resources or T/Y grafting techniques cannot be applied, free grafts that require proximal anastomosis should be used. In this situation, using alternative inflow areas such as IA[27,29,30], subclavian artery, AA[28,30,81] and carotid artery [23,82] may be considered. Extra-anatomic CABG procedure is a safe and reliable method to minimize the prevalence of perioperative stroke and systemic embolization [29,30]. Demirsoy *et al*[30] preferred IA as the proximal anastomosis site in six of eight patients who underwent extra-anatomic bypass surgery because of the PA, they preferred the AA in one patient and the subclavian artery in another. Postoperative graft patency was evaluated by contrast-enhanced electron beam coronary angiography, and only one saphenous vein graft to the right coronary artery was occluded. Bonatti *et al*[28] have also demonstrated patency in 11 out of 13 extra-anatomic vein grafts with a 3D multislice CT scan performed in 13 patients during the first postoperative year. Agrifoglio *et al*[82] have identified a case in which CABG was performed off-pump and the saphenous vein graft was anastomosed proximally to the left common carotid artery. In addition to these methods, the coronary - coronary bypass is an alternative technique that can be used to bypass isolated atherosclerotic coronary lesions in the presence of PA[83,84]. In hemodynamically unstable patients or in whom aortic manipulation cannot be performed due to severely atherosclerotic aorta, performing CABG with the off-pump technique under CPB support and without application of CC can be a good choice to prevent neurologic complications [29,30].

Anastomotic support devices

The use of anastomosis support devices allows proximal aortic anastomoses to be performed without a side-clamp. The use of a sutureless proximal anastomotic device during OPCAB is safe and significantly reduces cerebral microembolism compared with the conventional bypass method[5,8,9]. Guerrieri *et al*[5] used TCD ultrasound to determine and compare the number and nature of microembolisms in patients. These patients underwent off-pump coronary artery bypass grafting during proximal anastomosis with three different techniques (aortic side-clamps and two separate unclamped devices Enclose II and Heartstring). It was seen that most of the microembolisms occurred during the application/insertion and removal of each device into the ascending aorta. During the anastomosis using the Heartstring device, the median number of total microembolisms was found to be higher than the other two groups, but there was no statistically significant difference ($P = 0.239$). The solid microembolism rate was significantly higher in the side-clamping group (23%) compared to 6% and 1% in the Enclose and Heartstring groups ($P < 0.01$). Avoiding aortic side clamping resulted in a significant reduction in the rate of solid microembolism detected by TCD. Similarly, Akpınar *et al*[80] found that the use of side-biting-clamps causes more microembolic load than Enclose II device [the median number of microemboli: 68 (range 35-290) *vs* 15 (range 5-48), $P < 0.05$]. Hilker *et al*[9] performed 542 off-pump proximal anastomoses using the Heartstring device in 412 consecutive patients. The overall postoperative stroke incidence was lower than the predicted stroke risk score (0.48% observed *vs* 1.37% predicted), and a 35% reduction in solid particle embolism has been observed.

In a study in which proximal anastomoses were performed using a sutureless Symmetry aortic connector device (St Jude Medical, St Paul, Minn); OPCAB was compared with conventional coronary artery bypass (cardiopulmonary bypass and hand-stitched proximal anastomoses). Patients were evaluated by intraoperative TCD ultrasonography to determine right- and left-sided cerebral microembolic counts. Patients in the OPCAB group experienced fewer left-sided cerebral embolic events

intraoperatively (mean, 24.9 ± 19.2 ; median, 26.0) compared to the patients who are in the conventional CABG group (mean, 189.9 ± 60.4 ; median, 180.0; $P < 0.0001$). A similarly significant difference in embolic counts was also noted in the right cerebral circulation (mean of 21.9 ± 20.7 and median of 18.0 for the OPCAB group *vs* mean of 181.6 ± 85.3 and median of 173.0 for the S-CABG group, $P < 0.0001$)[8].

CROSS-CLAMPING, ENDARTERECTOMY OR REPLACEMENT OF PA

Aortic CC is associated with high mortality and morbidity rates in patients with PA. Different techniques have been described to clamp the PA. Hartert *et al*[63] have reported the results of aortic cross-clamping in 42 patients with PA who underwent valve replacement [aortic valve ($n = 33$) or mitral valve ($n = 9$)] by using the open proximal ascending aorta technique. Longitudinal aortotomy was performed under total CPB after distal aortic arch or FA cannulation. The aorta was gently clamped, allowing the mobilized atherosclerotic material to leave the aorta through the open incision. After the main operation, the aorta was opened gradually and the plaques were cleared through the aortotomy which was still open. Surgical revision was required in three patients (7.1%) due to major bleeding and aortic dissection was not observed in any patients. The stroke rate was 7.1% and the 30-day mortality rate was 6.9%. The authors have suggested that cross-clamping with the “open proximal ascending aorta” technique is an effective method, with a low incidence of stroke and low risk of systemic embolization in patients with PA.

Another method used to avoid an embolic event in patients with PA is the “staged aortic clamp” procedure. This procedure includes (1) Short-term cessation of circulation and aortotomy during moderate hypothermia; (2) Balloon occlusion of the ascending aorta during low flow CPB; (3) Endarterectomy using an ultrasonic surgical aspirator to allow aortic CC; and (4) Felt reinforced CC and full-flow CPB steps[85]. The authors stated that they did not encounter any thromboembolic events with this method.

Nishi *et al*[86] suggested that by carefully selecting the direction of cross-clamping of the aorta with the help of preoperative CT and EU, they could successfully overcome the problem of the severely calcified ascending aorta. They performed a preoperative CT assessment for developing the clamping strategy in a severely calcified aorta. They found that the degree of calcification just below the IA was significantly less compared to the ascending aortic clamp site. After confirming that the extent of calcification in this area is less than 75% of the entire circumference, a soft CC calcification was carefully placed in the ascending aorta. All surgeries were completed under normal CPB with mild hypothermia, and no postoperative neurologic complications were observed in the patients. However, the utility of this technique is questionable, since aortic cross-clamping may cause an increase in the frequency of postoperative cerebrovascular events when calcification covers the entire aortic wall.

In high-risk patients with severe atherosclerosis of the ascending aorta short-period (3.4 ± 1.5 min) and moderately hypothermic (29.0 ± 2.3 °C) circulatory arrests allow internal inspection or debridement of atheroma plaques, thus allowing safe aortic cross-clamping[87]. Culliford *et al*[88] have also cooled 13 patients, with excessive calcification in the ascending aorta and transverse arch, to 18 degrees during CPB, and manipulation of the aorta during cooling was not allowed. During DHCA (for 3.5 to 12 min), the aorta was widely opened to remove ulcerated plaques and friable debris and to find a safe place for CC. In 12 patients the presence of PA was known before surgery, whereas one patient was found to have PA after CC. In this latter patient, occipital infarctions developed, and ascending aortic endarterectomy was necessary. Endoaortic balloon occlusion of the atherosclerotic ascending aorta has been proposed as an alternative to conventional CC to prevent vascular damage and distal embolization of atherosclerotic plaques. However, Zingone *et al*[89] found that endoaortic occlusion was ineffective, and associated with a significantly higher risk of in-hospital death (25%) and a higher risk of stroke (3.8%).

In patients undergoing cardiac surgery, hypothermic circulatory arrest enables safe resection of the severely atherosclerotic ascending aorta and graft replacement with an acceptable postoperative stroke rate and provides long-term protection from subsequent embolic cerebrovascular events[49,90]. Replacement of the atherosclerotic aorta with graft during DHCA is a radical option and has high mortality rates (14%)[64]. In the study by Rokkas *et al*[90], among 81 patients who were noted to have severe atherosclerosis of the ascending aorta on epiaortic screening and who un-

derwent CABG, 80 received [partial (5) or complete (75)] ascending aorta replacement by using hypothermic circulatory arrest. In the remaining patient, resection of a protruding aortic atheroma was performed. The 30-day mortality rate was reported as 8.6% (for 7 patients) and the incidence of stroke has been reported as 4.9%. Zingone *et al*[91] replaced the ascending aorta in 36 out of 152 patients who were noted to have severe aortic atherosclerosis which was detected on EU screening and CT. In 13 of them (36.1%), the aortic replacement was extended to the aortic arch. While DHCA was used in 34 patients, proximal aortic disease allowed conventional CC administration in 2 patients. The hospital mortality rate was 5.6%, one patient had a stroke (2.8%) and five patients (13.9%) had a neurocognitive impairment. Four patients (11.1%) experienced excessive bleeding requiring re-exploration.

Aortic endarterectomy may be an option in the management of patients with calcification of the aorta[64,92]. Vogt *et al*[93] performed complete thromboendarterectomy to the ascending aorta and the aortic arch during hypothermic circulatory arrest on 22 patients (CABG, $n = 21$ and aortic valve replacement, $n = 8$), and reported a 4.5% mortality rate and a 9% adverse neurologic event (one early and one late) rate. The follow-up of the patients was performed by magnetic resonance imaging and transthoracic echocardiography, and the endarterectomized aorta did not develop a dilation. The authors above have suggested that for patients with advanced-stage (Grade IV and V) plaques, ascending aorta and transverse arch thromboendarterectomy can be performed with acceptable surgical risk and a low recurrence rate for cerebrovascular events. On the contrary, Takami *et al*[87] performed reoperations in two patients (2/40, 5%) during the follow-up period, at postoperative 8th month in one and 44th month in the other, due to pseudoaneurysm in the suture line of the aortic patch. The authors suggested that the aortic wall undergoing endarterectomy should be considered as a risk factor for pseudoaneurysm formation and that the aortic suture line should be enforced during surgery.

CONCLUSION

Perioperative stroke is still one of the most crucial complications of CABG surgery with its high patient morbidity and mortality. During CABG, most emboli occur during active aortic clamp applications (cross-clamps, side-biting clamps) or the insertion and removal of unclamped aortic anastomotic devices. Therefore, in procedures that involve cannulation, clamping, or proximal anastomosis where aortic manipulation is inevitable, preassessment of the atherosclerotic aortic plaques is crucial. Imaging methods including preoperative CT or intraoperative EU enable modification of the surgical technique according to the severity of atherosclerosis. The use of anastomosis support devices to prevent lateral clamping and to support the proximal anastomosis may be an important strategy to minimize cerebral damage during proximal anastomoses in, especially high-risk groups. Since a soft or non-calcified aortic segment is needed to use anastomotic support devices, the need for aortic manipulation cannot be eliminated. The best approach to prevent embolic events is the utilization of alternative surgical techniques which aim to minimize or eliminate the manipulation of a severely atherosclerotic or completely calcified aorta.

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Angiotensin receptor blocker neprilysin inhibitors

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Abstract

Heart failure (HF) is a clinical syndrome that results from a structural or functional cardiac disorder that reduces the ability of the ventricle of the heart to fill with, or eject, blood. It is a multifaceted clinical condition that affects up to 2% of the population in the developed world, and is linked to significant morbidity and mortality; it is therefore considered a major concern for public health. Regarding the mechanism of HF, three neurohumoral factors - the renin-angiotensin-aldosterone system, the sympathetic nervous system, and natriuretic peptides - are related to the pathology of chronic HF (CHF), and the targets of treatment. Angiotensin receptor blocker and neprilysin inhibitor (angiotensin-receptor neprilysin inhibitor), namely sacubitril/valsartan (SAC/VAL), has been introduced as a treatment for CHF. SAC/VAL is an efficacious, safe, and cost-effective therapy that improves quality of life and longevity in patients with HF with reduced ejection fraction (HFrEF), and reduces hospital admissions. An in-hospital initiation strategy offers a potential new avenue to improve the clinical uptake of SAC/VAL. In the last five years, SAC/VAL has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. On the other hand, further work, with carefully designed and controlled preclinical studies, is necessary for understanding the molecular mechanisms, effects, and confirmation of issues such as long-term safety in both human and animal models.

Key Words: Angiotensin receptor blocker and neprilysin inhibitor; Chronic heart failure; Renin-angiotensin-aldosterone-system; Sympathetic nervous system; Natriuretic peptide;

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Core Tip: Heart failure (HF) is a multi-faceted clinical condition that affects up to 2% of the population in the developed world, and is linked to significant morbidity and mortality; it is therefore considered a major concern for public health. In 2014, a newly developed angiotensin receptor blocker and neprilysin inhibitor (angiotensin-receptor neprilysin inhibitor), namely sacubitril/valsartan (SAC/VAL), was introduced as a treatment for chronic HF (CHF), and it proved to have the efficacy, safety, and cost-effectiveness to improve quality of life and longevity in patients with heart failure with reduced ejection fraction and reduces hospital admission. In this review, we first summarize the current knowledge regarding HF, then provide an overview of the current knowledge on SAC/VAL for CHF, together with relevant clinical trials and future perspectives.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome resulting from a structural or functional cardiac disorder, diminishing the ability of the cardiac ventricle to fill with, or eject, blood[1-3]. It is a multi-faceted clinical condition that affects up to 2% of the population in the developed world, and it is linked to both significant morbidity and mortality; it is therefore considered a major concern for public health[4].

According to several researches in Japan, HF results from myocardial injury due to a variety of causes, including age > 80 years old, male, underlying heart disease; ischemic, hypertensive, cardiomyopathy, valvular heart disease, medical history; prior hospitalization for HF, hypertension, dyslipidemia, diabetes mellitus (DM), smoking, atrial flutter/fibrillation, chronic respiratory disease, stroke/transient ischemic attack, continuous positive airway pressure, pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy, and hemodialysis[1,5,6]. The etiology and frequency of HF is shown in Table 1.

Regarding the mechanism of HF, vasoconstriction and fluid retention are caused by the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), and the natriuretic peptides (NPs) secreted by the myocardium, which is itself both volume- and pressure-overloaded, promote vasodilation and diuresis[7,8]. The three neurohumoral factors related to the pathology of chronic heart failure, and the target of conventional remedies, are shown in Figure 1.

In this review, we first summarize the current knowledge of HF, then provide an overview of the current knowledge on angiotensin receptor blocker and neprilysin inhibitor [angiotensin-receptor neprilysin inhibitor (ARNI)], namely sacubitril/valsartan (SAC/VAL) for chronic HF (CHF), together with the structure, expression, regulatory roles, effects on CHF and other diseases, relevant clinical trials, and future prospects.

HF

Classification

HF is associated with a number of symptoms, including shortness of breath, breathing difficulties, nausea, diminished appetite, fatigue, intolerance to exercise, retention of fluid, coughing, weight gain from pulmonary congestion, and peripheral edema and

Table 1 The etiology of heart failure

Arrhythmia
Cardiomyopathy
Cardiotoxic drug
CKD
Congenital heart disease
DM
Hypertensive heart disease
Hypertension
Infection
Ischemic heart disease
Myocardial disease
Pericardial disease
Pulmonary hypertension
Systemic toxins
Valvular disease

CKD: Chronic kidney disease; DM: Diabetes mellitus.

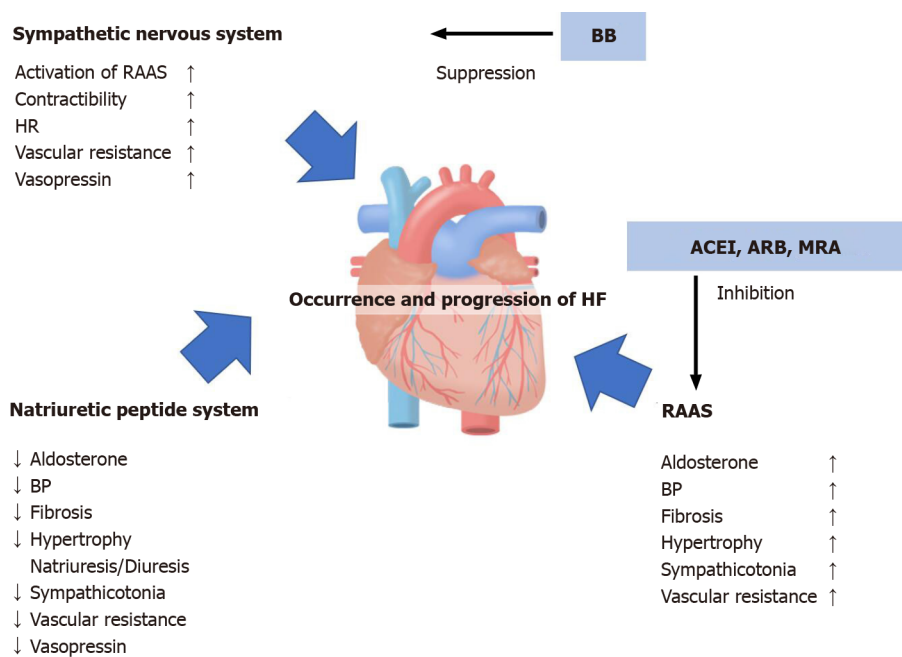


Figure 1 Three neurohumoral factors related to the pathology of chronic heart failure, and the targets of conventional remedies. ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; BB: β -blocker; BP: Blood pressure; HF: Heart failure; HR: Heart rate; MRA: Mineralocorticoid receptor antagonist; RAAS: Renin-angiotensin-aldosterone-system.

ascites due to impaired venous return[1,3]. HF severity can be classified under the New York Heart Association (NYHA) classification system as follows: Class I, no symptoms; Class II, symptoms with ordinary activity; Class III, symptoms with less than ordinary activity; and Class IV, symptoms at rest or with any minimal activity[3].

HF can be further categorized based on ejection fraction (EF)[3]. In 2013, The American Heart Association (AHA) and American College of Cardiology (ACC) assigned an EF range to HFrEF and HFpEF[3,9]. This classification created a “gray area” of patients who have EF of 41–49%; this has ultimately come to be known as “HF with mid-range” (HFmrEF)[3,9]. “HF with preserved EF” (HFpEF) is defined as left

ventricular (LV) EF (LVEF) of 50% or greater; HFmEF is defined as LVEF of 41%–49%, and HF with reduced EF (HFrEF) is defined as LVEF of up to 40%[3,9]. Of these, HFmrEF patients represent a group with heterogeneous clinical characteristics, sometimes resembling HFrEF, sometimes resembling HFpEF, and sometimes even resembling a unique phenotype entirely[9]. There are no randomized controlled trials (RCTs) for patients with HFmrEF, though HFrEF and HFpEF studies that include overlap suggest some potential benefits from β -blockers (BBs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and ARNI[9]. HFrEF occurs at LVEF of 40% or below, and is accompanied by progressive LV dilatation and adverse cardiac remodeling[2]. HF assessment begins with obtaining the patient's medical history and performing a physical examination[2]. Other key factors for diagnosis are NPs that are elevated above age- and context-specific thresholds, and identifying LV systolic dysfunction with LVEF of 40% or less using echocardiography [2]. Worldwide, HF now affects an estimated 23 million people, approximately 50% of whom are HFrEF cases[2].

Management

Management of HF depends on each individual's NYHA classification and EF, but generally, treatment involves pharmacotherapies[3]. HF treatment strategies include the use of diuretics for symptom relief, and the application of an expanding armamentarium of disease-modifying drug and device therapies[2].

The foundation of HFrEF treatment is a number of pharmacotherapies that have been shown in large multinational RCTs to reduce morbidity and mortality[10]. With the exception of cases with specific contraindications, patients with HFrEF should be treated with BB, and one of ARNI, an angiotensin-converting enzyme (ACE) inhibitor (ACEI), or ARB, as foundational therapy, as well as diuretics, and additionally MRA which is recommended to reduce mortality and hospitalization in all the patients with HFrEF and EF \leq 35%; until recently, however, it was unclear how to augment the beneficial effects of NPs in HF patients[2,7,10]. Of these, this review article covers ARNI in more detail below. In some cases, digoxin, ivabradine, ivabradine and hydralazine with isosorbide dinitrate, and hydralazine/isosorbide dinitrate also play roles in the care of some HFrEF patients[2]. More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have led to further improvements in disease outcomes, bringing about significant reductions in cardiovascular and all-cause mortality, regardless of patient diabetes status; additionally, the soluble guanylate cyclase stimulator vericiguat has reduced hospitalization for HF in high-risk HFrEF patients [2]. Pharmacotherapy efficacy does not vary by age; therefore, each of these therapies should be considered for every patient, no matter their age[10]. Other factors, including co-morbidities such as renal dysfunction, may limit use of some of these drugs for elderly patients[10]. Building on this foundation, other, more advanced treatments, including implantable cardioverter defibrillators and cardiac resynchronization therapy, are recommended by HFrEF treatment guidelines; for a select few, mechanical circulatory support and cardiac transplantation also remain options[2,10]. Conversely, there are only limited options for HFpEF[10]. In the absence of robust outcome data from large randomized trials, MRA is a reasonable therapy for the reduction of hospitalization risk for HF in patients with HFpEF[10].

