

# World Journal of *Cardiology*

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2014-2017

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## Sudden cardiac death in patients with rheumatoid arthritis

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### Abstract

An increased cardiovascular morbidity and mortality, including the risk of sudden cardiac death (SCD), has been shown in patients with rheumatoid arthritis (RA). Abnormalities in autonomic markers such as heart rate variability and ventricular repolarization parameters, such as QTc interval and QT dispersion, have been associated with sudden death in patients with RA. The interplay between these parameters and inflammation that is known to exist with RA is of growing interest. In this article, we review the prevalence and predictors of SCD in patients with RA and describe the potential underlying mechanisms, which may contribute to this. We also review the impact of biologic agents on arrhythmic risk as well as cardiovascular morbidity and mortality.

**Key words:** Sudden death; Rheumatoid arthritis; Cardiovascular; QT; Autonomic nervous system; Arrhythmia

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**Core tip:** Patients with rheumatoid arthritis are twice as likely to experience sudden cardiac death (SCD). This excess risk can only partially be explained by the higher rates of heart failure and ischaemic heart disease. Abnormalities of the autonomic nervous system, such as decreased heart rate variability, and abnormalities of ventricular repolarization parameters, such as QTc interval and QT dispersion, have also been implicated. In this article we review the interplay between these parameters and inflammation, exploring whether biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition which affects 0.8% of the adult population<sup>[1]</sup>. It causes significant morbidity as a result of synovial inflammation, joint destruction, and associated disability. In addition to articular manifestations, there is substantial data demonstrating excess cardiovascular morbidity and mortality in RA<sup>[2,3]</sup>. Studies as early as the 1950s have shown that RA is associated with premature death<sup>[4]</sup>, with 50% of excess deaths being attributed to cardiovascular disease<sup>[2,5]</sup>. Sudden cardiac death (SCD) is estimated to account for 50% of cardiovascular deaths in the general population<sup>[6,7]</sup>. Patients with RA are twice as likely to experience SCD<sup>[8]</sup>, a figure comparable to patients with diabetes mellitus<sup>[9]</sup>. This review will seek to explore the risk factors that make SCD more prevalent in RA, including coronary artery disease (CAD), structural heart disease, electrophysiological abnormalities including myocardial repolarization (QTc interval, QT dispersion) and autonomic dysfunction [heart rate variability (HRV) analysis], and the interplay of inflammation on all these factors<sup>[10]</sup>. We will also review the effect that the new biologic agents may have on the incidence of cardiovascular events and SCD.

## DEFINING SCD AND ITS PREVALENCE IN RA

Sudden death is defined as "non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event"<sup>[11]</sup>. The term SCD is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes have been identified by post-mortem examination, and therefore an arrhythmic event is a likely cause of death<sup>[11]</sup>. SCD is largely thought to result from fatal arrhythmias, in particular, ventricular tachycardia degenerating to ventricular fibrillation<sup>[12,13]</sup>. Bradyarrhythmia or electromechanical dissociation can also be associated with SCD but these tend to occur in patients with advanced cardiac disease<sup>[12,14]</sup>.

In the general population sudden death accounts for 60% of cardiovascular deaths in those with known CAD<sup>[15]</sup>, and is the first presentation of CAD in 15% of cases<sup>[16]</sup>. Over 70% of fatal arrhythmias are thought to be secondary to CAD<sup>[12]</sup>. These arrhythmias can occur

acutely secondary to direct repolarisation changes occurring during ischaemia, or remotely, typically due to initiation of re-entry circuits within areas of electrically unexcitable scar tissue or diseased myocardium in patients with established myocardial infarction (MI)<sup>[17]</sup>. Dilated and hypertrophic cardiomyopathies account for the second largest number of sudden deaths followed by valvular, congenital, infiltrative, ion-channel disorders which only account for the small remainder<sup>[12,13]</sup>.