New therapeutic strategies that aim to tackle the rising socio-economic burden of HF have become a significant priority, and timely, efficient drug treatments play key roles in improving quality of life (QOL) and prognosis for HF patients[11,12]. Enhancing NP bioavailability through exogenous NP administration, and inhibiting neutral endopeptidase, are valuable therapeutic strategies for HF; current therapeutic concepts combine inhibition of the RAAS with blockage of the sympathetic system[8, 12]. New therapeutic approaches, including selective heart rate reduction, attenuation of NP degradation through neutral endopeptidase inhibition, and treatment of comorbidities (such as iron deficiency, DM, or hyperkalemia) have led to further improvements to affected patient survival, time out of hospital, and QOL[8,12]. In addition, this approach has been proven to demonstrate beneficial effects, and reduce adverse events, in HF patients[8].

Prognosis

Typically, the natural course of HF is associated with repeated hospitalizations and the subsequent deterioration of patient prognosis[13,14]. In the past twenty years, the prognosis for HFrEF has steadily improved due to drug treatment advances and consistent implementation of evidence-based drug therapy as recommended by guidelines[12]. Therefore, a history of multiple previous admissions for HF was found to be a strong independent risk factor for adverse events following index admission,

and number of hospitalizations could serve as a simple yet valuable surrogate indicating subsequent adverse events in HF patients[13]. Furthermore, another study conducted in Japan reported a 23.6%–26.2% HF readmission rate within one year after discharge for HF[15]. Overall, despite the underlying pathophysiological mechanisms of HF being well understood, the disease still has significant morbidity, with three-year mortality of 30% and five-year mortality of 50%[1,3,16].

As a classification of HF, HFrEF is a major public health concern that has substantial morbidity and mortality; however, recent developments such as SGLT2 inhibitors, vericiguat, and transcatheter mitral valve repair all incrementally improve prognosis beyond what was possible through foundational neurohormonal therapies[2]. On the other hand, one of the most common reasons for prolonged hospital admission is poor management of HF symptoms from decompensated HFpEF[17]. The high morbidity and mortality rates associated with HFpEF are compounded by poor understanding of the underpinning pathophysiology[17].

CHF

Though CHF is a common condition, if untreated, it will markedly impair QOL; it is associated with a high risk of recurrent hospitalization and death[18]. Availability of evidence-based treatment options is limited to congestive HF with low EF; the medication has been approved in the United States by the Food and Drug Administration (FDA) for the treatment of chronic HFrEF patients of NYHA class II, III, or IV [18,19]. Alongside the past decade's marked progress in device therapy, more recent advances in CHF management have led to exciting new pharmacological options[20]. Pharmacotherapy is based on neurohumoral inhibition of the RAAS and the adrenergic system[18]. Previously, it has been reported that higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk in CHF patients, and that these confer complementary and incremental prognostic value[21]. On the other hand, a recent article reported further prognostic improvements for patients with this condition by introducing ARNI[18]. Modern implantable devices serve as another component of treatment[18]. The use of implantable defibrillators and special pacemakers for cardiac resynchronization is well established; there is still a need for further studies to investigate the utility of alternative devices (such as baroreflex modulation or cardiac contractility modulation) [18]. The treatment of chronic systolic HF as recommended in relevant guidelines, using drugs and implanted devices as indicated, can greatly improve clinical outcomes [18].

INTRODUCTION OF ARNI

In the early 1980s, the NP system was extensively characterized, with investigations into its potential influence on the development and progression of HF; in recent years, the NP system has drawn increasing attention[22]. Indeed, this new class of drugs for HF management is supported by recent results and a vast clinical development program, and may prompt a paradigm shift in HF treatment, moving from inhibition of RAAS and SNS, to more integrated targeting of rebalanced neurohormonal dysregulation in HF[22]. The study of NPs has become highly relevant, as they mediate beneficial effects at the cardiovascular level, such as diuresis, natriuresis, and decreased cardiac remodeling; their metabolism is mediated by neprilysin, a metallo-proteinase that is widely expressed in humans, and which is capable of catalyzing various substrates[23]. One of these, neprilysin, is an endopeptidase that breaks down endogenous vasoactive peptides, including NP, bradykinin, and adrenomedullin[3]. Neprilysin inhibition increases the levels of vasoactive substances, helping to counter the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and other maladaptive processes of HF[3]. The modulation of these functions has been studied for decades, giving rise to the use of sacubitril, the first neprilysin inhibitor; in conjunction with ARB, it has demonstrated high efficacy and tolerability among HF patients[23].

The association of an angiotensin II receptor antagonist and a neprilysin inhibitor is a new actor in HF management; recently, a newer pharmacotherapy, SAC/VAL, has become available for this purpose[3,24]. The stimulation of counter-regulatory systems, in addition to neurohormonal blockade, constitutes a new paradigm, known as “neurohormonal modulation,” and SAC/VAL is the first example of this new approach[3,8,16,19]. This new pharmacological class of ARNI has prompted a substantial conceptual change in HF treatment, with a transition from only inhibition

of the RAAS and SNS, to a strategy built around concomitant pharmacological enhancement of endogenous NPs[11].

STRUCTURE, EXPRESSION, AND REGULATORY ROLES OF ARNI

The ARNI, namely SAC/VAL, is a single molecule that is synthesized through the co-crystallization of valsartan and the neprilysin inhibitor prodrug sacubitril (1:1 molar ratio)[25]. The substrates for neprilysin are multifarious, and include biologically active NPs, adrenomedullin, substance P, endothelin, and angiotensin II, among others; it is unclear which of those substrates, or combination(s) of substrates, might be responsible for the benefit observed[26]. In addition, it can exert an additive action, because it may increase the levels of compounds that can protect against lung and heart injury (NPs, adrenomedullin, substance P, bradykinin, and apelin)[27].

In humans, this peptidase is widely distributed throughout the body, expressed with broad substrate specificity that preferentially hydrolyses oligopeptide substrate [28,29]. It is also an endogenously induced peptidase, for modulation of the production and degradation of various peptides; it present in the most abundance in the kidneys, and regulates the intrinsic renal homeostatic mechanism[30]. However, despite intensive research into neprilysin structure in different organisms, it is still not fully understood when it comes to changes in its expression and regulation during brain development and aging, especially for age-related pathologies, as well as the exact mechanisms underlying therapeutic benefit[26,28].

However, despite intensive research into neprilysin functions in various organisms, and into changes in how it is expressed and regulated during brain development and ageing, especially in age-related pathologies, concrete resolution is still not fully understood[28]. Currently, it is known that neprilysin regulates the cardiovascular, nervous, and immune systems[28,29]. SAC/VAL modulates the neurohormonal axis through inhibition of both angiotensin receptors and neprilysin, which additionally improves neurohormonal balance more than blocking the RAAS alone would[31]. Of these, unfavorable outcomes are attributed primarily to NP degradation[30]. NPs are involved in the RAAS inhibition and sympathetic system activation contributing to tubular and glomerular injury, and ARNI possesses the ability to counteract the effects of angiotensin II, as well as to increase NP activity[30,32]. Neprilysin exerts a beneficial effect by converting angiotensin-1 to angiotensin-(1-7), which activates the MAS-related G-protein coupled receptor[30]. Mas-related genes antagonize the angiotensin type 1 receptor (AT1R), reducing reactive oxygen species and inflammation, which ameliorates renal injury[30]. Neprilysin expression is increased by cytokines on the surface of the lung fibroblasts[27]. The current understanding of the mechanism of SAC/VAL, progressing to HF, is shown in Figure 2. According to the latest knowledge, neprilysin activity is elevated in acute respiratory distress syndrome; it is conceivable that it is also high in severe acute respiratory syndrome coronavirus 2 – namely, infections of coronavirus disease-2019 (COVID-19) – and neprilysin/AT1R inhibitor SAC/VAL may increase the levels of these molecules, blocking AT1Rs required for ACE2 endocytosis in COVID-19 infections[27]. In addition, green tea and various other natural compounds that are capable of upregulating neprilysin expression have been proposed as preventive medicine for both prostate cancer and Alzheimer's disease[28].

EFFECTS OF ARNI ON CHF

The approval of SAC/VAL, a first-in-class ARNI, marked the first novel pharmacological class in over a decade for HFrEF treatment[28,30,33]. Neprilysin plays a role as its mechanism, degrading the gross excess of circulating NPs in HF patients[7]. Compared to enalapril, SAC/VAL leads to reductions in symptoms of HF, cardiovascular death or HF hospitalization, sudden cardiac death, and disease progression, and improved QOL, in patients undergoing evidence-based contemporary medical therapy for HFrEF, and the NP assays for B-type NP (BNP) and N-terminal-proBNP (NT-proBNP) assays have been shown to have similar diagnostic accuracy for the differentiation of HF from other etiologies of shortness of breath[11, 17,32,34-36]. In real-world settings, SAC/VAL was found to be associated with improved survival and reduced HF-related hospitalization compared to enalapril in Asian HF patients, with consistent effectiveness even in older populations[37]. SAC/VAL use has been shown to result in a modest, chronic elevation of BNP while

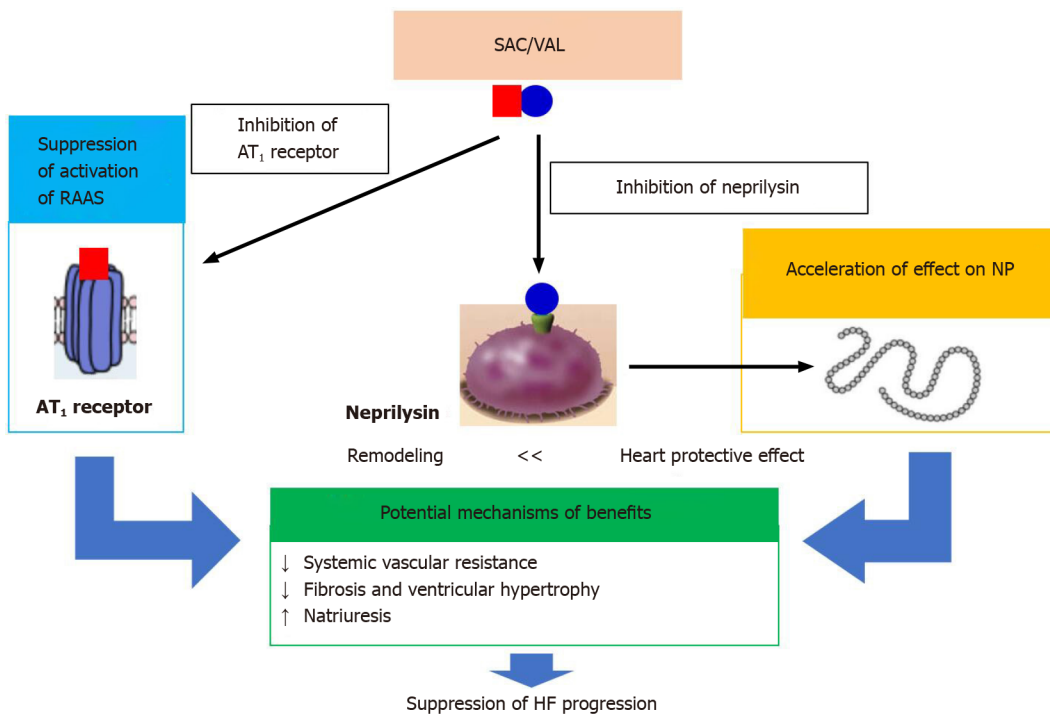


Figure 2 Mechanism of sacubitril/valsartan on heart failure progression. AT₁: Angiotensin II type 1; HF: Heart failure; NP: Natriuretic peptide; RAAS: Renin-angiotensin-aldosterone-system; SAC/VAL: Sacubitril/valsartan.

reducing levels of NT-prBNP[35].

The European Society of Cardiology, the Canadian Cardiovascular Society, and the ACC HF guidelines all currently recommend the use of ACEI or ARB and BB in HFrEF treatment[38]. In addition, HFrEF patients should first be treated with a BB and an ACEI or ARB (or ARNI), followed by add-on therapy with MRA and a diuretic, based on volume status[19,38-40]. Due to the different mechanisms of action in SAC/VAL, this combination may be regarded as a potential treatment option for patients who remain symptomatic despite optimized therapy with other alternatives[3]. While SAC/VAL is indicated for HF NYHA class II or III severity, it is unclear whether there is sufficient evidence from clinical trials or observational studies to support their use in combination, from the perspectives of both effectiveness and safety[3]. On the other hand, although it remains unclear what the optimal timing is for initiation of SAC/VAL, early use seems likely to positively impact patient outcomes[3,33]. We present the therapeutic options and treatment lines of CHF, especially HFrEF, based on the European Society of Cardiology, the Canadian Cardiovascular Society, and the ACC HF guidelines, in Figure 3.

Other point of discussion regarding ARNI for HF include evaluating the prevalence and significance of hyperkalemia in HF patients, which is essential for optimized use of potassium sparing agents, such as RAAS inhibitors or ARNI and MRA, which represent a well-established cornerstone of life-saving therapy[41]. SAC/VAL has already proven highly effective for HFrEF, and there is convincing data available regarding the cardioprotective effects of dapagliflozin, an SGLT2 inhibitor[20,38]. These two treatments have earned class I and class II recommendations, respectively, in the European Society of Cardiology guidelines for the diagnosis and treatment of HF[20]. However, more research is necessary on the mechanisms of action of disease modification[38]. Another point of discussion, raised in 2017, is that it was recommended that “patients who are eligible for treatment with ivabradine may also be eligible for treatment with SAC/VAL”, but there was no evidence evaluating the combination of SAC/VAL and ivabradine, or assessing the comparative safety and efficacy of the two treatments[3]. An additional novel point of discussion is that SAC/VAL also has a positive impact on acute HF, as observed very frequently in deceased COVID-19 patients[27].

On the other hand, there seems to be no evidence of a difference between SAC/VAL and valsartan in patients with HFpEF[17,39]. Therefore, there are, at present, no universal treatment strategies recommended for HFpEF; instead, management should take an individualized approach, with consideration given to each patient’s

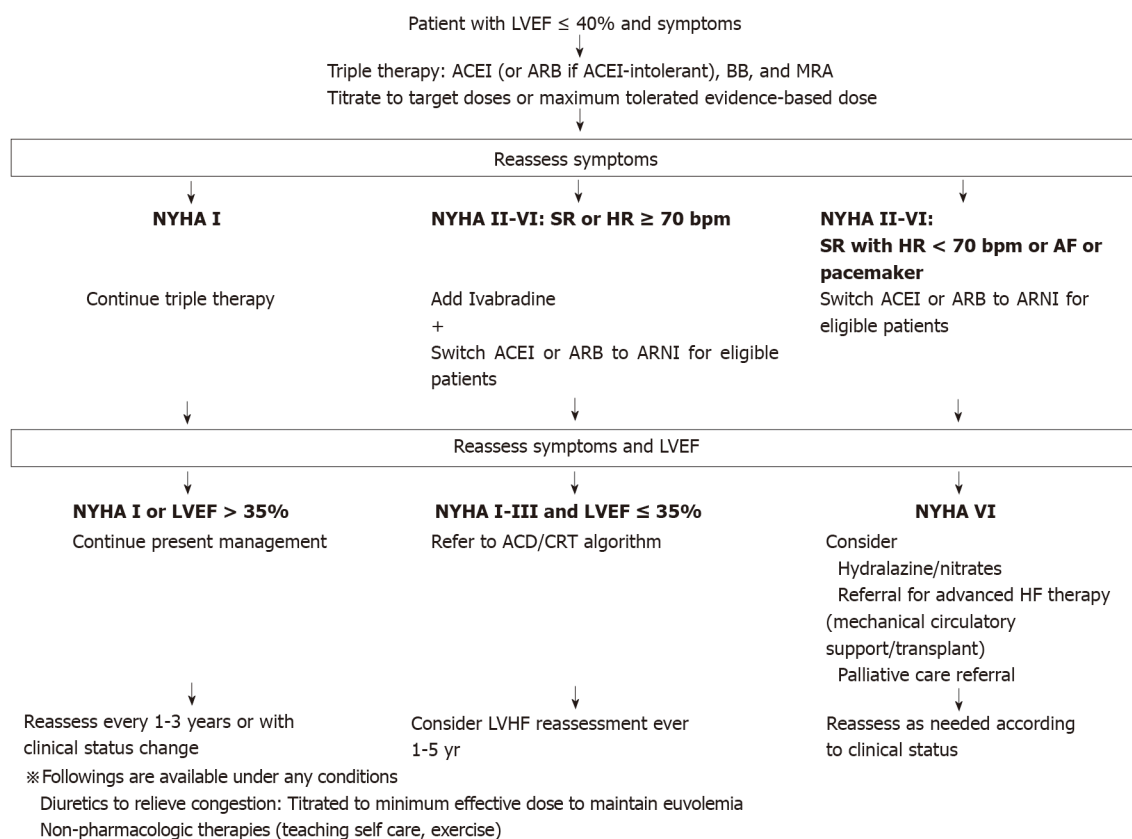


Figure 3 The therapeutic options and treatment lines of patients with symptoms of heart failure with reduced ejection fraction. ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; BB: β -blocker; bpm: Beats per minute; CRT: Cardiac resynchronization therapy; HR: Heart rate; ICD: Implantable cardioverter defibrillator; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SR: Sinus rhythm.

comorbidities[17]. Additionally, modern guidelines should emphasize this lack of evidence for the combined use of ARB and BB for HFrEF, with the exception of candesartan[42]. Even as practice moves towards widespread adoption of ARNI (which contain the ARB valsartan) for HF, this distinction has significant implications for the ongoing role of combination therapy with BB, which has, to date, only been assumed, but not proven[42].

OTHER EFFECTS OF ARNI

ARNI plays an important role in proteolytic processes in the kidney, as well as in cardiovascular regulation, immune response, cell proliferation, fetal development, and more[28]. First, in an exploratory study of patients with HFrEF who were treated with SAC/VAL using echocardiography, it was demonstrated to significantly decrease the ratio of early transmitral doppler velocity to early diastolic annular velocity (E/e') ratio, a simple, straightforward parameter of heart diastolic function[43]. Further, SAC/VAL may improve cardiac volume and function markers at twelve months[43]. Secondly, SAC/VAL is effective in treatment of hypertension, and short-term RCTs have found that the highest doses of SAC/VAL (200 and 400 mg q.d.) are more effective at lowering both office and ambulatory blood pressure than either ACEI or ARB alone; it should particularly be used as a first-line therapy for hypertensive patients with HFrEF[25,44]. They seem promising as antihypertensive agents for HFpEF, but investigation is ongoing[44]. Thirdly, although no effect was found on kidney function (compared to the irbesartan control), allocation to SAC/VAL did cause more reduction in cardiac biomarkers than irbesartan did, which suggests that this treatment could improve cardiovascular outcomes for this population[5]. Fourthly, there is growing evidence of neprilysin's role in glucose homeostasis: Because its activity in type 2 DM (T2DM) and obesity may potentially negatively impact metabolic processes in various tissues, it therefore plays a preventive role in the development of obesity and T2DM[28,29]. Thus, by raising the levels of various

peptides that exert beneficial effects on glucose metabolism, such as glucagon-like peptide-1 (GLP-1), NPs, and bradykinin, the inhibition of neprilysin in nutrient excess conditions could prove to be a powerful strategy for improving glucose homeostasis [29]. However, because of the action of other enzymes (such as DPP-4) on neprilysin substrates, which results in reduced inhibitor efficacy, as well as the concomitant elevation of neprilysin substrates that can impair sensitivity to insulin and function of beta cells, the use of a combination of drugs is preferable to the use of a neprilysin inhibitor alone for the treatment of T2DM [29]. Moreover, the increased angiotensin II levels that are associated with neprilysin inhibition limit its utility as a monotherapy for T2DM patients; a neprilysin inhibitor should always be prescribed along with an ARB, which is preferred over ACEI in order to avoid angioedema [29]. Fifthly, in some cases, administering SAC/VAL at appropriate doses has allowed for recovery of the sinus rhythm; consequently, upstream therapy of atrial fibrillation may demonstrate good results [45]. Sixthly, it may play a preventive role in cancer development [28]. Seventhly, viral dependence on ACE-2, as entry receptors, has been a recent focus, driving research into the impact of RAAS on COVID-19 pathogenesis [46]. Several pieces of evidence have pointed to neprilysin as a pulmonary RAAS components [46]. Considering neprilysin's protective effects against pulmonary inflammatory reactions and fibrosis, this suggests that future efforts should be directed towards its potential role in the pathophysiology of COVID-19 [28,46].

On the other hand, the most frequently reported adverse events are hypotension and hyperkalemia [47]. Other adverse effects include teratogenicity from the ARB component; this medication should therefore be avoided during pregnancy [48]. In addition, though it was reported in 2018 that SAC/VAL could increase the risk for dementia, the risk was lower than the proportions reported for other medications [48].

EVIDENCE FROM TRIALS

To date, there have been a number of global clinical trials regarding SAC/VAL: PARAMOUNT, PARADIGM-HF, TRANSITION, PIONEER-HF, PARAGON-HF, and PARALLEL-HF. The detail is shown in Supplement material.

PARAMOUNT trial

PARAMOUNT was a phase-2, randomized, parallel-group, double-blind multicenter trial in patients of NYHA class II-III HF, LVEF 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1), by a central interactive voice response system, to either ARNI LCZ696 titrated to 200 mg twice daily, or valsartan titrated to 160 mg twice daily, and treated for 36 wk [49]. The primary endpoint was changes in NT-proBNP, a marker of LV wall stress, from baseline to twelve weeks; the analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment [49]. The trial concluded that, in patients with HFpEF, SAC/VAL reduced NT-proBNP to a greater extent at twelve weeks than valsartan, and that it was well tolerated [49]. In this trial, the most common adverse event reported with SAC/VAL was symptomatic hypotension, with 19% frequency [48].

PARADIGM-HF trial

In the 2014 PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial of 8399 outpatient subjects with HFrEF, SAC/VAL was found to be more effective than enalapril for slowing disease progression by decreasing the risk of worsening HF leading to the need for hospitalization or emergency admission and the need for intensified therapy; it also reduced the rates of 30-day HF readmission, as well as all-cause readmission after HF hospitalization, HF devices, or cardiac transplantation [24, 31,37]. In addition, treatment with SAC/VAL was associated with statistically important reductions in cardiovascular death, a 16% reduction in all-cause mortality, and a 20% reduction in the composite of cardiovascular-related death or HF-related hospitalization (composite primary endpoint) compared to treatment with enalapril [16,26,33,37,47,48,50,52].

Accordingly, in 2016, the European and American cardiology societies (ACC/AHA/Heart Failure Society of America) simultaneously issued a class I recommendation to replace ACEI with SAC/VAL for management of patients with HFrEF NYHA II-IV [4,16,26,33,48,50,52]. The results indicate that SAC/VAL should be started from the earliest symptomatic stages of the disease [31,37]. However, more, longer-

term trials may be necessary in order to conclusively compare the efficacy of the two drugs, as well as their safety; though this is beyond the scope of this review, it is nevertheless in crucial need of evaluation[4]. Moreover, the results of the above trials should be taken with caution, as several limitations have been identified that may affect the generalizability and applicability of these results in real-life clinical practice [4].

Biomarker-based mechanistic studies have also provided further insight into potential pathways that may prove relevant to the benefits that have been observed with ARNI[26]. In this trial, treatment with SAC/VAL was associated with greater increases in BNP and urinary levels of cyclic guanosine monophosphate compared to treatment with enalapril; the latter reflects the increased intracellular second-messenger levels that result from NP action, as well as the other direct and indirect effects of mediators increased by inhibition of neprilysin[26]. However, most of the patients treated showed only a modest increase in BNP levels after initiation of SAC/VAL[26]. In contrast, neprilysin has a greater affinity for A-type NP (ANP) than for BNP, and after SAC/VAL initiation, ANP increased more consistently and robustly [26]. It is conceivable that ANP or perhaps other neprilysin substrates (such as C-type NP, urodilatin, adrenomedullin, substance P, apelin, bradykinin, vasoactive intestinal peptide, calcitonin gene-related peptide, or GLP-1) may play a predominant role in the mechanism of action of SAC/VAL; indeed, further mechanistic studies are currently ongoing, in order to elucidate the processes that underlie the clinical benefits that were observed in this study[26]. In addition, treatment with SAC/VAL led to significantly reduced levels of aldosterone, soluble ST2, matrix metalloproteinase-9, and its specific inhibitor (tissue inhibitor of metalloproteinases-1), reflecting reduced profibrotic signaling[26]. The levels of procollagen amino-terminal propeptide types I and III also were lower than with enalapril, reflecting reduced synthesis of collagen[26].

This study also compared safety outcomes: the SAC/VAL group had a higher risk of hypotension compared to conventional therapy (OR, 3.14; 95% CI, 0.94–10.55), with 18% frequency[48,53]. Thus, in order to prevent serious adverse events, clinicians must monitor for hypotension, dizziness, cough, angioedema, hyperkalemia, and renal dysfunction[53]. The risk of other adverse effects of ARNI use, such as hyperkalemia, cough, and diminished renal function, have been demonstrated to be lower than when using ACEI on its own[48,53].

TRANSITION trial

The TRANSITION trial was a randomized, multi-center, open-label study comparing two treatment initiation modalities of SAC/VAL, to assess tolerability and optimal time point for initiation of SAC/VAL in patients stabilized after acute HF: Either at least twelve hours pre-discharge, or days 1–14 post-discharge[54]. In summary, approximately half of the HFrEF patients who had stabilized after an acute HF decompensation event were able to achieve the recommended target dose of SAC/VAL within ten weeks, and at least 86% were able to maintain any dose of SAC/VAL for more than two weeks, following the label recommendations for initiation and up-titration[54]. There were few adverse events or permanent treatment discontinuations, particularly given the extreme vulnerability of the post-acute decompensated HF population[54]. The findings from this study complement those from the PIONEER-HF study, showing that early initiation of SAC/VAL in a wide range of HFrEF patients who have recently been admitted for acute decompensated HF is feasible, either as hospital patients or shortly after discharge[54].

PIONEER-HF trial

The PIONEER-HF trial (Comparison of SAC/VAL Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute HF Episode) was a multicenter, randomized, double-blind trial of in-hospital initiation of SAC/VAL ($n = 440$) compared to enalapril ($n = 441$), in patients who were stabilized during hospitalization for acute decompensated HF[55]. In this trial, a heterogeneity in the effect of SAC/VAL on these efficacy and safety outcomes were evaluated in the following selected subgroups of clinical concern: Patients with baseline systolic blood pressure ≤ 118 mmHg, baseline NT-pro BNP > 2701 pg/mL, estimated glomerular filtration rate < 60 mL/min per 1.73 m 2 , ≥ 1 additional hospitalization for HF within the prior year, admission to the ICU during the index hospitalization, inotrope use during the index hospitalization, and severe congestion[55]. As a result, the trial found that treatment with SAC/VAL after initial stabilization led to a consistent reduction in cardiovascular death or rehospitalization for HF in high-risk subpopulations admitted for acute decompensated HF, and that SAC/VAL was well tolerated[55].

PARAGON-HF trial

The recently completed PARAGON-HF trial found that SAC/VAL modestly reduced total HF hospitalization and cardiovascular death risks, compared to valsartan, in patients with HFpEF, although this finding fell just short of being statistically significant[7,26,56]. Clinical benefits were observed in secondary endpoints, including QOL and kidney endpoints; more specifically women and patients who are at the lower end of the LVEF spectrum appeared to preferentially benefit[26]. In addition, the safety profile of SAC/VAL was found to be largely consistent with prior trials[26]. In this trial, 15.4% of the SAC/VAL group discontinued use of the trial drug due to an adverse event, and 58.9% patients had at least one serious adverse event; the most common serious adverse events ($n \geq 2\%$ in the group) during the double-blind period, regardless of study drug relationship, by preferred term and SAC/VAL group, were cardiac failure (14.6%), atrial fibrillation (6.7%), pneumonia (6.7%), acute kidney injury (6.7%), congestive cardiac failure (3.6%), acute cardiac failure (3.5%), anemia (2.8%), acute myocardial infarction (2.5%), urinary tract infection (2.2%), hypotension (2.2%), and unstable angina (2.1%)[56]. By the time of the final visit, among the patients continuing therapy, the target dose was being taken by 82.0% of the SAC/VAL group [56].

SAC/VAL group patients had a greater likeliness of having hypotension, but were less likely to demonstrate creatinine and potassium level increases than valsartan group patients, and the mean systolic blood pressure at eight months was 4.5 mmHg (95%CI, 3.6–5.4), or lower in the SAC/VAL group than in the valsartan group; however, this difference did not correlate with the potential treatment effect[56].

PARALLEL-HF trial

The objective of the PARALLEL-HF trial was to describe the baseline characteristics and treatment of Japanese HFrEF patients[57]. The trial concluded that the patients studied were largely representative of contemporary ambulatory HFrEF patients who were well treated using evidence-based therapies[57]. In addition, PARALLEL-HF will assist in determining whether SAC/VAL provides clinical outcome improvements in Japanese HFrEF patients similar to those that were observed in the PARADIGM-HF study[57].

FUTURE PROSPECTS

Though guidelines have changed worldwide to include SAC/VAL for HFrEF patients, even now, some seven years after PARADIGM-HF trial, there remains some uncertainty regarding when to start SAC/VAL, and in whom[7]. A treatment's estimated long-term effects can serve as a helpful adjunct to clinical trial results, in order to provide patients with easily understood information regarding one treatment's potential benefits compared to those of another[26]. Furthermore, both HFpEF diagnosis and treatment remain challenging, as do the management of advanced and acute HF[7,34]. Though progress remains slow with respect to HFpEF, both ARNI and SGLT2 inhibitors also hold great promise for this condition, and there are currently large clinical trials underway (PARALLAX)[20,26,32]. In addition, the recent development of new diagnostic algorithms, to improve HFpEF diagnostic accuracy, will assist in future clinical trials' efforts to find effective therapies[20].

There are currently several other ongoing trials that aim to clarify and explore the benefits of SAC/VAL for HF management, as well[48]. It is unclear whether inhibition of neprilysin has a direct effect on extracellular matrix homeostasis, or if these profibrotic benefits reflect hemodynamic improvement; the completed PROVE-HF trial (prospective study of biomarkers, symptom improvement, and ventricular remodeling during SAC/VAL therapy for HF) will continue to examine a wide variety of biomarkers, including collagen homeostasis markers, in 795 HFrEF patients being treated with open-label SAC/VAL[26]. The currently ongoing PARADISE-MI trial (prospective ARNI *vs* ACEI trial to determine superiority in reducing HF events after myocardial infarction (MI)) aims to evaluate the effects of inpatient SAC/VAL compared to ramipril, for reducing cardiovascular death and HF hospitalization in post-acute MI patients who have evidence of LV systolic dysfunction ($EF < 40\%$) and/or pulmonary congestion, and who have no known prior history of CHF[26,48]. Another dedicated, randomized, cardiac-magnetic-resonance-based trial, comparing SAC/VAL to valsartan in patients who have asymptomatic LV systolic dysfunction and a history of MI, RECOVER-LV (effects of SAC/VAL compared to valsartan on LV remodeling in asymptomatic LV systolic dysfunction after MI), is also expected to

provide further insight into ARNI's potential remodeling effects[26].

The effects of SAC/VAL on hypertensive organ damage have only been sparsely investigated; to date, no studies have established SAC/VAL's impact on cardiovascular event rates[25]. Therefore, future studies should focus on comparing SAC/VAL to combination therapies already in use, such as ARB and calcium channel blockers[25]. Additionally, COVID-19 is an ongoing viral pandemic disease that induces severe pneumonia in human patients[46]. A report has aimed to elucidate the potential beneficial effects of neprilysin pathways, as a novel target for COVID-19 therapy, through a summary of its possible molecular mechanisms[46]. Additional experimental and clinical studies that further explain the relationships between neprilysin and COVID-19 will be of great benefit when designing future treatment approaches[46].

Finally, the barriers that prevent SAC/VAL from being prescribed for eligible patients may include practitioners' unfamiliarity with ARNI, safety concerns, and payer reimbursement issues[53].

CONCLUSION

SAC/VAL is an efficacious, safe, and cost-effective therapy that improves QOL and longevity in patients with chronic HFrEF, and reduces hospital admission. An in-hospital initiation strategy offers a potentially new avenue to improve clinical uptake of SAC/VAL. In the last five years, SAC/VAL has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. In the next five years, we should see SAC/VAL being brought into wider implementation in practice, with potential expansion of its therapeutic indications. Further work is necessary, with carefully designed and controlled preclinical studies, in order to better understand its molecular mechanisms and effects, and to confirm issues such as long-term safety in both human and animal models.

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Case Control Study

Association of marital status with takotsubo syndrome (broken heart syndrome) among adults in the United States

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Informed consent statement: Patients were not required to give informed consent to the study

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Abstract

BACKGROUND

The pathophysiology of takotsubo syndrome (TTS) is not well understood, however, it is often precipitated by psychological or physical stress. Marital status is related to emotional stress, but its associations with TTS are limited.

AIM

To explore the potential association between marital status and TTS.

METHODS

We conducted a case-control study using data on patients aged ≥ 40 years with marital status data in the National Hospital Discharge Survey (2006-2010). The International Classification of Diseases Ninth Revision codes were used to identify cases with TTS and other comorbid conditions. Each case was matched to 5 controls by age, sex, year of TTS diagnosis and bed size of hospital. Two sets of controls were selected: Acute myocardial infarction (AMI) controls and non-cardiovascular disease (CVD) controls. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of marital status with TTS.

RESULTS

The 59 patients with TTS who had information on marital status were matched to 295 controls with AMI and 295 non-CVD controls, resulting in a sample of 649

because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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

Data sharing statement: All data are from the National Hospital Discharge Survey and are publicly available through the Centers for Disease Control and Prevention: <https://www.cdc.gov/nchs/nhds/index.htm>.

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patients. The average age of cases was 69.7 ± 11 years with 90% being women and 88% reporting White race. In multivariable-adjusted models, compared to singles, patients who were married had lower odds of TTS (OR = 0.86, 95%CI: 0.79–0.93) while those who were widowed (OR = 1.14, 95%CI: 1.05–1.23) or divorced/separated (OR = 1.32, 95%CI: 1.21–1.45) had elevated odds for TTS when compared to non-CVD controls. Similar results were observed when cases were compared to controls with AMI.

CONCLUSION

In this study, being married was associated with lower odds for TTS while being divorced/separated or widowed was related to elevated odds for TTS. These novel findings that underscore the potential importance of social factors like marital status in the development of TTS need confirmation in larger studies.

Key Words: Stress-induced cardiomyopathy; Takotsubo syndrome; Marital status; Epidemiology; Case-control; Marriage

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Core Tip: Being married was associated with lower odds for takotsubo syndrome (TTS) while being divorced/separated or widowed was related to elevated odds for TTS.

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INTRODUCTION

Takotsubo syndrome (TTS), also known as “broken heart syndrome” is a transient dysfunction of the left ventricle (LV)[1]. Its initial presentations are similar to acute coronary syndrome, and it is characterized by varying combinations of chest pain, ischemic electrocardiographic changes pertaining to ST-segment elevation and/or T-wave inversion, and moderate elevations in cardiac biomarkers such as troponin[2]. Almost 80% of all cases occur in older women[1,3]. In the United States, the incidence of TTS has been increasing over the years. During the period of 2007 to 2012, the incidence of TTS increased by more than 300% from 52 per 1000000 discharges to 178 per 1000000 discharges[4]. Although the pathophysiology is not well understood, it is often precipitated by psychological or physical stress[5], as well as acute neurologic and psychiatric diseases[6].

While the prognosis is favorable with recovery of LV function in some patients, growing evidence suggests that TTS is associated with severe morbidity and mortality [7]. Patients with TTS are at high risk for recurrence after the first events[6]. Emerging evidence suggest that more than half of patients with TTS develop severe complications, and that TTS-related mortality is comparable to those amongst patients with myocardial infarction or acute coronary syndrome[8,9].

Due to the observed stress triggers, it has been suggested that TTS may be related to some social and emotional factors that influence psychological wellbeing. Marital status is related to emotional stress[10]. However, investigations into the relation of marital status with TTS are limited, with most of these being case reports[11,12].

We aimed to explore the association of marital status with TTS in a national sample of hospitalized adults from the United States.

MATERIALS AND METHODS

The National Hospital Discharge Survey (NHDS) which is administered by the National Center for Health Statistics is a continuous survey of inpatient utilization of

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short-stay (< 30 d) hospitals in the United States. The NHDS which was conducted from 1965-2010 used a multistage cluster sampling technique to provide nationally representative data. All procedures were approved by the institutional review board of the National Center for Health Statistics with all patients providing written informed consent for their information to be included in this database. All data from the NHDS are publicly available through the Centers for Disease Control and Prevention: <https://www.cdc.gov/nchs/nhds/index.htm>. Because the NHDS data is deidentified and publicly available, the Texas Tech University Health Sciences Center Institutional Review Board determined that this current study did not require a review.

We conducted a case-control study using discharge records from 2006 to 2010. Patients who were aged ≥ 40 years with no missing data on marital status and did not have a diagnosis of myocarditis or pheochromocytoma were eligible for this study. Marital status information which was obtained from the National Center for Health Statistics was classified as single, married, divorced, separated or widowed. Similar to other reports from national samples[2,4,13], the International Classification of Diseases Ninth Revision codes were used to identify cases with TTS (ICD-9-CM: 429.83) and other comorbid conditions. Acute myocardial infarction (AMI) was identified using ICD-9 codes: 410 while stroke was defined with ICD-9 codes 430 to 438.

Cases were defined as patients with TTS who underwent diagnostic coronary angiography and did not receive any percutaneous coronary interventions or revascularizations. A control was defined as any patient without TTS diagnosis during hospitalization. Each case was matched to 5 controls by age, sex, year of TTS diagnosis and bed size of hospital. Hospital bed size, defined as the number of beds per hospital, was used as a measure of hospital volume. The greedy matching strategy with a fixed number of controls per case was used[14]. Matched controls were selected from among all patients' who met the eligibility criteria listed above. Two sets of controls were selected for each case. Thus, for each case, 5 controls with AMI were selected (considered as AMI controls) and also 5 non-cardiovascular disease (CVD) controls were selected (considered as non-CVD controls). Patients with AMI or stroke were considered eligible for CVD controls.

Means and percentages were used to describe the characteristics of patients. Conditional logistic regression incorporating sampling weights was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of marital status with TTS. Besides the matching variables of age, sex, year of TTS diagnosis and bed size of hospital, adjustments were made for race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes and chronic obstructive pulmonary disease. Additional analyses were performed with further adjustment for neurological and psychiatric disorders. A 2-tailed *p* value less than 0.05 was used to determine statistical significance, and all analyses were performed with SAS version 9.4 (SAS Institute Inc).

RESULTS

The 59 patients with TTS who had information on marital status were matched to 295 controls with AMI and 295 non-CVD controls, resulting in a sample of 649 patients. Characteristics of the 649 participants included in the study are presented in Table 1. The average age of cases was 69.7 ± 11 years with 90% being women and 88% reporting White race. Overall, a greater proportion of participants were from the southern region of the United States with about two-thirds of participants having Medicare as their principal expected source of payment. Approximately 39% of cases were married, 17% were single, and 27% were widowed. There were significant differences in race/ethnicity between cases and AMI controls or non-CVD controls. Although AMI controls and non-CVD controls had higher prevalence of neurologic and psychiatric disorders than patients with TTS, these differences did not meet statistical significance ($P > 0.05$).