Within the RA population, there is a wealth of data regarding the rates of cardiovascular death, however few studies have looked specifically at the epidemiology of SCD. In an inception cohort of 1010 RA patients, Goodson *et al.*<sup>[18]</sup> found an excess of cardiovascular mortality without a corresponding increase in cardiovascular admission rates as compared to controls, suggesting that cardiovascular disease has a higher case fatality in the RA population, or that it often goes unrecognized before the fatal event. Indeed, Solomon *et al.*<sup>[19]</sup> found that the rate ratio for cardiovascular death was highest in young RA adults and those with no known prior cardiovascular events. Whilst Van Doornum *et al.*<sup>[20]</sup> demonstrated that RA patients have a higher 30-d case fatality following MI as compared to controls, 17.6% vs 10.8%. In a large population cohort study of 603 RA patients followed up for 15 years, Maradit-Kremers *et al.*<sup>[5]</sup> demonstrated that RA patients were twice as likely to experience SCD (hazard ratio 1.94, 95%CI: 1.06-3.55)<sup>[8]</sup>, a figure similar to the risk of SCD amongst patients with diabetes mellitus<sup>[21]</sup>. The authors also noted a higher risk of unrecognized MIs and a lower likelihood of angina symptoms, suggesting that CAD manifests differently in RA and is more likely to manifest as cardiovascular death<sup>[8]</sup>. Similarly Mantel *et al.*<sup>[22]</sup> demonstrated that RA is associated with higher risk acute coronary syndromes, higher cumulative incidence of SCD (0.2% vs 0.13% over 3 years), and higher short term case fatality rate at 7 and 30 d. Indeed, certain RA genetic polymorphisms have been linked to premature cardiovascular disease and mortality<sup>[23-26]</sup>, although none with a strong clinical implication<sup>[27,28]</sup>.

## RISK FACTORS FOR SCD IN RA

### *Accelerated CAD, congestive cardiac failure and inflammation*

Whilst there is a higher incidence of ischaemic heart disease (IHD) in RA, several authors have shown that this increased incidence cannot be explained by traditional risk factors alone<sup>[5,29]</sup>, as such there has been growing interest in the role of inflammation as novel risk factor for atherosclerosis<sup>[30]</sup>. Indeed, in the general population, modest increases in C-reactive protein (CRP) have been associated with increased cardiovascular events<sup>[31]</sup>, and RA has been likened to diabetes as a risk factor for CAD<sup>[32]</sup>.

Studies have also suggested different patterns of CAD in RA with chronic inflammation leading to early endothelial dysfunction<sup>[33,34]</sup>, and a higher incidence of unstable plaques attributed to inflammatory cytokines<sup>[35]</sup>. Indeed tumour necrosis factor alpha (TNF- $\alpha$ ) has been implicated in all stages of atherosclerosis including endothelial dysfunction, plaque formation, rupture and promotion of the clotting cascade<sup>[36,37]</sup>. Systemic inflammation has also been associated with dyslipidaemia, impaired glucose metabolism, platelet activation and increased clotting factors<sup>[36]</sup>. However, despite the evidence linking inflammation to accelerated atherosclerosis and IHD, Maradit-Kremers *et al*<sup>[8]</sup> demonstrated that the two-fold risk of SCD seen in the RA population persisted after adjustments for history of hospitalized, or unrecognized, MI, revascularization procedures and cardiovascular risk factors. This suggests that the increased risk of SCD in RA cannot be explained by increased rates of IHD alone<sup>[10,38]</sup>.

In two studies<sup>[39,40]</sup> the excess risk of congestive cardiac failure (CCF) among RA subjects could not be explained by the increased frequency, or effect of, either cardiovascular risk factors, or IHD. In the same cohort, Gabriel *et al*<sup>[41]</sup> demonstrated that whilst 80% of CCF in the general population is attributed to classical CVD risk factors, in RA, classical risk factors only explained 40% of the incident heart failure.