A significant association was observed between marital status and TTS (Table 2) in multivariable models. Compared with singles, patients who were married had lower odds for TTS (OR = 0.86, 95%CI: 0.79-0.93) while those who were widowed or divorced/separated had 14% (OR = 1.14, 95%CI: 1.05-1.23) and 32% (OR = 1.32, 95%CI: 1.21-1.45) elevated odds for TTS, respectively, when compared to non-CVD controls. Similar results were observed when cases were compared with controls with AMI. Compared to patients who were currently married, non-married patients (single, widowed or divorced/separated) were at elevated risk for TTS, whether compared to AMI controls (OR = 1.66, 95%CI: 1.58-1.75) or non-CVD controls (OR = 1.40; 95%CI:

Table 1 Characteristics of participants according to case-control status, National Hospital Discharge Survey 2006-2010

Characteristics	Cases (n = 59)	AMI controls (n = 295)	P value ²	Non-CVD controls (n = 295)	P values ³
Age, (mean ± SD, yr) ¹	69.7 (11.4)	(69.8 (11.1)	-	69.7 (11.3)	-
Sex, female ¹	89.8%	89.8%	-	89.8%	-
Race			0.009		0.021
White	88.1%	67.1%		70.5%	
Black	5.1%	16.3%		14.6%	
Other	6.8%	16.6%		14.9%	
Current smoker	15.3%	8.5%	0.104	17.3%	0.701
Type of insurance			0.424		0.537
Medicaid	8.5%	5.8%		5.8%	
Private	22.0%	29.2%		27.8%	
Medicare	69.5%	65.1%		66.4%	
Health condition					
Obese	6.8%	8.8%	0.597	5.1%	0.593
Hypertension	42.4%	50.5%	0.241	52.5%	0.133
Dyslipidemia	20.3%	15.9%	0.404	27.1%	0.272
Diabetes	15.3%	16.3%	0.845	17.6%	0.660
COPD	27.1%	16.3%	0.051	22.0%	0.390
Neurological disorders	6.8%	13.2%	0.178	13.2%	0.173
Psychiatric disorders	3.4%	7.1%	0.295	5.1%	0.577
Marital status			0.375		0.583
Married	39.0%	45.1%		42.7%	
Not married	61.0%	54.9%		57.3 %	

¹These variables are among the characteristics by which cases were matched to controls.

²P values for comparison of characteristics between cases and AMI controls.

³P values for comparison of characteristics between cases and non-CVD controls. AMI: Acute myocardial infarction; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease.

1.34–1.46). These associations remained largely the same when additional adjustments were made for neurological and psychiatric disorders (Table 3).

DISCUSSION

In this case-control study using a nationally representative sample, being married was associated with lower odds for TTS while being divorced/separated or widowed was associated with elevated odds for TTS. These novel findings corroborate previous reports of marriage being related to good cardiovascular health while being single or encountering marital disruptions such as divorce/separation or widowhood is associated with poor overall and cardiovascular health outcomes[10].

To our knowledge, this is the first observational study to evaluate the association of marital status with TTS. Although the relationship of family or social history with TTS have not been extensively investigated, previous case reports and case series have observed TTS among elderly women who were recently widowed[11,12] or had loss of a close family member[15]. Emotional stresses such grief, interpersonal conflicts, fear, panic, anxiety and anger have been frequently observed in women with TTS compared to physical stressful event[16]. Among the few studies on TTS that obtained marital status information, TTS was more common among patients who were not married compared to those who were currently married[3], results that are similar to findings of the current study.

Table 2 Adjusted estimates for the association of marital status with takotsubo syndrome by acute myocardial infarction and non-cardiovascular disease controls, National Hospital Discharge Survey 2006-2010¹

Marital status	Cases (n = 59)	AMI controls (n = 295)	Non-CVD controls (n = 295)	Odds ratios (95%CI) for AMI controls	Odds ratios (95%CI) for non-CVD controls
Single	10	53	40	1	1
Married	23	133	126	0.69 (0.63-0.75)	0.86 (0.79-0.93)
Widowed	16	76	93	1.09 (1.01-1.19)	1.14 (1.05-1.23)
Separated/divorced	10	33	36	1.27 (1.16-1.39)	1.32 (1.21-1.45)
Married	23	133	126	1	1
Not married	36	162	169	1.66 (1.58-1.75)	1.40 (1.34-1.46)

¹Each case was matched to five controls based on age, sex, year of takotsubo cardiomyopathy diagnosis and bed size of hospital. Adjusted for age, sex, year of TTS diagnosis, bed size of hospital, race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes and chronic obstructive pulmonary disease. AMI: Acute myocardial infarction; CI: Confidence interval; CVD: Cardiovascular disease.

Table 3 Estimates from fully adjusted models for the association of marital status with takotsubo syndrome by acute myocardial infarction and non-cardiovascular disease controls, National Hospital Discharge Survey 2006-2010¹

Marital status	Cases (n = 59)	AMI controls (n = 295)	Non-CVD controls (n = 295)	Odds ratios (95%CI) for AMI controls	Odds ratios (95%CI) for non-CVD controls
Single	10	53	40	1	1
Married	23	133	126	0.62 (0.57-0.68)	0.86 (0.79-0.93)
Widowed	16	76	93	1.04 (0.96-1.14)	1.19 (1.10-1.28)
Separated/divorced	10	33	36	1.30 (1.18-1.43)	1.36 (1.25-1.49)
Married	23	133	126	1	1
Not married	36	162	169	1.80 (1.71-1.91)	1.44 (1.38-1.51)

¹Each case was matched to five controls based on age, sex, year of takotsubo cardiomyopathy diagnosis and bed size of hospital. Adjusted for age, sex, year of TTS diagnosis, bed size of hospital, race, type of health insurance, smoking status, obesity, hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, neurologic and psychiatric disorders. AMI: Acute myocardial infarction; CI: Confidence interval; CVD: Cardiovascular disease.

There are several plausible explanations for these observations. Marriage offers certain behavioral, social and psychological benefits that may help in the prevention of TTS. Many married couples tend to have better CVD risk profiles namely healthier meals, physical activity, adequate sleep and better financial benefits that often lead to less stress than singles, divorced/separated or widowed persons[10,17]. Married couples often have larger social networks and support, and are known to report greater happiness and life satisfaction as well as higher compliance with medical screenings and uptake of medications[10]. The protective benefits of marriage for TTS and other CVD may also simply reflect the fact that healthy individuals usually select other healthy individuals for marriage[17].

Marital disruptions (*i.e.*, divorce/separation or widowhood) typically have deleterious effects on health. Acute events like widowhood, especially if unexpected, can lead to sudden heightened psychological stress, depression and loss of some social support[10]. Persons in troubled marriages which often end in divorce/separation may also experience these conditions. Some studies have observed high levels of catecholamines especially epinephrine in individuals experiencing marital conflicts [17]. Evidence from animal studies and histologic findings suggest that a surge in circulating epinephrine may induce transient LV dysfunction due to their toxicity on myocardial cells resulting from a rise in cyclic AMP-mediated calcium overload of cardiocytes[12,18]. This calcium overload of cardiocytes triggers the formation of free oxygen radicals, expression of stress response genes, and also the induction of apoptosis in a subset of myocardial cells[12]. However, with the full resumption of LV function weeks after the occurrence of TTS in some patients, it holds to reason that this cascade of molecular activities leading to apoptosis in some cardiomyocytes may not

fully explain the role of catecholamines in the development of TTS[12,19].

Other factors such as neurologic and psychiatric disorders at the time of admission have been reported to be significantly associated with in-hospital complications among patients with TTS[6,20]. Some studies have reported higher prevalence of neurologic and psychiatric disorders in patients with TTS compared to controls; however, results for the association of these disorders with TTS have been mixed[21]. In the current study, there was no significant difference between patients with TTS and AMI controls or non-CVD controls, and additional adjustment for neurologic and psychiatric disorders did not appreciably change the reported estimates between marital status and TTS. The discrepancy in findings between the current study and some prior studies may, in part, be explained by differences in sample size and study designs. Patients with TTS often have recurrent events, with the risk of reoccurrence being higher among patients with pre-admission psychiatric disorders[22]. With about 39% of patients with TTS reporting a neurological disease and 50% of patients with TTS reporting at least one mental disorder about 17.5 mo from their index event[23], future studies are warranted to investigate the potential role of therapeutics in preventing the incidence or reoccurrence of TTS in patients with neurologic and psychiatric disorders.

A strength of this study is the usage of a population representative sample that enhance the generalizability of the findings. Limitations of this study include the small sample of TTS cases due to exclusion of patients without data on marital status, and the inability to study the quality of marriage or sex differences on the relation of marital status with TTS. Also, data on the severity of the acute disease between cases and controls were not available. Finally, ICD codes which are susceptible to error during the coding process were used to identify diseases and comorbid conditions. However, the use of ICD codes is the standard procedure for identifying TTS cases in national samples from the United States[2,4,13]. For TTS, information for confirming the diagnosis such as cardiac enzymes as well as echocardiographic or electrocardiographic readings were not available. Therefore, patients with conditions like coronary spastic angina could not be excluded. Finally, even though we controlled for several potential confounders, the possibility of residual confounding influencing these results cannot be entirely ruled out.

CONCLUSION

In conclusion, these novel findings show that being married is associated with lower odds for TTS, whereas the occurrence of divorce/separation, or widowhood is associated with higher odds of TTS. These results have substantial clinical and public health importance. Given that growing evidence suggests that TTS is associated with severe morbidity and mortality[7], understanding the specific pathophysiologic pathways that may be involved in the association of social stress factors and TTS holds promise in providing avenues to prevent this disease. Therefore, confirmation of these observed associations from prospective studies are warranted to better understand the relation of marital status with TTS and elucidate specific pathophysiologic pathways that are involved in the association between marital status and TTS.

ARTICLE HIGHLIGHTS

Research background

The incidence of takotsubo syndrome (TTS) is increasing in the United States. However, the pathophysiology of TTS is not well understood, although, it is often precipitated by psychological or physical stress.

Research motivation

Marital status is related to emotional stress. However, not many studies have been conducted to evaluate the association of family relationships or social history with TTS.

Research objectives

The objective of this study was to evaluate the association of marital status namely being single, married, widowed or divorced/separated with TTS in an elderly population.

Research methods

A case-control study was performed using data on 649 patients from the United States National Hospital Discharge Survey.

Research results

Findings from this study showed that being married was associated with lower odds for TTS while being divorced/separated or widowed was associated with elevated odds for TTS.

Research conclusions

With marital status associated with TTS, understanding the underlying mechanisms for this association is of substantial clinical and public health importance.

Research perspectives

Confirmation of these observed associations from prospective studies are warranted to better understand the relation of marital status with TTS.

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Clinical Trials Study

Nutritional supplement drink reduces inflammation and postoperative depression in patients after off-pump coronary artery bypass surgery

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Abstract

BACKGROUND

Coronary artery bypass grafting is a surgical treatment for ischemic heart disease. Although development in surgical technique and improvement of perioperative management reduced the postoperative complications, some patients still delayed in progress of postoperative rehabilitation. In this study, we aimed to investigate the effect of daily intake of an herbal medicine-containing drink for rehabilitation after surgery in patients with ischemic heart disease.

AIM

To investigate the effect of taking an herbal medicine-containing, commercially available drink for postoperative rehabilitation in those patients.

METHODS

Patients who underwent isolated off-pump coronary artery bypass (OPCAB) surgery were divided into two groups depend on the timing of the admission to the hospital: the Yunker (YKR) group, that consumed one bottle of a caffeine-free nutritional supplement drink on a daily basis and the control group (CTL) that

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Sato Pharmaceutical Co., Ltd supported this study by providing the nutritional supplement drink (Yunker DCF®) and by defraying the fee for cytokine level measurement.

Data sharing statement: No additional data are available.

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

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underwent regular rehabilitation.

RESULTS

A total of 229 patients (CTL = 130, YKR = 99) were enrolled. No significant differences were observed in the baseline characteristics between the two groups. The YKR group had a significantly increased number of daily steps postoperatively ($P < 0.05$) and had significantly lower postoperative serum tumor necrosis factor- α levels ($P < 0.01$), while no significant differences were observed in the levels of other inflammatory or stress-related cytokines (interleukin-6, adiponectin, superoxide dismutase, and urine 8-hydroxy-2'-deoxyguanosine) between the two groups. Also, the YKR group showed a significant improvement in the Hospital Anxiety and Depression Score ($P < 0.05$). Moreover, there were no differences in postoperative complications and the duration of postoperative hospital stay between the two groups.

CONCLUSION

Our results demonstrated that the daily intake of an herbal medicine-containing drink after OPCAB surgery may have beneficial effects on cardiac rehabilitation by reducing inflammation markers and depression.

Key Words: Herbal medicine; Inflammation; Cardiac rehabilitation; Moderate-to-vigorous intensity physical activity; Off-pump coronary artery bypass

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Core Tip: Ischemic heart disease is still a major cause of death in the developed country. Cardiac rehabilitation for the patients who underwent coronary artery bypass grafting surgery has known to be associated with early recover. Daily intake of an herbal medicine-containing drink after the surgery enhances the postoperative cardiac rehabilitation by reducing inflammation and improving depression.

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INTRODUCTION

Ischemic heart disease is still a major cause of death in the developed country. Coronary artery bypass grafting (CABG) is a surgical treatment for ischemic heart disease. Although postoperative complications are reduced with the technical development of the surgery, such as the off-pump technique[1,2], or with the improvement of perioperative management, variable amounts of physical and mental stress still occur after surgery. Postoperative rehabilitation following cardiac surgery is highly recommended since it increases motion tolerability[3,4], improves cardiac function[5,6], and reduces postoperative depression[7,8]. The recent guideline recommended the early induction of postoperative rehabilitation for the prevention of perioperative heart or respiratory failure, resulting in short hospital stay and early social recovery[9]. Despite the abovementioned recommendation, patients with low cardiac function, high age, frail, or complicated conditions often show delay. With the recent increase in the elderly population, the number of octogenarians who underwent CABG has also increased. These patients are potentially frail and exhibit systemic deterioration.

Consuming a commercially available nutritional supplement “energy” drink when a person experiences fatigue or develops illnesses such a cold is a widely accepted practice in the Japanese society. Some people habitually consume this type of drink as a treatment for chronic fatigue or to maintain motivation. Various kinds of nutritional supplement drinks are commercially available in Japan. Although, many of these

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products commonly contain multiple vitamins, caffeine, and sugar, only few contain herbal products, of which some have been known to reduce the physical and mental stresses. In this study, we aimed to investigate the effect of taking an herbal medicine-containing drink for postoperative rehabilitation in patients with ischemic heart disease.

MATERIALS AND METHODS

Design and participants

Adult patients (≥ 20 years of age) who were scheduled for elective isolated off-pump coronary artery bypass (OPCAB) surgery at Juntendo University Hospital were enrolled consecutively in the study from January 2014 to December 2017. The patients were assigned to one of two groups as follows: Those enrolled from January to June 2014 and September 2016 to December 2017 were assigned to the control group (CTL), and those enrolled from June 2014 to September 2016 were assigned to the treatment group. Patients in the treatment group consumed 30-mL of a caffeine-free, herbal nutritional supplement from a commercially available bottle, (Yunker DCF, Sato Pharmacy. Co. Ltd, Tokyo, Japan) every day after being granted permission to resume a liquid diet following surgery (YKR group). Patients with liver dysfunction (defined by tests exceeding the normal value in any of the following markers at the time of administration: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, or γ -glutamyl transpeptidase), who underwent hemodialysis due to kidney dysfunction, or who experienced preoperative gait disturbance were excluded from the study. The contents of the drink are shown in Table 1. Patients in the CTL underwent the regular post-cardiac surgery course and did not consume the supplement drink. Both groups were treated according to our post-CABG clinical path. In addition, patients who received concomitant surgery due to the surgeon's decision during surgery and those who experienced stroke (including transient ischemic attack) or infections such as pneumonia postoperatively were excluded from the study.

Activity measurements

The primary endpoint of the study was whether the YKR enhanced the activity postoperatively. To evaluate perioperative activity, we used an accelerometer (Omron HJA-350IT, Kyoto, Japan). As indices of the activity, the number of daily steps, daily total activity [metabolic equivalent (MET) \times hour], and moderate-to-vigorous intensity physical activity (MVPA) were used. Total activity was determined by calculating the integrated METs per minute for 1 h (60 min), while MVPA was calculated using more than three METs of total activity.

The maximum value in each period (pre-/postoperative) was compared between the two groups. If preoperative or postoperative data were lacking, they were excluded from the activity analysis.

Laboratory measurements

Results of blood tests performed upon admission and on the 2nd and 7th postoperative day (2 POD and 7 POD, respectively) were used in this study. In addition, the levels of the following inflammatory cytokines were measured in serum and urine (SRL, Inc., Tokyo, Japan) and compared between the two groups: interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), adiponectin, superoxide dismutase (SOD), and the ratio of urine 8-hydroxy-2'-deoxyguanosine and creatinine (8-OHdG/Cr).

Anxiety and depression scores

Before and on 7 POD, the levels of depression and anxiety were assessed. We used the Hospital Anxiety and Depression Scale (HADS) and Geriatric Depression Scale-15 (GDS). The HADS has two subscales: HADS_A, used to measure the level of anxiety; and HADS_D, used to measure the degree of depression. Each value and changes in intra-patient values were compared between the groups.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of data distribution, and further statistical analyses were subsequently performed. Patients' baseline data were compared using the chi-square test and Student's *t*-test. In the development data set, we formulated a predictive equation based on sex, age, body mass index, ischemic heart disease, treatment with cardiopulmonary bypass, hypertension, diabetes

Table 1 Contents of the nutritional supplement drink (per 120 mL)

Contents	
Agkistrodon meat and bones tincture	100 mg
Civet tincture	250 mg
Ginseng fluid extract	600 mg
Hawthorn flower extract	30 mg
Rehmannia root extract	120 mg
Royal jelly	100 mg
Vitamin B1 nitrate	10 mg
Vitamin B2 phosphate ester	5 mg
Vitamin B6	10 mg
Tocopherol acetate	10 mg
Nicotinamide	25 mg
Panthenol	10 mg
Chondroitin sulfate sodium	120 mg

mellitus, dyslipidemia, preoperative hemodialysis, smoking (present/history), persistent atrial fibrillation (AF), serum brain natriuretic peptide level, New York Heart Association classification, left atrial diameter, and left ventricular ejection fraction. Multicollinearity among the variables in the predictive equation was considered. Data were analyzed using SPSS 22.0 (SPSS, Tokyo, Japan). All data are expressed as mean \pm SE. Statistical significance was set at a level of $P < 0.05$. The statistical methods of this study were reviewed by an expert Biostatistician Dr. Minematsu K.

RESULTS

Characteristic of the patients

Altogether, 280 patients were eligible to enroll in this study (Figure 1). Fifteen patients did not consent for enrollment and 10 were excluded preoperatively because of liver dysfunction. Thirteen patients who were initially eligible did not undergo isolated OPCAB surgery due to their physician's decision, one withdrew from the study, and four other patients were excluded because they developed hemiplegia of the right hand, postoperative pneumonia, pneumothorax, or a drug allergy. Furthermore, eight patients were excluded for missing data. In total, 229 patients were analyzed; 130 were in the CTL group and 99 were in the YKR group. The characteristics of the patients are shown in Table 2. There were no differences in these indices between the two groups.

Activity

Figure 2 shows the number of preoperative and postoperative steps, activity, and MVPA, which were recorded using an accelerometer, in each group. The mean number of postoperative steps (Figure 2A) was increased in both groups, but only the increase in the YKR group was significant (preoperative *vs* postoperative: CTL, 2301 \pm 253 steps *vs* 2787 \pm 257 steps, $P = 0.096$; YKR: 2223 \pm 225 steps *vs* 2943 \pm 272 steps, $P < 0.05$).

The total activity (Figure 2B) significantly increased both in the CTL and YKR groups postoperatively (preoperative *vs* postoperative: CTL, 45.6 \pm 1.9 METs-h *vs* 55.1 \pm 2.8 METs-h, $P < 0.01$; YKR, 44.8 \pm 2.6 METs-h *vs* 56.6 \pm 3.4 METs-h, $P < 0.01$). The postoperative MVPA, an integrated activity of >3 METs, showed a nonsignificant decreasing trend in both groups (Figure 2C; preoperative *vs* postoperative: CTL, 0.76 METs-h *vs* 0.61 METs-h, $P = 0.275$; YKR, 0.83 METs-h *vs* 0.79 METs-h, $P = 0.749$). Despite the decreasing trend of the MVPA, the ratio of the MVPA to the total activity in the individual patients (Figure 2D) increased postoperatively in the YKR group. By contrast, it decreased in the CTL group, although no significant differences were found in the two groups (CTL, 0.084% \pm 0.014% *vs* 0.055% \pm 0.010%, $P < 0.094$; YKR, 0.081% \pm

Table 2 Patient characteristics

	CTL	YKR	P value
Number of patients	130	99	
Age, yr	69.4 ± 0.8	68.5 ± 1.0	0.437
Female (%)	20 (15.4)	12 (12.1)	0.481
BMI	24.5 ± 0.3	24.7 ± 0.3	0.644
Hypertension (%)	90 (69.2)	74 (74.7)	0.360
Diabetes mellitus (%)	70 (53.8)	49 (49.5)	0.407
Dyslipidemia (%)	94 (72.3)	75 (75.8)	0.791
Smoking history (%)	78 (60.0)	59 (59.6)	0.950
Preoperative AF (%)	4 (3.1)	1 (1.0)	0.261
NYHA	1.6 ± 0.1	1.7 ± 0.1	0.725
LAD, mm	37.3 ± 0.4	37.9 ± 0.5	0.316
LVDd, mm	47.8 ± 0.5	49.1 ± 0.7	0.131
LVDs, mm	32.0 ± 0.6	32.7 ± 0.8	0.537
IVST, mm	9.7 ± 0.1	9.9 ± 0.1	0.266
PWT, mm	9.8 ± 0.1	10.0 ± 0.1	0.195
LVEF, %	61.0 ± 0.8	60.0 ± 1.4	0.540
Operation time, min	253.6 ± 5.7	248.4 ± 6.8	0.555
Intubation time, h	6.7 ± 0.7	5.6 ± 0.4	0.176
Number of distal anastomosis	3.2 ± 0.1	3.2 ± 0.1	0.964
Right gastroepiploic artery graft (%)	66 (50.8)	52 (52.5)	0.793
Saphenous vein graft (%)	47 (36.2)	32 (32.3)	0.470
Blood transfusion (%)	23 (17.7)	19 (19.2)	0.662
Postoperative AF (%)	31 (23.8)	24 (24.2)	0.936
ICU stay, d	1.2 ± 0.0	1.2 ± 0.0	0.895
Hospital stay, d	10.1 ± 0.3	10.7 ± 0.4	0.187

AF: Atrial fibrillation; BMI: Body mass index; ICU: Intensive care unit; IVST: Interventricular septum thickness; LAD: Left atrium diameter; LVDd: Left ventricular diastolic diameter; LVDs: Left ventricular systolic diameter; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association classification; PWT: Posterior wall thickness; CTL: Control group; YKR: Yunker group.

0.013% *vs* 0.091% ± 0.025%, $P < 0.690$).

Blood and urine test

The results of blood tests performed upon admission and on 2 POD and 7 POD are shown in Table 3. No significant differences were observed in the investigated indices between the groups at any period.

Next, the levels of inflammatory or stress-related cytokines (IL-6, TNF- α , adiponectin, and SOD, Figure 3A-D) and urinary stress hormones (8-OHdG/Cre ratio, Figure 3E) were measured on 2POD and 7POD. IL-6 Level significantly decreased in both groups (CTL: 81.5 ± 4.9 pg/mL to 21.5 ± 2.9 pg/mL, $P < 0.01$; YKR: 75.8 ± 7.2 pg/mL to 17.3 ± 2.7 pg/mL, $P < 0.01$, 2 POD to 7 POD, respectively). In addition, there were no significant differences between the two groups on 2 POD ($P = 0.498$) and on 7 POD ($P = 0.301$). A nonsignificant increasing trend was observed in TNF- α level in the CTL group, while a nonsignificant decreasing trend was observed in the YKR group (CTL: 3.2 ± 0.7 pg/mL to 5.0 ± 1.2 pg/mL, $P = 0.686$; YKR: 3.7 ± 0.9 pg/mL to 1.9 ± 0.2 pg/mL, $P = 0.052$, 2 POD to 7 POD, respectively). Notably, the TNF- α level in the YKR group was significantly lower than that in the CTL group ($P < 0.01$) on 7 POD, although no significant difference was observed on 2 POD ($P = 0.623$). Adiponectin level significantly increased in both groups (CTL: 6.8 ± 0.3 μ g/mL to 8.5 ± 0.4 μ g/mL,

Table 3 Perioperative blood test results

	Group	Pre	P value	2 POD	P value	7 POD	P value	7-2 POD	P value
WBC, $\times 10^9/L$	CTL	6.1 \pm 0.3	0.991	12 \pm 0.3	0.962	7.6 \pm 0.2	0.534	-4.4 \pm 0.2	0.568
	YKR	6.1 \pm 0.2		12 \pm 0.4		7.8 \pm 0.2		-4.2 \pm 0.3	
Hb, g/dL	CTL	13.3 \pm 0.1	0.645	11.2 \pm 0.1	0.876	11.7 \pm 0.1	0.130	0.5 \pm 0.1	0.027 ^a
	YKR	13.4 \pm 0.2		11.3 \pm 0.1		11.5 \pm 0.1		0.2 \pm 0.1	
Hct, %	CTL	39.2 \pm 0.4	0.315	33.3 \pm 0.3	0.854	34.6 \pm 0.3	0.194	1.3 \pm 0.2	0.053
	YKR	39.8 \pm 0.5		33.4 \pm 0.4		34.0 \pm 0.4		0.6 \pm 0.3	
TP, g/dL	CTL	6.8 \pm 0.0	0.616	5.7 \pm 0.0	0.904	6.1 \pm 0.1	0.789	0.4 \pm 0.1	0.684
	YKR	6.8 \pm 0.0		5.7 \pm 0.1		6.2 \pm 0.1		0.5 \pm 0.0	
Alb, g/dL	CTL	4.0 \pm 0.0	0.482	3.5 \pm 0.0	0.337	3.4 \pm 0.0	0.385	-0.1 \pm 0.0	0.821
	YKR	4.0 \pm 0.0		3.5 \pm 0.0		3.3 \pm 0.0		-0.1 \pm 0.0	
ChE, IU/L	CTL	301.7 \pm 6.9	0.953	176.3 \pm 4.0	0.258	183.0 \pm 4.0	0.227	6.7 \pm 2.4	0.934
	YKR	302.3 \pm 7.8		183.3 \pm 4.7		190.5 \pm 4.6		7.0 \pm 2.3	
CK, IU/L	CTL	101.3 \pm 6.9	0.565	482.4 \pm 22.7	0.443	67.8 \pm 5.3	0.736	-391.7 \pm 16.9	0.878
	YKR	95.3 \pm 7.6		458.0 \pm 19.8		70.2 \pm 4.3		-387.8 \pm 18.2	
ALP, IU/L	CTL	217.2 \pm 6.1	0.491	142.7 \pm 3.1	0.734	201.4 \pm 6.0	0.103	58.7 \pm 5.3	0.097
	YKR	210.8 \pm 6.9		141.0 \pm 4.1		222.8 \pm 13.0		81.9 \pm 12.8	
T-Bil, mg/dL	CTL	0.8 \pm 0.1	0.194	1.2 \pm 0.1	0.100	0.9 \pm 0.0	0.580	-0.3 \pm 0.1	0.123
	YKR	0.7 \pm 0.0		1.0 \pm 0.1		0.8 \pm 0.1		-0.2 \pm 0.0	
AST, IU/L	CTL	21.8 \pm 0.7	0.133	28.9 \pm 0.9	0.748	20.1 \pm 0.9	0.245	-8.8 \pm 1.1	0.556
	YKR	23.6 \pm 1.0		29.3 \pm 1.0		21.6 \pm 0.8		-7.9 \pm 1.0	
ALT, IU/L	CTL	21.4 \pm 1.1	0.388	16.4 \pm 1.0	0.543	20.3 \pm 1.2	0.101	3.9 \pm 1.3	0.244
	YKR	23.1 \pm 1.6		17.4 \pm 1.3		23.7 \pm 1.7		6.2 \pm 1.5	
γ GTP, IU/L	CTL	33.1 \pm 2.0	0.352	24.3 \pm 1.3	0.555	38.2 \pm 3.2	0.540	14.0 \pm 2.7	0.489
	YKR	36.0 \pm 2.5		25.5 \pm 1.6		41.4 \pm 3.9		16.9 \pm 3.2	
BUN, mg/dL	CTL	16.8 \pm 0.5	0.814	20.6 \pm 0.5	0.667	17.7 \pm 0.8	0.619	-2.9 \pm 0.7	0.840
	YKR	16.6 \pm 0.6		21.0 \pm 0.7		18.3 \pm 1.0		-2.7 \pm 0.9	
Cre, mg/dL	CTL	0.9 \pm 0.0	0.606	1.0 \pm 0.0	0.954	1.0 \pm 0.1	0.828	0.0 \pm 0.0	0.633
	YKR	0.9 \pm 0.0		1.0 \pm 0.0		0.9 \pm 0.0		0.0 \pm 0.0	
eGFR	CTL	72.1 \pm 1.9	0.219	68.0 \pm 2.2	0.688	68.2 \pm 2.0	0.816	0.2 \pm 1.1	0.726
	YKR	68.7 \pm 2.0		66.7 \pm 2.3		67.5 \pm 2.3		0.8 \pm 1.3	
Na, mmol/L	CTL	140.9 \pm 0.2	0.752	140.9 \pm 0.3	0.269	140.7 \pm 0.2	0.604	-0.2 \pm 0.3	0.101
	YKR	140.8 \pm 0.3		140.4 \pm 0.3		140.9 \pm 0.3		0.5 \pm 0.3	
K, mmol/L	CTL	4.3 \pm 0.0	0.768	4.1 \pm 0.0	0.416	3.9 \pm 0.0	0.792	-0.1 \pm 0.3	0.360
	YKR	4.3 \pm 0.0		4.1 \pm 0.0		3.9 \pm 0.0		0.2 \pm 0.3	
CRP, mg/dL	CTL	0.3 \pm 0.1	0.407	15.7 \pm 4.4	0.176	3.8 \pm 2.4	0.586	-11.9 \pm 4.0	0.233
	YKR	0.4 \pm 0.1		14.9 \pm 4.4		3.7 \pm 1.8		-11.2 \pm 4.1	
BNP, pg/mL	CTL	90.4 \pm 15.8	0.692	346.0 \pm 30.1	0.554	264.0 \pm 23.6	0.881	-72.0 \pm 12.6	0.653
	YKR	99.0 \pm 13.3		321.6 \pm 24.5		258.6 \pm 27.4		-63.0 \pm 15.7	

^a $P < 0.05$. Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; ChE: Cholinesterase; CK: Creatine kinase; Cre: Creatinine; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; γ GTP: Gamma-glutamyl transpeptidase; Hb: Hemoglobin; Hct: Hematocrit; K: Potassium; Na: Sodium; T-Bil: Total bilirubin; TP: Total protein; WBC:

White blood cells; POD: Postoperative day; CTL: Control group; YKR: Yunker group.

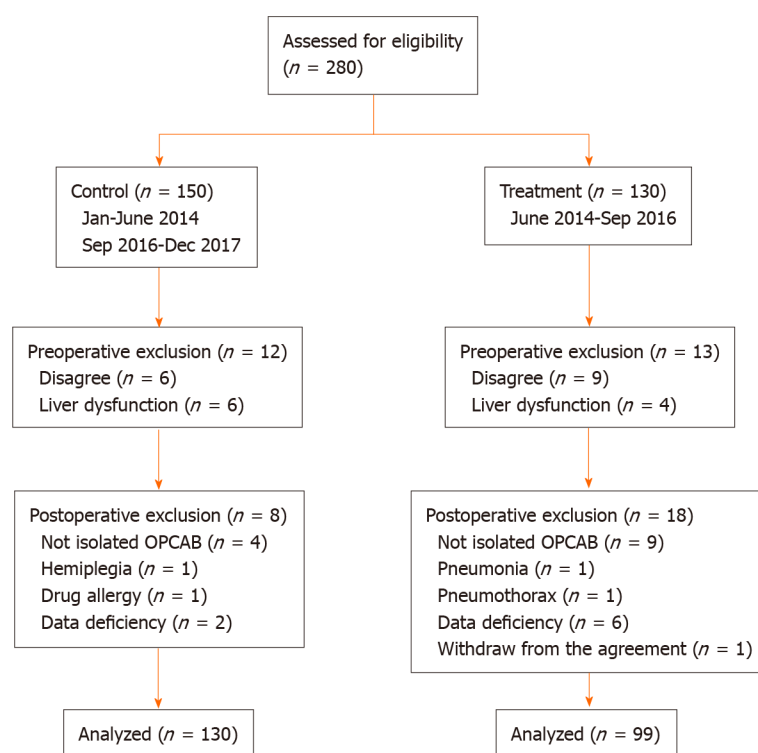


Figure 1 Flow diagram of the study. OPCAB: Off-pump coronary artery bypass.

$P < 0.01$; YKR: $6.0 \pm 0.3 \mu\text{g/mL}$ to $7.4 \pm 0.4 \mu\text{g/mL}$, $P < 0.01$, 2 POD to 7 POD, respectively). In addition, there was no significant difference between the two groups in each time point ($P = 0.085$ at 2 POD, $P = 0.056$ at 7 POD). SOD activity did not change significantly in the CTL and YKR groups (CTL: $3.1 \pm 0.2 \text{ U}$ vs $3.0 \pm 0.2 \text{ U}$, $P = 0.263$; YKR: $2.9 \pm 0.2 \text{ U}$ vs $2.9 \pm 0.2 \text{ U}$, $P = 0.925$, 2 POD to 7 POD, respectively) and neither at each time point between the two groups ($P = 0.392$ at 2 POD; $P = 0.831$ at 7 POD). Urine 8-OHdG/Cr ratio significantly decreased in both groups (CTL: $11.5 \pm 0.8 \text{ ng/mgCr}$ to $9.4 \pm 0.4 \text{ ng/mgCr}$, $P < 0.01$, YKR: $10.4 \pm 0.7 \text{ ng/mgCr}$ to $9.0 \pm 0.4 \text{ ng/mgCr}$, $P < 0.01$, 2 POD to 7 POD, respectively). In addition, there was no significant difference between the two groups at each time point ($P = 0.349$ at 2 POD, $P = 0.986$ at 7 POD).

Depression and anxiety score

To assess anxiety and depression, the HADS and GDS were administered the patients were enrolled (preoperative) and on 7 POD. If the questionnaire was not completed, the sheet was considered as void and the answers were not included in the results. Finally, 144 of 229 (87 from the CTL group and 57 from the YKR group) HADS sheets and 151 of 229 (92 from the CTL group and 60 from the YKR group) GDS sheets were eligible for analyses. The HADS can assess both anxiety and depression. If each score was more than 11 points, the patients was considered “positive” for anxiety and depression. For GDS, a score of > 5 was considered as “positive” for anxiety and depression. The number of patients with positive anxiety and depression is shown in Table 4, while the actual points (Figure 4A-C) and changes in scores (Figure 4D) are shown in Figure 4. HADS_A (anxiety) significantly increased postoperatively in the CTL group (12.6 ± 0.2 points vs 13.4 ± 0.3 points, preoperative vs postoperative, $P < 0.01$). YKR also showed an increasing trend in HADS_A; however, the trend was not statistically significant (12.8 ± 0.3 points vs 13.3 ± 0.3 points, preoperative vs postoperative, $P = 0.078$; Figure 4A). In addition, as shown in Figure 4D, there was no significant difference in perioperative HADS_A between the two groups (0.8 vs 0.5 , CTL vs YKR, respectively, $P = 0.317$).

Table 4 Number of positive patients in the Hospital Anxiety and Depression Scale and Geriatric Depression Scale-15 tests

	Group	Pre (%)	Post (%)	Pre vs post	Improve	Worsen
HADS_A (≥ 11)	CTL	74 (85.1)	82 (94.3)	< 0.05	3 (3.4)	11 (12.6)
	YKR	50 (87.7)	50 (87.7)	1.00	4 (7.0)	4 (7.0)
HADS_D (≥ 11)	CTL	31 (35.6)	43 (49.4)	< 0.05	7 (8.0)	19 (21.8)
	YKR	29 (50.9)	23 (40.4)		14 (24.6)	9 (15.8)
GDS (≥ 5)	CTL	26 (28.3)	25 (27.2)		10 (10.9)	9 (9.8)
	YKR	14 (23.7)	12 (20.3)		6 (10.5)	3 (5.3)

GDS: Geriatric Depression Scale-15; HADS_A: Anxiety scale of Hospital Anxiety and Depression Scale; HADS_D: Depression scale of Hospital Anxiety and Depression Scale; CTL: Control group; YKR: Yunker group.

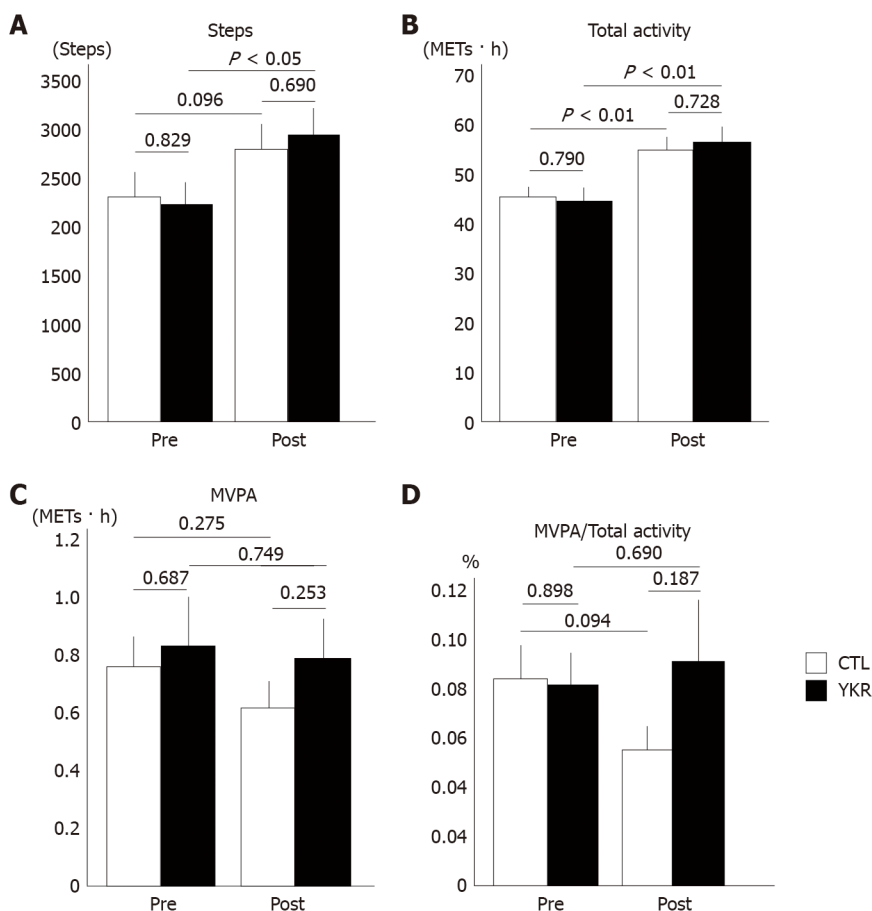


Figure 2 Perioperative activity was assessed using an accelerometer. A: Daily steps increased significantly in Yunker group postoperatively ($P < 0.05$), while control group (CTL) did not reach statistical differences ($P = 0.096$); B: Total activity increased significantly in both groups ($P < 0.01$, respectively); C: Moderate-to-vigorous intensity physical activity (MVPA) tended to decrease in both groups, although there were no significant differences; D: The ratio of the MVPA to the total activity was decreased in the CTL group. By contrast, it increased in the Yunker group, although no statistically significant differences were found in both groups. MET: Metabolic equivalent; MVPA: Moderate-to-vigorous intensity physical activity; CTL: Control group; YKR: Yunker group.