Amongst RA patients experiencing new-onset heart failure, ESR levels were highest in the 6 mo immediately preceding diagnosis, suggesting that ESR may signal the onset of heart failure in patients with RA<sup>[42]</sup>. However, the relationship between SCD and severity of CCF is not as clear-cut as that seen with SCD and IHD, and less is known about RA and CCF. Data from the general population suggests that as left ventricular (LV) systolic function deteriorates, all-cause mortality and the absolute number of sudden deaths increases, but the proportion of deaths due to arrhythmias decreases<sup>[14,43]</sup>. Thus, the degree of LV systolic dysfunction lacks specificity as a predictor of death secondary to cardiac arrhythmias, because it is also powerful measure of the risk of death<sup>[12]</sup>. In line with these results, Nicola *et al*<sup>[44]</sup> found CCF contributed to the excess cardiovascular mortality in RA, primarily through the increased incidence of CCF in RA rather than increased case fatality. Studies have also shown that patients with RA have higher rates of diastolic dysfunction<sup>[45]</sup>, and heart failure with preserved ejection fraction<sup>[46]</sup>.

### **Abnormal ventricular repolarization, autonomic dysfunction and inflammation**

Inflammation, as an independent predictor of cardiovascular mortality and sudden death, has been the focus of recent research<sup>[30,47,48]</sup>. Indicators of abnormal ventricular repolarization such as QTc prolongation, QT interval dispersion, and autonomic dysfunction have

been implicated in the aetiopathogenesis of SCD. The QT interval represents the time from onset of ventricular depolarization (beginning of the Q wave) to completion of repolarization (end of T wave). The corrected QT interval (QTc) estimates the QT at a standardized heart rate of 60 bpm, while QT interval dispersion (QTd) is measure of the dispersion of ventricular repolarization (maximum QT interval - minimum QT interval). In the general population both prolongation of QTc and increased QTd are known risk factors for SCD<sup>[49,50]</sup>, and there is data linking both CRP to prolongation of QTc<sup>[51]</sup> and to SCD<sup>[47]</sup>. In animal models, prolonged QTc is associated with depolarization during phases 2 and 3 of the action potential prior to completion of repolarization<sup>[52]</sup>. These premature action potentials also known as early after depolarizations (EADs) can generate fatal ventricular arrhythmias, such as torsade de pointes, which can progress to ventricular fibrillation and SCD<sup>[12,53]</sup>.

Several studies have also shown an association between RA and prolonged QTc or increased QT dispersion variables, as well as an association between RA disease activity and QTc length<sup>[54-62]</sup> (Table 1), with the strongest evidence available for CRP as a marker of disease activity, compared with clinical scoring systems and ESR<sup>[10]</sup>. Moreover, there is growing evidence from basic science studies demonstrating that pro-inflammatory cytokines, particularly TNF- $\alpha$ , directly prolong cardiomyocyte action potential duration (APD) by regulating ion channels involved in ventricular repolarization<sup>[10]</sup>. In particular, several experimental studies have shown that TNF- $\alpha$  prolongs APD, triggering re-entrant ventricular arrhythmias<sup>[63,64]</sup>. TNF- $\alpha$  prolongs APD by inhibiting both the transient outward potassium current<sup>[65]</sup>, and the rapid delayed-rectifier potassium current<sup>[10,66]</sup>. Similarly, animal studies have shown that the pro inflammatory cytokines IL-1 and IL-6, prolong APD in ventricular myocytes *via* their effects on calcium channels<sup>[67,68]</sup>. Interestingly both levels of CRP<sup>[48]</sup> and levels of soluble TNF- $\alpha$  receptors (sTNFR) are strong and independent predictors of cardiovascular death amongst RA patients<sup>[69]</sup>.

As early as 1998, a cross-sectional study by Gödeli *et al*<sup>[54]</sup>, demonstrated a significant increase in QT dispersion variables when comparing RA patients with matched controls, as well as an increase in complex premature ventricular beats. More recently a large prospective study of 357 RA patients demonstrated that prolonged QTc was a strong predictor of death, with a 50 ms increase in QTc being associated with a doubling of the hazard for all-cause mortality<sup>[60]</sup>. The authors also showed that QTc prolongation was independently associated with CRP levels, and that the association between QTc and mortality was lost after adjustment for CRP, further supporting the role of inflammation in the increased rates SCD seen in this patient group<sup>[60]</sup>. No association was found between QTc and the presence of cardiovascular disease at baseline,



**Table 1** Studies demonstrating associations between rheumatoid arthritis and QT parameters, inflammation and mortality

Ref.	Design	RA patients	Controls	Impact of RA and QT dispersion (QTd) and QTc	Association between QT parameter, and disease activity/duration (1), arrhythmia (2), autonomic dysfunction (3), mortality (4)
[54]	Cross-sectional	42	42	↑ QTd variables (QTd, QTcD, JTD, JTcD) <i>vs</i> controls No difference in QTc <i>vs</i> controls	(1) ESR, CRP (2) Complex premature ventricular beats
[55]	Cross-sectional	40	48	↑ QTd variables (QTd, QTcD) <i>vs</i> controls	(1) Disease duration
[56]	Cross-sectional	40	40	↑ QTd <i>vs</i> controls	(1) Extra-articular manifestations, erosive disease
[57]	Cross-sectional	58	29	↑ QT <i>vs</i> controls	(1) Secondary Sjögren's syndrome
[58]	Cross-sectional	100	100	↑ QTd <i>vs</i> controls	(1) Disease duration, DAS28, ESR, number of joints involved
[59]	Cross-sectional	25	21 controls 76 with spondylarthropathy	↑ QTc <i>vs</i> controls and those with spondyloarthropathies Infliximab therapy duration inversely correlated to QTc ( $P < 0.01$ )	(1) CRP (3) ↑ QTC associated with ↑ HR, autonomic dysfunction, particularly sympathetic dysfunction as assessed by spectral parameters of heart rate variability
[60]	Prospective cohort	357	–	↑ QTc 10% males (QTc $\geq 450$ ms) and 5.6% of females (QTc $\geq 460$ ms)	(1) CRP (4) Doubled risk of all-cause mortality per 50 ms increase in QTc, (lost after adjustment for CRP) HR = 2.17 (95%CI: 1.21-3.90)
[61]	Retrospective cohort	417	422	↑ % of RA patients with QTc prolongation ( $> 450$ ms males, $> 460$ ms females) <i>vs</i> controls 20 yr after disease onset (48% <i>vs</i> 38%, $P = 0.004$ )	(1) ESR (4) Any cause QTc prolongation was associated with ↑ all-cause mortality HR = 2.99 (95%CI: 1.93-4.65)
[62]	Prospective cohort	17	–	↑ QTc ( $> 440$ ms) in 76% of patients Tocilizumab associated with 47% ↓ in No. patients with QTc prolongation ( $P = 0.006$ )	(1) CRP and TNF- $\alpha$
[70]	Cross-sectional	117	–		(1) CRP, TNF- $\alpha$ , IL-1 $\beta$ and IL 10 (QTc BAZ) (1) IL-1 $\beta$ and IL 10, trend towards TNF- $\alpha$ (QTc FHS)

RA: Rheumatoid arthritis; QTd: QT interval dispersion; QTc: Heart-rate corrected QT interval; QTcD: Heart-rate corrected QT interval dispersion; JTD: JT interval dispersion; JTcD: Heart-rate corrected JT interval dispersion; DAS28: Disease activity score in 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ms: Milliseconds; QTc BAZ: QTc calculated using Bazett formula; QTc FHS: QTc calculated using Framingham formula.