Similarly, HADS_D (depression) significantly increased postoperatively in the CTL group (9.8 ± 0.3 points *vs* 10.3 ± 0.2 points, preoperative *vs* postoperative, $P < 0.05$, Figure 4B). In contrast, HADS_D decreased in the YKR group (10.5 ± 0.3 points *vs* 10.1 ± 0.3 points, preoperative *vs* postoperative, $P = 0.192$), and the change was statistically significant compared with that in the CTL group (Figure 4D, $P = 0.018$).

The GDS score in both groups showed a decreasing trend, although no significant difference was observed between the two groups (CTL: 3.0 ± 0.3 points *vs* 3.0 ± 0.3 points, preoperative *vs* postoperative, $P = 0.849$, YKR: 3.0 ± 0.3 points *vs* 3.0 ± 0.3 points, preoperative *vs* postoperative, $P = 0.327$). In addition, the change in HADS_D

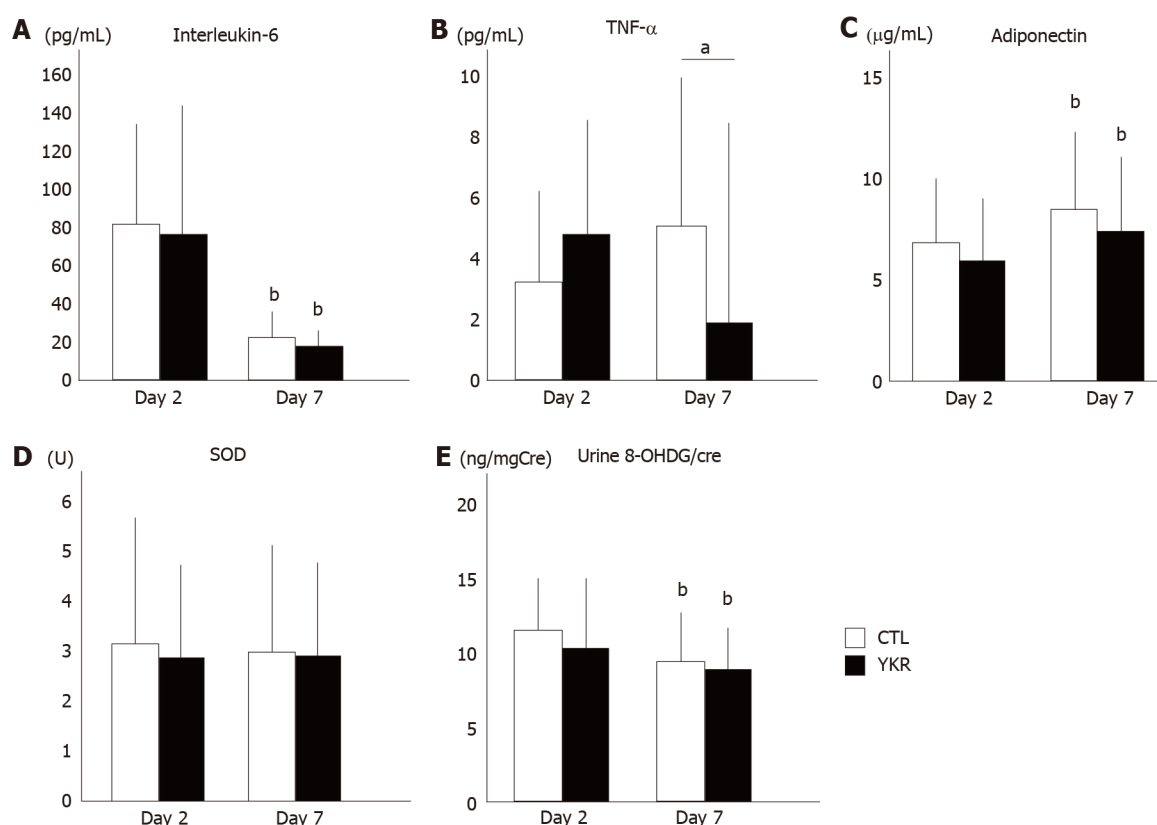


Figure 3 The levels of cytokines in serum and urine are shown. A: Interleukin-6 decreased significantly at 7th postoperative day in both groups ($P < 0.01$), although there were no differences between the two groups; B: Tumor necrosis factor- α level was significantly lower in the Yunker group ($P < 0.05$); C: Adiponectin increased significantly in both groups, while there were no differences between the groups; D: No significant differences were observed in the levels of superoxide dismutase in both groups; E: The ratio of urine 8-hydroxy-2'-deoxyguanosine and creatinine decreased significantly in both groups, while there were no differences between the groups. ^a $P < 0.05$; ^b $P < 0.01$. TNF- α : Tumor necrosis factor- α ; SOD: Superoxide dismutase; 8-OHdG/Cr: 8-Hydroxy-2'-deoxyguanosine and creatinine; CTL: Control group; YKR: Yunker group.

was not statistically different between the two groups ($P = 0.588$), although the YKR group seemed to show a more decreasing trend in score change.

DISCUSSION

In this study, we demonstrated that the daily intake of a nutritional supplement drink postoperatively has positive effects including enhancement of rehabilitation, reduction of inflammation, and improvement of anxiety score in patients who underwent OPCAB surgery.

Anxiety and depression after surgery

Previous studies revealed that 30%-50% of patients who experience coronary artery disease are likely to show depression[10]. In our experiment, 41.7% of the patients experienced depression (HADS_D positive) and 86.1% felt anxious (HADS_A positive) preoperatively. Unexpectedly, the number of patients who expressed anxiety and depression increased after rather than before surgery in the CTL group. As the mean length of postoperative hospital stay was around 10 days, many patients at 7 POD might feel anxiety concerning their lives after returning to home in a few days. By contrast, the number of patients who experienced depression (HADS_D) decreased in the YKR group, which suggests that consuming the drink may alleviate depressive moods. In fact, some of the contents of the drink (Table 1) are reported to improve stress and depression. Crude medicines, such as the extract from Ginseng roots or leaves, Rehmannia root, or royal jelly, have been widely used as herbal medications, especially in East Asian countries. Although the mechanism of the effect has not been fully elucidated, it has been demonstrated that the administration of ginseng saponin (ginsenoside Rb1) reduced stress and anxiety in both animal[11] and human models after a few days[12]. Catalpol, a major compound found in Rehmannia roots, showed

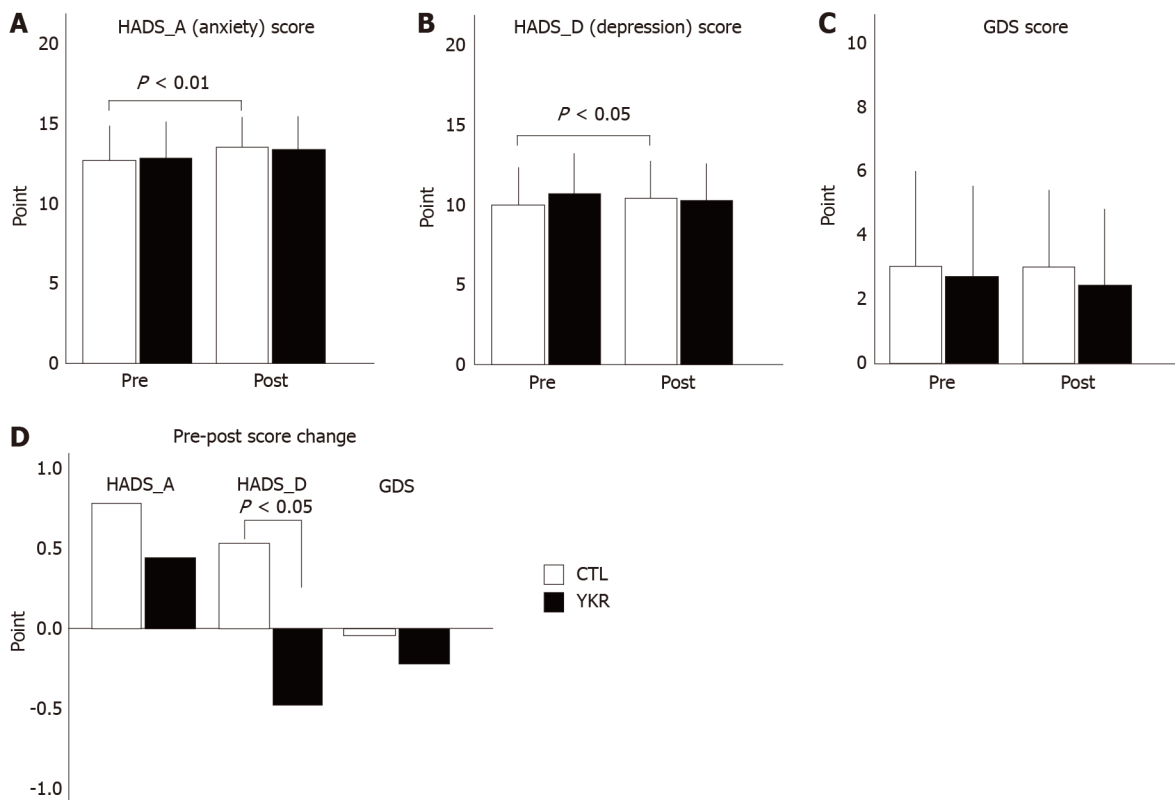


Figure 4 Perioperative anxiety and depression levels were assessed using the Hospital Anxiety and Depression Scale and Geriatric Depression Scale-15. A and B: The control group showed significant increase in anxiety scale of Hospital Anxiety and Depression Scale (A) and depression scale of Hospital Anxiety and Depression Scale (B) postoperatively ($P < 0.01$ and $P < 0.05$, respectively), while Yunker (YKR) group showed no statistical differences; C: Geriatric Depression Scale-15 showed no significant differences between the groups; D: While comparing the changes in the scores pre- and postoperatively, the HADS_D score was significantly decreased in the YKR group ($P < 0.05$). HADS_A: Anxiety scale of Hospital Anxiety and Depression Scale; HADS_D: Depression scale of Hospital Anxiety and Depression Scale; GDS: Geriatric Depression Scale-15; CTL: Control group; YKR: Yunker group.

antidepressant properties in rat models[13]. In addition, consuming Melbrosia, a mixture of royal jelly and bee pollen, improved depression and irritability scores in postmenopausal women[14]. These findings suggest that consuming these contents can improve the anxiety score, although it was difficult to specify which content was effective or if ingestion of multiple contents may enhance the effect. In addition, another study reported that women were more likely experience depression; however, our analysis did not show sex differences in preoperative depression or anxiety as well as in score change (data not shown).

Activity

We evaluated the patients' level of physical activity using an accelerometer. The device used in this study can measure both the number of steps and activity. Recently, MVPA ($3 > \text{METs} \times \text{hour}$) has been shown to be important[15-17].

In this study, the number of steps was significantly increased postoperatively in the YKR group, but no significant differences were found between the groups preoperatively and postoperatively. In addition, the postoperative total activity increased in both groups. By contrast, the MVPA decreased in the postoperative period in both groups, indicating that vigorous movement was limited postoperatively owing to the presence of pain, intravenous catheters, or drains. However, the ratio of the MVPA to the total activity was increased in the YKR group, despite that it was decreased in the CTL group, indicating that the YKR group had more vigorous and quantitative movements than the CTL group. These results indicate that the YKR group can perform more favorable postoperative rehabilitation.

Inflammation

Inflammation plays an important role in maintaining homeostasis against injury, which can be due to surgical stress. Especially for cardiac surgery, extracorporeal perfusion is one of the important factors that can enhance inflammation due to exposure to artificial materials and non-physiological blood flow to the organs.

Excessive activation and prolongation of inflammation may cause organ dysfunction. The expression of inflammatory cytokines, such as TNF- α and IL-6, is associated with postoperative complications[18,19]. Although the reports were controversial, the off-pump technique attenuates increase in inflammatory cytokine levels, such as TNF- α , IL-6, and IL-8[19-24], which may decrease the risk of renal dysfunction or surgical complications[25-28]. The levels of these inflammatory cytokines peaked during or within 48 h postoperatively in patients who underwent OPCAB, with an IL-6 Level of 35-400 pg/mL[25,26] and TNF- α level of 4-25 pg/mL[20,23,29].

In this study, we recruited patients who underwent OPCAB surgery, which was our standard procedure for isolated CABG cases (97.9% in last five years). We measured the cytokine levels on 2POD and 7POD; the average IL-6 level was 80 pg/mL, while the average TNF- α level was < 5 pg/mL. Compared with results of previous studies, our results exceeded the peak value. Under these conditions, the levels of one of the inflammatory markers, TNF- α , was significantly reduced in the YKR group (2 POD *vs* 7 POD), while they remained high in the CTL group. Some herbal medicines, contained in the drink, such as ginseng, Jiou, and royal jelly, have been reported to reduce the inflammation[12,30]. This result indicates that YKR prevents the prolongation of inflammation, although the level of other cytokines did not reach significance.

One of the most common complications after cardiac surgery is AF, which occurs in 20%-40% of patients postoperatively. The occurrence of AF has been shown to be associated with inflammation. In this study, despite the reduction in inflammation after consuming the supplement drink, no differences were observed in the occurrence of postoperative AF between the two groups. In addition, no differences were observed in the length of hospital stay and other postoperative complications. Importantly, results of perioperative blood tests suggest that the drink had no harmful effects on the kidney, liver, or other organs. In addition, a caffeine-free drink was used in this study since caffeine enhances sympathetic activity, which may increase the risk of arrhythmia.

Limitation

This study has some limitations. First, the drink contains several crude medications; hence, it is difficult to detect which contents contributed to the effect. Furthermore, since no placebo group was included in this study, it was unclear whether the behavior of "consuming a special drink" affected the results. Second, although the characteristics of the patients were not different between the groups, the social backgrounds of the patients varied. This difference may have an effect on a patient's level of anxiety or may motivate them to discharge early from the hospital. Third, we did not assess the seasonal effect of taking these medications in these patients. Last, we did not assess the long-term effect of the medications in the patients.

CONCLUSION

We demonstrated that consuming commercially available nutritional supplement drinks after OPCAB surgery reduced inflammation and mental deterioration. This may be associated with enhancement of postoperative rehabilitation as well as improvement of outcome and postoperative quality of life. Consuming the drink may be a novel option as a supplemental medication for high-risk patients.

ARTICLE HIGHLIGHTS

Research background

Some patients who underwent coronary artery bypass graft surgery still suffered from depression and prolongation of hospital stay after surgery, although postoperative complications are reduced with the technical development such as the off-pump technique. Recently, patients with low cardiac function, high age, frail, or complicated conditions who often delayed postoperative rehabilitation are increased. These patients are potentially frail and exhibit systemic deterioration.

Research motivation

Consuming nutritional supplement drink when a person experiences fatigue or develops illnesses such a cold is a widely accepted practice in our society. Various

kinds of nutritional supplement drinks are commercially available in Japan. These drink should be safe and useful for these patients after surgery.

Research objectives

We aimed to investigate the effect of taking an herbal medicine-containing, commercially available drink for postoperative rehabilitation in those patients.

Research methods

Patients who underwent isolated off-pump coronary artery bypass (OPCAB) surgery were divided into two groups: (a) consumed one bottle of a caffeine-free nutritional supplement drink on a daily basis (YKR group), and (b) underwent regular rehabilitation (CTL group).

Research results

Although there were no differences in postoperative complications and the duration of postoperative hospital stay between the two groups, the YKR group had a significantly increased number of daily steps postoperatively ($P < 0.05$) and had significantly lower postoperative serum tumor necrosis factor- α levels ($P < 0.01$), while no significant differences were observed in the levels of other inflammatory or stress-related cytokines (interleukin-6, adiponectin, superoxide dismutase, and urine 8-hydroxy-2'-deoxyguanosine) between the two groups. Also, the YKR group showed a significant improvement in the Hospital Anxiety and Depression Score ($P < 0.05$).

Research conclusions

The daily intake of an herbal medicine-containing drink after OPCAB surgery may have beneficial effects on cardiac rehabilitation by reducing inflammation markers and depression.

Research perspectives

The drink contains herbal medicine, vitamin and other materials. We should investigate what contain works the most effectively.

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Observational Study

Role of coronary angiogram before transcatheter aortic valve implantation

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Author contributions: Alkhalil M was conceptualized; Mohammed A, Das R, Edwards R, Zaman A, and Alkhalil M were investigated; Beska B, Manoharan D, and Alkhalil M are responsible for the methodology and project management; Alkhalil M carried out data processing and software formal analysis; Beska B, Manoharan D, Mohammed A, Das R, Edwards R, Zaman A, and Alkhalil M are responsible for the resources; Beska B and Alkhalil M were responsible for the preparation of the first draft; all authors have written reviews and edited.

Institutional review board statement: The current analysis was based on a clinical audit on the work up of transcatheter aortic valve implantation with focus on invasive coronary angiography. Ethical review was waived as part of the audit process and all

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Abstract

BACKGROUND

Coexistent coronary artery disease is commonly seen in patients undergoing transcatheter aortic valve implantation (TAVI). Previous studies showed that pre-TAVI coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA).

AIM

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

METHODS

This was a retrospective non-randomised single-centre analysis of consecutive patients undergoing TAVI. A selective approach for performing CA tailored to patient clinical need was developed. Clinical outcomes were compared based on whether patients underwent CA. The primary endpoint was a composite of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure.

RESULTS

Of 348 patients (average age 81 ± 7 and 57% male) were included with a median follow up of 19 (9-31) mo. One hundred and fifty-four (44%) patients, underwent CA before TAVI procedure. Patients who underwent CA were more likely to have previous myocardial infarction (MI) and previous percutaneous revascularisation. The primary endpoint was comparable between the two group (22.6% vs 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and MI ($P = 0.007$). In those who underwent CA, the presence of flow

collected data were anonymised during the analysis

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limiting lesions did not affect the incidence of primary endpoint, or its components, except for increased rate of repeat CA.

CONCLUSION

Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials

Key Words: Transcatheter aortic valve implantation; Angiogram; Revascularisation; Coronary angiogram

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Core Tip: Previous studies showed that pre-transcatheter aortic valve implantation coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA). A selective approach for performing CA tailored to patient clinical need was developed. In 348 patients, the primary endpoint of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure was comparable between patients who underwent CA vs no CA (22.6% vs 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and myocardial infarction ($P = 0.007$). The clinical value of routine CA should be challenged in future randomised trials.

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INTRODUCTION

Aortic stenosis is the most common valve disease requiring intervention in Europe and North America and is largely a disease of older adults[1]. Transcatheter aortic valve implantation (TAVI) is now a standard treatment option for management of severe aortic stenosis[1,2]. Given the ageing population and increasing prevalence of disease, the volume of patients requiring valve intervention is likely to increase. Moreover, a paradigm shift towards the use of TAVI in lower-risk patients is becoming more evident[3,4].

Coexistent coronary artery disease (CAD) is commonly seen in those with severe aortic stenosis, with shared traditional cardiovascular risk factors[5,6]. Whether revascularisation for bystander coronary artery disease pre-TAVI can improve procedural and long-term outcomes remains a matter of debate. Current guidelines recommend routine coronary angiography and revascularisation of proximal lesions with $\geq 70\%$ stenosis prior to TAVI[1,2]. These recommendations are largely extrapolated from data in patients who underwent surgical aortic valve replacement[7-9]. Nonetheless, previous meta-analyses highlighted that pre-TAVI revascularisation was not associated with improved one-year mortality, and demonstrated increased 30-d major vascular complications and mortality[10,11]. Similarly, there was no significant difference between TAVI plus revascularisation versus TAVI alone in terms of 30-d mortality or morbidity with similar resolution of symptoms between the groups[12].

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram (CA) before TAVI procedure. However, there has not been any previous report on the safety of such approach or an attempt to identify a group of patients who may benefit from coronary angiography before TAVI. We report a single-centre experience using a selective approach to coronary angiography in patients with severe aortic stenosis referred for TAVI.

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MATERIALS AND METHODS

Study population

This was a retrospective observational analysis of consecutive patients undergoing TAVI at the Freeman Hospital in Newcastle-upon-Tyne over 4 years. Patients with inaccessible electronic follow-up were excluded. The TAVI programme is a regional service and ascertaining clinical follow up was an essential criterion to be included in this study.