ECG abnormalities suggestive of myocardial ischemia, LV hypertrophy, or the use of common cardiovascular medications<sup>[60]</sup>. Similarly, Chauhan *et al.*<sup>[61]</sup> found a higher incidence of idiopathic QTc prolongation amongst RA patients and demonstrated that any cause QTc prolongation was significantly associated with all-cause mortality (HR = 2.99, 95%CI: 1.93-4.65) but only marginally associated with cardiovascular mortality (HR = 2.68, 95%CI: 0.84-5.6,  $P = 0.09$ ). The authors used a cut off of  $\geq 450$  ms in males and  $\geq 460$  ms in females to define QTc prolongation<sup>[61]</sup>, but interestingly, amongst the general over 55 population even a borderline increased QTc interval, defined as 451 to 470 ms in women, and 431 to 450 ms in men, was associated with a two-fold increase in the risk of SCD<sup>[53]</sup>. Following this, Lazzerini *et al.*<sup>[62]</sup> showed that treating RA patients with 3 mo of the anti-IL 6-receptor

antibody, tocilizumab, was associated with a significant reduction in the QTc interval. The fact improvement was seen in such a short time frame suggests that QTc prolongation is driven by an inflammatory process rather than subclinical coronary atherosclerosis<sup>[62]</sup>.

There is also emerging data about the role of pro and anti-inflammatory cytokines in QTc prolongation amongst patients with RA. Lazzerini *et al.*<sup>[62]</sup> recently demonstrated a strong association between QTc and circulating TNF- $\alpha$  levels, more so than CRP, although sample sizes were small. Adlan *et al.*<sup>[70]</sup> performed a cross-sectional study of 112 patients with RA examining the relationship between QTc and cross-sectional sampling of several pro and anti-inflammatory cytokines. The authors demonstrated an association between QTc prolongation and CRP, TNF- $\alpha$ , IL-1 $\beta$  and the anti-inflammatory cytokine IL-10. A surge of IL-10

often follows the release of pro-inflammatory cytokines and its release is stimulated by adrenaline<sup>[70,71]</sup>.

Sympathetic excitation has been associated with prolongation of the QTc<sup>[72]</sup>, while cholinergic stimulation with pyridostigmine shortens QTc interval in patients with CAD<sup>[73]</sup>. RA has been associated with both reduced parasympathetic tone and increased sympathetic tone, with a recent systematic review demonstrating a 60% prevalence of autonomic dysfunction amongst patients with RA<sup>[52]</sup>. The majority of studies assessed autonomic dysfunction using clinical cardiovascular tests (CCTs) or by measuring HRV parameters<sup>[52]</sup>. CCTs include blood pressure and heart rate response to orthostasis, deep breathing and Valsalva manoeuvres, with many studies using Ewing's battery of CCTs<sup>[74]</sup>. HRV analysis attempts to assess cardiac autonomic regulation through quantification of variation in sino-atrial activity with rapid variations reflecting vagal modulation and slower variations reflecting a combination of both parasympathetic and sympathetic modulation and non-autonomic factors. HRV can be measured using time domain methods or frequency domain methods. Examples of time domain measures include; mean heart rate, AVNN (Average of all the NN intervals, with "NN" used in place of "RR" to emphasize that these are normal sinus beats), and the difference between the longest and shortest NN interval<sup>[75]</sup>. More complex statistically derived time domain measures include either those, derived from direct measurements of the NN intervals, such as SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the average of NN intervals in all 5-min segments of a 24 h recording) or those derived from the differences between NN intervals such as RMSSD (square root of the mean of the squares of the differences between adjacent NN intervals) and pNN50 (percentage of differences between adjacent NN intervals that are > 50 ms)<sup>[75]</sup>. Conversely, frequency domain methods assign bands of frequency, and through fast Fourier transformation quantify the NN interval in each band<sup>[75]</sup>. The bands are typically high frequency (HF) from 0.15 to 0.4 Hz, low frequency (LF) from 0.04 to 0.15 Hz, and very low frequency from 0.0033 to 0.04 Hz. Vagal activity is the major contributor to the HF component with a combination of both sympathetic and parasympathetic activity contributing to the LF and LF/HF ratio<sup>[75]</sup>.