The TAVI procedure and valve choice was left to the operators' discretion. Clinical, echocardiographic and procedural characteristics were prospectively entered into a dedicated TAVR database which was retrospectively interrogated. All patients had an echocardiogram and computed tomography (CT) prior to TAVI procedure.

Angiographic prior to TAVI

A selective approach to perform CA was developed during the study period. This was tailored to patient's clinical status and invasive angiogram was performed if: (1) Patient reported typical exertional chest pain which was relieved at rest and was suggestive of angina; (2) Impaired left ventricle systolic function (ejection fraction $\leq 50\%$), particularly if there were regional wall motion abnormalities; or (3) Extensive calcifications ($> 70\%$ of lumen diameter stenosis) involving the proximal segments of left or right coronary arteries detected on CT as part of TAVI work up.

Coronary revascularisation was recommended prior to TAVI, if patients had angiographically flow limiting lesions.

Study endpoints and follow up

The primary endpoint was a combination of all-cause mortality, myocardial infarction (MI), repeat CA, and re-admission to hospital with heart failure. Secondary endpoints included the individual or combination of two components of the primary endpoint. Procedural MI was excluded, and only spontaneous MI was included. Repeat CA after TAVI was indicated in the presence of symptoms, signs of ischaemia, or elevated cardiac biomarkers. Flow limiting lesion was defined as degree of stenosis $\geq 70\%$ on epicardial coronary artery of ≥ 2.5 mm in size.

Mortality data were provided by the Office of National Statistics. Other clinical endpoints were retrieved using dedicated electronic databases for clinical follow up. MI events were cross-checked by evaluating troponin measurements and referral letter for invasive CA. Heart failure readmissions were similarly assessed using reported chest X-ray.

Statistical analysis

Data were assessed for normality of distribution using the Shapiro-Wilk test. Normally distributed data were expressed as mean \pm SD or as median accompanied by inter-quartile range for non-parametric data. Continuous variables were compared by using unpaired T test or Mann-Witney U test as appropriate, while frequencies comparisons were made using Chi square test or Fisher's exact test, as appropriate. Kaplan-Meier methodology and the associated log-rank test were performed to determine the differences in the primary endpoint. All statistical analysis was performed using SPSS 26.0 (SPSS, Inc Chicago, IL, United States) and a $P < 0.05$ was considered statistically significant.

RESULTS

Of 480 patients undergoing TAVI, 348 (73%) patients with accessible electronic records were included in this analysis. Patients were followed for a median of 19 (9-31) mo.

The average age was 81 ± 7 and 57% of patients were male. Two-thirds of patients were markedly symptomatic with NYHA class III/IV. 295 (85%) patients received balloon expanding valve and 34 (10%) had self-expanding valves. Less than half of the cohort, 154 (44%) patients, underwent coronary angiography before TAVI procedure. Almost three-quarters of patients had their TAVI procedure in an elective setting. There were no differences between patients who did or did not undergo CA in terms of age, gender, cardiovascular risk, body mass index, kidney function, or other vascular disease. Baseline clinical characteristics stratified according to CA pre-TAVI are presented in Table 1. Patients who underwent CA were more likely to have previous MI (14% *vs* 8%, $P = 0.07$), and previous percutaneous coronary intervention

Table 1 Baseline clinical characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Age (mean ± SD)	81 ± 7	82 ± 7	81 ± 7	NS
Male gender, n (%)	197 (57)	109 (56)	88 (57)	NS
Obesity, n (%)	83 (34)	43 (31)	40 (37)	NS
Hypertension, n (%)	136 (55)	79 (57)	57 (53)	NS
NYHA III/IV, n (%)	232 (67)	127 (66)	105 (68)	NS
Diabetes, n (%)	68 (20)	39 (20)	29 (19)	NS
Smoking history, n (%)	166 (48)	94 (49)	72 (47)	NS
Previous MI, n (%)	38 (11)	16 (8)	22 (14)	NS
Previous PCI, n (%)	52 (15)	20 (10)	32 (21)	< 0.01
Previous CABG, n (%)	43 (12)	33 (17)	10 (7)	< 0.01
COPD, n (%)	58 (17)	34 (18)	24 (16)	NS
CVA/TIA, n (%)	29 (8)	14 (7)	15 (10)	NS
AF, n (%)	83 (24)	47 (24)	36 (23)	NS
PVD, n (%)	55 (16)	24 (12)	31 (20)	< 0.05
Creatinine (mean ± SD)	112 ± 97	114 ± 117	110 ± 65	NS
Elective admission, n (%)	271 (78)	149 (77)	122 (79)	NS

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular event; TIA: Transient ischaemic attack; AF: Atrial fibrillation; PVD: Peripheral vascular disease; NS: No significant difference. Obesity was defined as body mass index > 30 kg/m².

(21% *vs* 10%, $P = 0.007$), but less likely to have previous coronary artery bypass graft (7% *vs* 17%, $P = 0.03$). There were no reported complications with any of the cases that underwent coronary angiography.

Echocardiographic and procedural characteristics are presented in [Table 2](#). There were no differences between the two groups in gradients, valve area, or left ventricle function. Transfemoral approach was performed in the majority of cases (89%). Patients who underwent CA were more likely to have undergone an alternative access TAVI *i.e.*, *via* subclavian, trans axillary, apical, or direct aortic. Similarly, general anaesthesia was more frequently used in CA *vs* no CA groups (12% *vs* 2%, $P < 0.001$).

The primary endpoint of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable between the two groups [22.6% *vs* 22.2%; hazard ratio (HR) 1.05, 95%CI: 0.67-1.64, $P = 0.82$] ([Figure 1](#) and [Table 3](#)). All-cause mortality was comparable between the two groups (19% *vs* 17%; HR 1.18, 95%CI: 0.71-1.95, $P = 0.52$). Patients who had CA were less likely to be readmitted with heart failure (1.3% *vs* 6.2%, $P = 0.022$) but more likely to have repeat CA (5.8% *vs* 0.5%, $P = 0.003$). Likewise, patients in the CA group had higher rate of subsequent MI (3.9% *vs* 1.0%, $P = 0.07$), although this did not reach statistical significance.

We also assessed whether flow limiting lesions on CA before TAVI were associated with events post TAVI. One-third (54/154) of patients had flow limiting lesions on CA before TAVI. There were no differences in the incidence of the primary endpoint (29.6% *vs* 19.0%, $P = 0.13$), readmission with heart failure (3.7% *vs* 1.0%, $P = 0.24$), or spontaneous MI (7.4% *vs* 3.0%, $P = 0.21$) between patients with flow limiting *vs* those with no flow limiting lesions on CA, respectively ([Figures 2](#) and [3](#)). Repeat CA following TAVI was statistically more frequent in those with flow limiting lesions (9.3% *vs* 0%, $P = 0.005$) ([Figure 3](#)). Two patients had percutaneous coronary interventions at a median of 40 mo post TAVI. One patient with known flow limiting lesion which was not revascularised before TAVI while the second patient developed *de novo* flow limiting lesion.

Table 2 Echocardiographic and procedural characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Peak gradient (mean \pm SD)	74 \pm 23	73 \pm 22	74 \pm 24	NS
Mean gradient (mean \pm SD)	43 \pm 15	44 \pm 15	43 \pm 15	NS
Valve area (mean \pm SD)	0.70 \pm 0.20	0.71 \pm 0.18	0.69 \pm 0.22	NS
Preserved LV function, n (%)	274 (79)	158 (81)	116 (75)	NS
Moderate MR, n (%)	35 (10)	20 (10)	15 (10)	NS
PA pressure (mean \pm SD)	39 \pm 20	40 \pm 15	39 \pm 25	NS
Indication for AR or mixed AoV disease, n (%)	19 (6)	9 (5)	10 (7)	NS
Bioprosthetic valve, n (%)	17 (5)	14 (7)	3 (2)	< 0.05
GA, n (%)	23 (7)	4 (2)	19 (12)	< 0.01
BAV, n (%)	34 (10)	15 (8)	19 (12)	NS
Transfemoral approach, n (%)	311 (89)	183 (94)	128 (83)	< 0.01
Balloon-expanding, n (%)	295 (85)	161 (83)	134 (87)	NS
Valve size (> 23 mm), n (%)	222 (64)	125 (64)	97 (63)	NS

LV: Left ventricle; MR: Mitral regurgitation; PA: Pulmonary pressure; AR: Aortic regurgitation, AoV: Aortic valve disease; GA: General anaesthesia; BAV: Balloon valvuloplasty performed for pre-dilatation; NS: No significant difference.

Table 3 Clinical endpoints following transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Primary endpoint, n (%)	78 (22.4)	44 (22.6)	33 (22.2)	NS
Death, n (%)	63 (18.1)	37 (19.0)	26 (17.0)	NS
Myocardial infarction, n (%)	8 (2.3)	2 (1.0)	6 (3.9)	NS
Readmission with heart failure, n (%)	14 (4)	12 (6.2)	2 (1.3)	< 0.05
Coronary angiogram post valve intervention, n (%)	10 (2.9)	1 (0.5)	9 (5.8)	< 0.01
Death & myocardial infarction, n (%)	69 (19.8)	38 (19.5)	31 (20.3)	NS
Death & readmission with heart failure, n (%)	70 (20.1)	43 (22.1)	27 (17.6)	NS
Myocardial infarction & readmission with heart failure, n (%)	21 (6)	13 (6.7)	8 (5.2)	NS

Primary endpoint was defined as a composite of death, myocardial infarction, revascularisation, and readmission with heart failure. NS: No significant difference.

DISCUSSION

The main finding of this study was that our devised approach of selective CA tailored to patient clinical characteristics was safe and feasible over a relatively short follow up. Second, a composite of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable irrespective of CA before TAVI procedure and importantly, there were no differences based on the obstructive nature of coronary lesions on CA before TAVI. Third, patients with flow limiting lesions pre-TAVI were more likely to have repeat CA following TAVI.

There is a strong association between CAD and aortic stenosis. In almost 16000 patients undergoing TAVI in the German Aortic Valve Registry, 50% of patients were

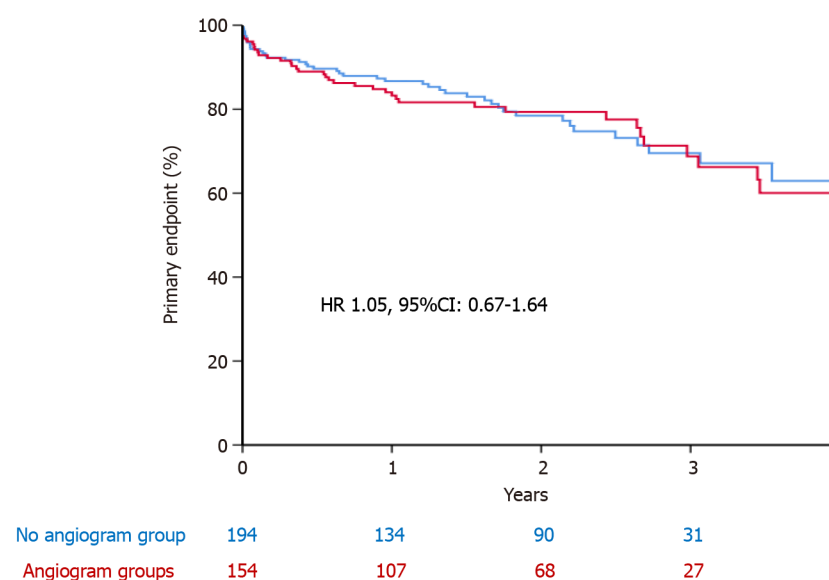


Figure 1 Primary endpoint of transcatheter aortic valve implantation patients stratified according to whether coronary angiogram was performed. Kaplan-Meier curves comparing cumulative incidence of all-cause mortality, myocardial infarction, repeat coronary angiogram, and re-admission to hospital with heart failure in patients with underwent coronary angiogram (in red) versus those who did not undergo coronary angiogram (blue). HR: Hazard ratio.

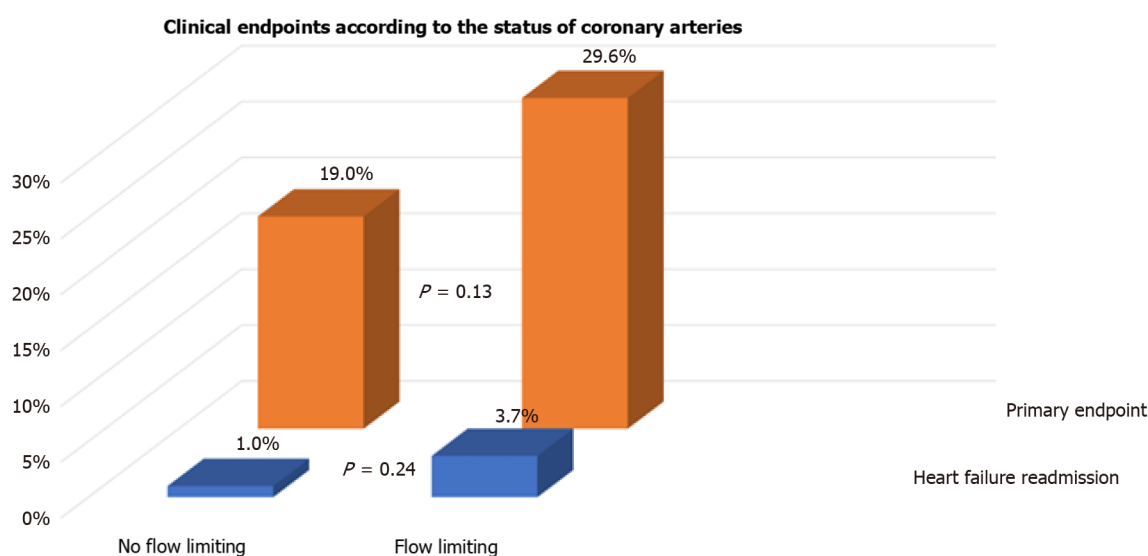


Figure 2 The incidence of the primary endpoint and heart failure readmission according to obstructive nature of coronary lesions. There was no difference in the incidence of the primary endpoint or readmission with heart failure between patients with obstructive versus non-obstructive coronary lesions.

reported to have concomitant coronary artery disease[13]. The management of CAD in this setting is controversial with previous studies highlighting the prognostic role of CAD in patients undergoing TAVI[14]. Moreover, observational data suggested a potential caveat when coronary arteries were not revascularised by demonstrating an association between rapid pacing and adverse outcomes in TAVI patients[15,16]. Coronary revascularisation was proposed to mitigate ventricular stunning and reduce prolong hypotension during rapid pacing, although this needs to be confirmed in randomised trials[17].

Nonetheless, percutaneous coronary intervention was not consistently associated with a reduction in adverse events following TAVI[10,18]. Recently, the percutaneous coronary intervention prior to TAVI (ACTIVATION) trial showed no difference in one-year survival or readmission to hospital according to whether coronary revascularisation was performed before TAVI[19,20]. This was the first randomised trial to test this hypothesis and challenges the current recommendation of performing routine coronary revascularisation for proximal CAD before TAVI[1,2]. Moreover, Snow *et al* [21] showed that the management of aortic stenosis and concomitant CAD can be

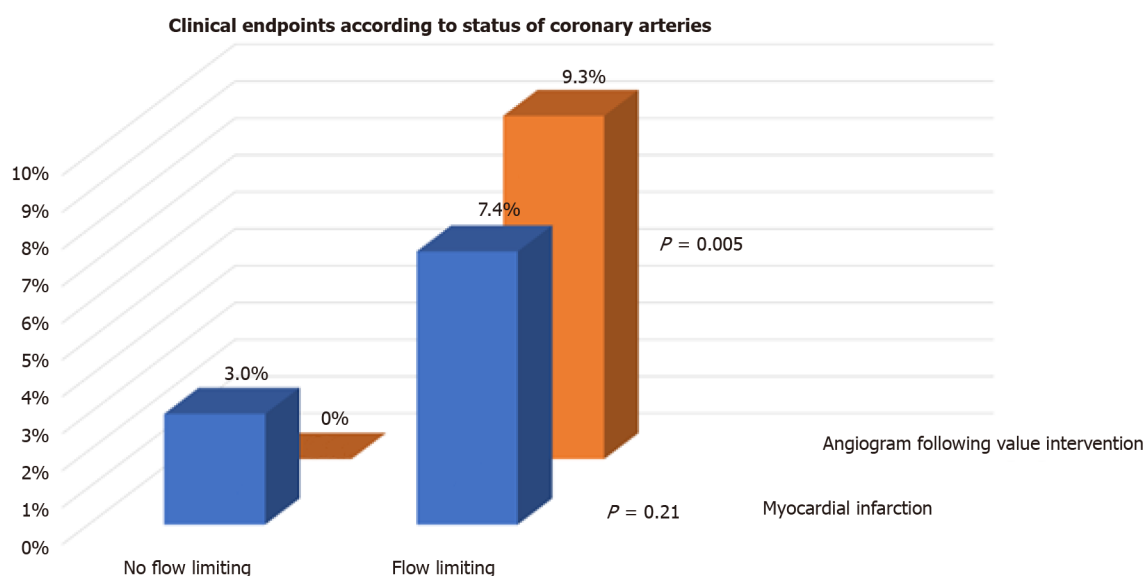


Figure 3 The incidence of the myocardial infarction and repeat coronary angiogram according to obstructive nature of coronary lesions. There was no difference in the incidence of myocardial infarction between patients with obstructive versus non-obstructive coronary lesions. Patients with flow limiting lesions were more likely to have repeat coronary angiograms following transcatheter aortic valve implantation procedure.

effectively managed by TAVI alone[21]. Importantly, our data are consistent with the results of these studies, and questions the need for CA, and revascularisation, before TAVI.

The current study suggests that the criteria for selective CA before TAVI is a safe and feasible. Patients with history of exertional chest pain suggestive of angina, left ventricle dysfunction, or extensive calcification on CT were deemed suitable for CA before TAVI. Up to 40% of patients with aortic stenosis may report angina symptoms and coronary revascularisation is indicated to relieve symptoms and improve quality of life. The presence of left ventricular dysfunction maybe related to CAD and suggests a second pathophysiological process, in addition to aortic stenosis, that needs to be addressed and managed. Advances in technology allowed CT-derived fractional flow reserve to assess CAD pre TAVI. This approach was illustrated to be safe and feasible in patients with severe aortic stenosis, and is currently assessed in the Functional Testing Underlying Coronary Revascularisation in aortic stenosis study[22].

Routine CA subjects patients to additional invasive procedure with associated risks, albeit small[23]. Contrast-induced nephropathy is a recognised risk with CA and is increased in the elderly and in patients with renal dysfunction[24,25]. These features are commonly observed in patients undergoing TAVI, and may exacerbate the renal risk associated following TAVI procedure itself[26]. Moreover, routine CA would add further delays to patients who are waiting for definitive valve intervention. There was an increase in mortality risk of almost 4% for each month delay while waiting for TAVI procedure[27].

Access to coronary arteries following TAVI has been reported to be challenging[28-30]. This was highlighted with self-expanding compared to balloon-expanding valves [31]. Therefore, it may be argued that upfront revascularisation of coronary lesions pre-TAVI would overcome the need to access the coronary arteries following TAVI. Nonetheless, these studies were of small sample size with success rate in engaging coronaries ranging from 50% to 100%[32]. Better understanding of the relationship between the bioprosthetic valve, particularly leaflets commissures, and coronary ostia would allow selective CA following TAVI[33].

Coronary events are relatively uncommon following TAVI. In our series, MI was reported in 2.3% of cases which was comparable to other contemporary studies[34]. Importantly, subsequent CAs did not always demonstrate culprit coronary lesions that required revascularisation. This should not be surprising since other mechanisms of MI were proposed such as coronary embolism secondary to subclinical leaflet thrombosis, late migration of the bioprosthetic valve, impaired coronary flow dynamic, and coronary hypo-perfusion related the valve bio-prosthesis[32]. Moreover, Faroux *et al*[30] showed that most coronary lesions were newly developed lesions that were not flow limiting prior to their valve procedure in patients presenting with acute coronary syndrome following TAVI[30]. This was reflected in our data whereby there

was no difference in events rates according to the presence of flow limiting lesions before TAVI. In other words, patients with non-obstructive CAD had similar incidence of ischaemic events to those with flow limiting lesions, and the use of CA did not identify a group of patients who were at a higher risk of future events. Interestingly, those with flow-limiting lesions were more likely to undergo repeat CA following TAVI. This is likely to reflect information bias as patients with known obstructive lesions will have a lower threshold to be brought back for CA compared to those with no flow limiting lesions.