In the general population reduced HRV has been associated with a significantly increased risk of death post MI<sup>[76]</sup>, although as yet there are no studies demonstrating the association between autonomic dysfunction and mortality amongst RA patients. This said, there is data to show that autonomic dysfunction, namely reduced HRV is associated with prolongation of the QTc in patients with RA<sup>[59]</sup>. A study of 100 patients with chronic inflammatory arthritis (CIA) demonstrated that while CRP was independently associated with HRV, there was no association between CRP and QTc in the multivariate model, with HRV parameters and

RR interval playing a predominant role in producing differences in QTc among the subjects<sup>[59]</sup>. These findings, together with the evidence that, even after sex-adjustment, QTc was correlated with heart rate and all HRV parameters suggests that the association between CRP and QTc prolongation is most likely an indirect consequence of the autonomic dysfunction and specifically increased sympathetic tone<sup>[59]</sup>. Indeed, there is growing evidence to show that the release of pro inflammatory cytokines in diseases such as RA increases sympathetic outflow activation *via* autonomic centres in brain<sup>[10]</sup>. This represents an adaptive response which dampens immuno-inflammatory activation and inhibits the release of further cytokines *via* stimulation of  $\beta$ 2-adrenoceptors in circulating lymphocytes and monocytes<sup>[77,78]</sup>. This negative feedback loop is known as the inflammatory reflex. However, sympathetic activation does not only affect the immune system, but all the systems throughout the body, and its effects may either directly<sup>[79]</sup>, or indirectly (by prolonging QT interval parameters *via* modification in calcium and/or potassium conductance) trigger the onset of arrhythmias and SCD<sup>[10]</sup>.

## IMPACT OF DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS AND BIOLOGICS ON CARDIOVASCULAR OUTCOMES?

Disease-modifying anti-rheumatic drugs (DMARDs) are a category of otherwise unrelated drugs defined by their use in RA to slow down disease progression. Throughout this review the term DMARD will be used to refer to synthetic DMARDs such as methotrexate, whereas biologic DMARDs will be simply referred to as biologics.

Whilst currently there are no studies specifically evaluating the impact of synthetic DMARDs and biologics on the incidence of arrhythmias and SCD in RA, the European League Against Rheumatism advocate early aggressive treatment with these agents, for the purpose of reducing cardiovascular morbidity and mortality<sup>[3]</sup>. These agents are expected to exert their benefits *via* their direct effect on reducing inflammation, but also by improving joint inflammation and function they will potentially lead to increased levels of physical activity and reduce the incidence of other risk factors such as diabetes mellitus and hypertension<sup>[3]</sup> (Figure 1). Indeed, a prospective cohort study and concurrent literature review conducted by Meek *et al.*<sup>[80]</sup> showed a trend towards reducing cardiovascular case fatality since the advent of DMARDs and biologics. However, no comparison was made to a control population, to ensure that the findings were not just tagging the observed reduction in cardiovascular disease burden, in the general population.

In this section, we will explore whether the advent of DMARDs and particularly Biologics, has indeed reduced cardiovascular mortality and morbidity. We

specifically examining the impact of biologics and DMARDS on CVE is perhaps explained by the number of patients that would be required to adequately power the studies, and the duration of follow-up that would be needed to detect an effect. Some studies have examined the impact of biologics on surrogate markers of IHD such as carotid intimal thickness and brachial artery flow mediated dilatation with conflicting results<sup>[87]</sup>. A single center RCT conducted by Hsue *et al*<sup>[88]</sup> demonstrated that depletion of B-cells with rituximab in RA patients improved both macrovascular (brachial artery flow-mediated dilation) and microvascular (reactive hyperemia) endothelial function, despite modest elevation in lipids. There is also an ongoing prospective imaging study, CADERA, bolted onto the single-center VEDERA RCT (very early vs delayed etanercept in RA, NCT 02433184), which will use cardiac MRI to explore the prevalence and change of cardiovascular abnormalities in patients receiving TNF inhibitors vs standard therapy over a 12-month period<sup>[89]</sup>. The evidence for a link between inflammation and cardiovascular disease is so compelling that 2 RCTS, the Cardiovascular Inflammation Reduction Trial (CIRT) and the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), have been commenced. CIRT will investigate whether low-dose methotrexate will reduce rates of recurrent MI, stroke, and cardiovascular death among stable post MI patients with type 2 diabetes or metabolic syndrome, two conditions that are associated with an enhanced