Our study has several limitations. This was a retrospective single centre study associated with the inherent limitations of the design of the study. We had to exclude almost 25% of patients who underwent TAVI in our centre as their post procedural follow up could not be ascertained. Clinical endpoints were not adjudicated and were defined according to hospital discharge letters. This bias may have been mitigated by including hard events such as mortality and heart failure admissions.

CONCLUSION

Selective CA is a feasible and safe approach. It is not associated with high adverse outcomes. The role of CA before TAVI is increasingly undermined by the low ischaemic event rate. Additionally, the disconnect between CAD and subsequent cardiac events question the pre-emptive approach of coronary revascularisation in TAVI. Large randomised trials are required to test this hypothesis in the future.

ARTICLE HIGHLIGHTS

Research background

Routine coronary revascularisation pre-transcatheter aortic valve implantation (TAVI) was not associated with improved outcomes, yet, coronary angiogram (CA) is still performed as part of TAVI work up.

Research motivation

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram before TAVI procedure.

Research objectives

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

Research methods

Retrospective analysis of consecutive patients undergoing TAVI who underwent CA *vs* those who did not was performed. Decision to undergo CA pre-TAVI was tailored to patients clinical characteristics.

Research results

The primary endpoint was a composite of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure was comparable between the two groups.

Research conclusions

Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials.

Research perspectives

Future randomised clinical trials are required to test whether selective CA is safe.

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Observational Study

Associations of new-onset atrial fibrillation and severe visual impairment in type 2 diabetes: A multicenter nationwide study

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Abstract

BACKGROUND

Many studies have demonstrated an association between type 2 diabetes mellitus (T2DM) and atrial fibrillation (AF). However, the potential independent contributions of T2DM and AF to the prevalence of visual impairment have not been evaluated.

AIM

To determine whether such an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

METHODS

We conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools. This study had evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. T2DM patients were categorized into two groups: patients without and with incident AF. T2DM patients without AF were selected as the reference group. The association between incident AF and visual impairment among T2DM patients was assessed using multivariate logistic regression.

RESULTS

statement: This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand (IRB# S007h/54).

Informed consent statement: All patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment.

Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

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

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A total of 27281 T2DM patients with available eye examination data were included in this analysis. The mean age was 60.7 ± 10.5 years, and 31.2% were male. The incident AF was 0.2%. The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. T2DM patients with incident AF were associated with an increased OR of 3.89 (95% CI: 1.17-13.38) for severe visual impairment compared with T2DM patients without AF.

CONCLUSION

T2DM patients with incident AF were independently associated with increased severe visual impairment. Therefore, early eye screening should be provided for these high-risk individuals.

Key Words: Type 2 diabetes mellitus; Atrial fibrillation; Visual impairment; Retinopathy; Blindness

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Core Tip: The independent contributions of diabetes mellitus and atrial fibrillation (AF) to the prevalence of visual impairments have not been evaluated. AF is relatively common in diabetic patients and should be regarded as a marker of adverse outcomes for cardiovascular diseases in type 2 diabetes mellitus (T2DM). In this study, we explored whether an association between T2DM with incident AF and visual impairment exists, and if so, the prevalence and magnitude of this association. We found a nearly three-fold higher prevalence of severe visual impairment in T2DM patients with incident AF compared to those without AF [OR of 3.89 (95%CI: 1.17-13.38)]. It may be useful to increase screening for visual impairments in T2DM patients with incident AF. The results of our study could encourage public health initiatives for the prevention of vision impairment by early eye screening in these high-risk individuals.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common chronic disease worldwide[1]. T2DM is associated with significant morbidity and mortality and has rapidly emerged as a global public health issue[2,3]. Diabetic retinopathy and visual impairment are among these common and severe complications of T2DM.

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in the world[4,5]. Its prevalence is predicted to more than double by 2050[6]. Previous studies found that AF may be relatively common in diabetic patients, and it should be regarded as a marker of increased adverse cardiovascular outcomes[7]. In addition, diabetes has long been recognized as a risk factor for AF[8,9]. The overlap of the pathophysiology of diabetes and AF concordantly increase the risk of thromboembolic events, and this has been well-established in the literature[10]. The potential independent contributions of diabetes and AF to the prevalence of visual impairment, however, has not been evaluated.

This study was thus aimed to determine whether such an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

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MATERIALS AND METHODS

Study design and population

This was an analysis of the DM/HT dataset from 2013[11]. This was a nationwide survey conducted annually in Thailand to evaluate the status of medical care in T2DM patients who visited the public hospitals of the Thai Ministry of Public Health and the clinics in the Thailand National Health Security Office's program. The inclusion criteria of this DM/HT survey consisted of T2DM patients aged ≥ 35 years who received regular medical care in the targeted hospital for at least 12 mo. Patients who received care at primary care units outside Bangkok and university hospitals were excluded from this study. A two-stage stratified cluster sampling method was utilized to select a nationally and provincially representative sample of T2DM patients in Thailand. The first stage of sample collection consisted of the provinces that constituted 77 strata. The second stage of sample collection was the hospitals' levels in each province, which were stratified into five strata according to the size of the hospital. These five strata were regional (> 500 beds), provincial (200-500 beds), large community (80-120 beds), medium community (60 beds), and small community (10-30 beds) hospitals. All regional ($n = 25$) and provincial ($n = 70$) hospitals were enrolled, but only 456 (62% out of 736) community hospitals were included. Of 456 community hospitals, 10%, 20%, and 70% were large, medium, and small community hospitals, respectively.

All patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment. This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects of the Ministry of Public Health of Thailand, due to the bureaucratic system regulations in Thailand. Well-trained research nurses reviewed medical records and collected data into a case record form. Data entry into this form was then transferred to the central data management of the Medical Research Network of the Consortium of Thai Medical Schools. This data management team adjudicated the process of data collection to ensure it was compiled according to the study protocol. This team was also responsible for inquiries to study sites to verify data. Site monitoring was randomly performed in approximately 10% of study sites. This study was conducted by the Strengthening the Reporting of Observational Studies in Epidemiology[12].

Data collection

Clinical characteristics, demographic information, medication, and laboratory data were collected using a manual data retrieval from the medical record as described above. The laboratory data included results from 12 mo prior to the consent process. Incident AF was identified by ICD10 code I48, and subsequently verified by medical record review during the 12 mo of the study period. This verification of AF consisted of electrocardiogram (ECG). The date of first ECG documenting the presence of AF was considered the onset of atrial fibrillation. We exclude patients who had prior history of AF before the start date. Estimated glomerular filtration rate (eGFR) was estimated based on age, sex, race, and most recent creatinine with calculation *via* the Chronic Kidney Disease Epidemiology Collaboration equation[13]. CHA2DS2VASc score was calculated by using clinical data from the medical record. Primary outcome was diagnosis of severe visual impairment within 12 mo of data collection. Binocular visual acuity (VA) was examined using a semi-qualitative assessment and documented by physicians. Severe visual impairment was based on the worst VA exam of both eyes that consisted of "counting fingers," "hand motions," "projection of light," "perception of light," and "no light perception."

Statistical analysis

Continuous variables were presented as mean \pm SD. Categorical variables were presented as count with percentage. Clinical characteristics and outcomes were compared among the different groups using the independent t-test for continuous variables, and Chi-squared test, and Fisher's exact test for categorical variables. T2DM patients were categorized into two groups: (1) T2DM patients without AF; and (2) T2DM patients with incident AF. T2DM patients without AF were selected as the reference group. Univariate and then multivariate logistic regression analysis, adjusting for priori-defined variables, were performed to assess the independent association between AF onset and severe visual impairment. Odds ratio (OR) with 95% confidence interval (CI) was reported. The adjusted variables consisted of age, sex, duration of T2DM, body mass index (BMI), smoking, comorbidities, complications,

and medications. Comorbidities and complications were hypertension, ischemic heart disease, cerebrovascular disease, diabetic retinopathy, eGFR, and CHA2DS2VASc score. Medications were insulin, antiplatelets, and anticoagulants. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL, United States).

RESULTS

Clinical characteristics

A total of 27339 adult T2DM patients with eye examination data from 831 public hospitals in Thailand were included in this analysis. Clinical characteristics are summarized in Table 1. The mean age was 60.7 ± 10.5 years, and 31.2% were male. The mean diabetic duration was 7.1 ± 4.8 years. The mean BMI was 25.6 ± 4.5 kg/m². The mean eGFR was 66.9 ± 25.9 mL/min per 1.73 m². The mean CHA2DS2VASc was 2.9 ± 1.0 . The prevalence of T2DM with incident AF was 0.2% (*n* = 48).

Association between of AF and severe visual impairment in T2DM

The prevalence of severe visual impairment in all T2DM was 1.4%. Severe visual impairment was documented in 1.4% of patients without AF and in 6.3% of patients with incident AF (Table 2).

In adjusted analysis, incident AF was associated with an increased OR of 3.89 (95% CI: 1.17-13.38) for severe visual impairment (Table 3).

DISCUSSION

An analysis of the baseline patient characteristics showed that T2DM with incident AF was associated with older age. Moreover, T2DM patients with AF had a higher prevalence of ischemic heart disease, cerebrovascular disease, and increased use of antiplatelet medications compared to patients without AF. These findings are consistent with a study performed by Nichols *et al*[14] and Benjamin *et al*[9], where AF was similarly found to be correlated with older age and ischemic heart disease. However, in their study, history of smoking was not associated with AF in T2DM patients. It is not surprising to find these associations, as it could be hypothesized that since these clinical characteristics are established risk factors for development of any cardiovascular diseases, it follows that they could also precipitate AF development in T2DM patients.

Prevalence of severe visual impairment in T2DM patients

The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. According to previous studies from the United Kingdom[15] and the United States[3], the overall prevalence of visual impairment in T2DM ranges between 0.75% to 3.80%. Etiologies of visual impairment in T2DM patients include retinopathy of any type (particularly diabetic retinopathy), glaucoma, and cataracts[16]. A recent meta-analysis found that diabetes was associated with an increased incidence of glaucoma[3].

Association between AF and severe visual impairment

This study showed that AF is independently associated with severe visual impairment in adult T2DM patients. No prior studies have investigated this association. The pathogenesis of poor vision in recently diagnosed AF may be multifactorial, including retinal emboli[17,18]. Retinal artery occlusion (RAO)[19] and retinal vein occlusion (RVO)[20] are increasingly common in older subjects. As age increases, the risk of AF also substantially increases. Previous studies from Hayreh *et al*[21] and Yen *et al*[19] draw a potential pathophysiologic association, as they have reported that patients with AF are at increased risk of developing RAO. A study by Christiansen *et al*[22] also found that RAO was associated with an increased risk of incident AF. O'Mahoney *et al* [23] and Christiansen *et al*[24] reported that RVO might be an important cause of blindness in populations with high atherosclerotic risk. These conditions share the same traditional risk factors as for cardiovascular diseases, possibly due to shared pathophysiologic mechanisms.

Table 1 Baseline characteristics

Characteristics	All	T2DM without AF	Incident AF	P value
N/n (%)	27339	27281 (99.8)	48 (0.2)	
Age (yr, mean \pm SD)	60.7 \pm 10.5	60.7 \pm 10.5	65.9 \pm 9.9	0.001
Male, n (%)	8518 (31.2)	8499 (31.1)	19 (39.6)	0.21
Duration of T2DM (yr, mean \pm SD)	7.1 \pm 4.8	7.1 \pm 4.8	6.6 \pm 3.4	0.46
Body mass index (kg/m ² , mean \pm SD)	25.6 \pm 4.5	25.6 \pm 4.5	24.8 \pm 4.5	0.24
Smoking, n (%)	1084 (4.0)	1080 (4.0)	4 (8.5)	0.12
Comorbidity and complication, n (%)				
Hypertension	19840 (72.6)	19801 (72.6)	39 (81.3)	0.18
Ischemic heart disease	947 (3.5)	939 (3.4)	8 (16.7)	< 0.001
Cerebrovascular disease	666 (2.4)	661 (2.4)	5 (10.4)	0.01
Diabetic retinopathy	2008 (7.4)	2005 (7.4)	3 (6.7)	1.00
Medication, n (%)				
Insulin use	5848 (21.4)	5840 (21.4)	8 (16.7)	0.42
Antiplatelets or anticoagulants	16321 (60.1)	16285 (60.1)	36 (75.0)	0.04
eGFR (mL/min/1.73 m ² , mean \pm SD)	66.9 \pm 25.9	66.9 \pm 25.9	60.5 \pm 25.7	0.09
CHA2DS2VASc score (mean \pm SD)	2.9 \pm 1.0	2.9 \pm 1.0	3.7 \pm 1.4	0.001

AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus; eGFR: Estimated glomerular filtration rate.

Table 2 Prevalence of severe visual impairments stratified by presence of incident atrial fibrillation in type 2 diabetes mellitus patients

Outcomes	All	T2DM without AF	Incident AF	P value
Severe visual impairment, n (%)	387 (1.4)	384 (1.4)	3 (6.3)	0.03
Counting finger, n (%)	181 (0.7)	181 (0.7)	0 (0)	1.00
Hand movement, n (%)	101 (0.4)	99 (0.4)	2 (4.2)	0.01
Projection of light, n (%)	18 (0.1)	18 (0.1)	0 (0)	1.00
Perception of light, n (%)	24 (0.1)	24 (0.1)	0 (0)	1.00
No light perception, n (%)	77 (0.3)	76 (0.3)	1 (2.1)	0.13

T2DM: Type 2 diabetes mellitus; AF: Atrial fibrillation.

Conditions like anterior ischemic optic neuropathy (AION)[25], age-related macular degeneration (AMD)[26,27], and cataracts may all be other potential etiologies for visual impairment in this population[28]. Callizo *et al*[25] found that AION may cause blindness in patients with AF. Clemons *et al*[26] and Topouzis *et al*[27] suggest an increased risk of AMD with diabetes mellitus. In a cohort study by Hahn *et al*[29], it was found that diabetic retinopathy might increase the risk of both dry and wet AMD. These studies support a potential similar pathophysiologic mechanism between diabetic retinopathy and AMD. Optimal diabetic control may reduce the development of AMD. Klein *et al*[28] found that T2DM is associated with an increased incidence and progression of cataracts, which may be worsened by suboptimal glycemic control. In summary, cardiovascular disease and its associated risk factors have an adverse effect on the incidence of age-related cataracts. These risk factors need to be promptly investigated in order to reduce ophthalmologic complications through early interventions.

Strengths

Our study consisted of a large-size sample from a multicenter and nationwide population-based design that provided detailed eye examination information while

Table 3 Association of incident atrial fibrillation and severe visual impairment in type 2 diabetes mellitus patients after multivariate logistic regression analysis

	Crude OR (95%CI)	P value	Adjusted OR (95%CI) ^{1,2}	P value
T2DM without AF	1 (Reference)		1 (Reference)	
Incident AF	4.67 (1.45-15.10)	0.01	3.89 (1.17-13.38)	0.03

¹Adjusted for age (continuous), gender (male or female), duration of T2DM (continuous), body mass index (continuous), smoking (yes or no), hypertension (yes or no), ischemic heart disease (yes or no), cerebrovascular disease (yes or no), diabetic retinopathy (yes or no), insulin (yes or no), antiplatelets or anticoagulants (yes or no), eGFR (continuous), and CHA2DS2Vasc score (continuous).

²Hosmer-Lemeshow test: Chi-square 13.31, P value 0.10.

AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus; eGFR: Estimated glomerular filtration rate.

accounting for potential confounders in order to allow an adequate estimate of severe visual impairment burden in T2DM patients with AF. Our analysis of the association between eGFR and DR utilized a multiple logistic regression model that accounted for several possible confounders, including age, sex, duration of T2DM, body mass index (BMI), smoking, other comorbidities, and medications. Comorbidities included hypertension, ischemic heart disease, cerebrovascular disease, and diabetic retinopathy. Medications that were adjusted for included insulin and antiplatelet medication. Lastly, visual impairment severity was measured using a semi-qualitative clinical scale composed of bedside testing items, which is an easy test to perform in the community setting.

Limitations

This study had several limitations. First, we identified AF using ICD 10 codes and then subsequently confirmed by medical record review for documented ECGs. As ECGs were usually performed when clinically indicated rather than universally, our study may have underdiagnosed asymptomatic AF. This may explain the low prevalence of AF in our study compared to previous reports[30-33]. Future studies utilizing advanced cardiac monitoring technology such as signal-averaged ECGs and Holter monitors would more accurately capture total prevalence of AF. In addition, AF could be paroxysmal, and periodic ECGs may not have detected these paroxysmal AF episodes. Thus, future studies are needed to better assess the associations of visual impairment with asymptomatic AF and AF subtypes among T2DM patients. Second, our study was cross-sectional in nature. A longitudinal study in the future may provide further details on the etiology of visual impairments in order to better confirm the association and elucidate the pathophysiology of new-onset AF and poor vision in T2DM patients. Third, information on prior eye surgeries, such as vitrectomy due to retinal hemorrhage, was scarce. These patients may have suffered a prior visual impairment rather than incorrectly associated with incident AF. Fourth, information on the etiology of visual impairment other than diabetic retinopathy was not available. Finally, although we performed multivariate analysis for further adjustment of potential confounders including CHA2DS2-VASC and anticoagulation, we did not have information on the specific type of AF, type of anticoagulation therapy used, international normalized ratio (INR) levels, previous AF medications for rate control, and outcomes of AF treatment. These are potential confounding factors that were unaccounted for. Therefore, this study was unable to determine the association between optimally treated AF and visual impairment in T2DM patients.

Implications

Our study found a nearly three-fold higher prevalence of poor vision in T2DM patients with incident AF. Several conditions such as glaucoma, cataracts, and retinopathy are potentially reversible causes of vision impairment, especially if treated early. It may be useful to screen for visual impairment and its etiologies in T2DM patients with recent-onset AF (less than 1-year). The results of our study could encourage public health initiatives to institute early eye screening in these high-risk individuals in order to prevent vision impairment. Further studies are needed to elucidate whether these interventions would translate into improved clinical outcomes.

CONCLUSION

The prevalence of severe visual impairment in T2DM patients with incident AF was nearly three times higher than the prevalence of impaired vision in all T2DM patients. Moreover, T2DM patients with incident AF were independently associated with severe visual impairment. Early eye screening should be performed in these high-risk individuals as it may provide an earlier diagnosis, allowing for prevention and treatment of potentially reversible causes of vision impairment.

ARTICLE HIGHLIGHTS

Research background

Previous studies have shown an association between type 2 diabetes mellitus (T2DM) and atrial fibrillation (AF). However, the independent contributions of T2DM and AF on the prevalence of visual impairment have not been evaluated.

Research motivation

Earlier studies have demonstrated that AF is relatively common in diabetic patients, and it should be regarded as a marker for adverse cardiovascular outcomes in T2DM.

Research objectives

To investigate whether an association between T2DM and incident AF with visual impairment exists, and if so, the prevalence and magnitude of this association.

Research methods

This study evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. The association between T2DM with incident AF and visual impairment were assessed using multivariate logistic regression.

Research results

A total of 27281 T2DM patients with available eye examination data were included in this analysis. The prevalence of incident AF in T2DM patients was 0.2%. The prevalence of severe visual impairment in all T2DM patients, T2DM patients without AF, and T2DM patients with incident AF were 1.4%, 1.4%, and 6.3%, respectively. T2DM patients with incident AF were associated with an increased OR of 3.89 (95%CI: 1.17-13.38) for severe visual impairment compared to those without AF.

Research conclusions

T2DM patients with incident AF were independently associated with severe visual impairment. Early eye screening should be provided for these high-risk individuals.

Research perspectives

Overlapping diabetes and AF leads to an increased risk of thromboembolic events. However, the independent contribution of T2DM and AF to the prevalence of visual impairments has not been evaluated. Therefore, it may be useful to screen for visual impairment and its etiologies in T2DM patients with incident AF.

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