inflammatory response (NCT01594333). CANTOS will evaluate whether interleukin-1 $\beta$  inhibition as compared to placebo can reduce rates of recurrent MI, stroke, and cardiovascular death among stable CAD patients who remain at high vascular risk due to persistent elevations of CRP (NCT01327846). In addition, tocilizumab and anakinra have been investigated as treatment for acute MIs with RCTs demonstrating an attenuation in CRP levels, CCF and cardiac remodeling following ST elevation MI<sup>[90,91]</sup>, and attenuation in CRP levels and post percutaneous intervention troponin release following non ST elevation MI<sup>[92]</sup>. There is a further ongoing trial TOCRIVA, which will assess the effects of tocilizumab on cardiovascular risk in RA patients (NCT 01752335).

The relationship between biologics and CCF is more complex and the data is conflicting. In the general population TNF- $\alpha$  levels are increased in CCF<sup>[93]</sup> and associated with severity of clinical signs and symptoms<sup>[94]</sup>. Experimental heart failure models have suggested that TNF inhibitors may improve ventricular dysfunction<sup>[95]</sup>; however, a large clinical trial assessing etanercept in the treatment of congestive heart failure showed no benefit<sup>[96]</sup>, while another one found that high-dose infliximab 10 mg/kg worsened heart failure in patients with moderate-to-severe chronic heart failure<sup>[97]</sup>. Consequently, a "black box" warning was introduced not to use these medications in patients with pre-existing heart failure<sup>[98]</sup>. The most recent data from the United States, which compared 8656 new users of synthetic DMARDs with 11587 new users of TNFi, suggested that TNFi were not associated with an increased risk of hospital admissions due to heart failure (HR = 0.85, 95%CI: 0.63 to 1.14), but identified that such a difference may well have existed prior to the introduction of the black box warning in 2002<sup>[99]</sup>. This study also noted a dose-dependent association between glucocorticoid use and heart failure. Importantly, the authors acknowledged that they were unable to adjust for potential differences in baseline disease severity between the TNFi and synthetic DMARD groups as this information was not collected<sup>[98]</sup>. The German RABBIT registry also reported similar results, with similar rates of heart failure reported in those receiving TNFi compared to those receiving combined synthetic DMARDs as well as a dose-dependent association with glucocorticoids<sup>[100]</sup>. The authors of that study suggested that the overall effect of TNFi is more beneficial than harmful, through improved control of disease activity and reduced need for glucocorticoid. Glucocorticoid use in RA patients has also been associated with a dose dependent increase in all-cause and cardiovascular mortality, at a threshold of 8 mg per day<sup>[101]</sup>. There is less data about the other biologics and CCF but a recent pilot study has shown that 12 mo of treatment with the anti-IL6 tocilizumab significantly increases LV ejection fraction and reduces LV mass index with a concomitant reduction in disease activity<sup>[102]</sup>. As aforementioned anakinra has also been associated with reduced heart

failure following ST elevation MIs<sup>[91]</sup>.

It has been suggested that by suppressing inflammation, biologics may attenuate the autonomic and electrophysiological disturbances that have been linked with SCD and arrhythmic risk amongst patients with RA. Indeed, in a small interventional study of 17 patients with active RA, 76% of which had a prolonged QTc, Lazzerini *et al*<sup>[62]</sup> demonstrated that tocilizumab was associated with significant shortening of the QTc within a 3 to 6 mo period. This was also correlated with a decrease in both CRP and TNF- $\alpha$  levels. Similarly, Senel *et al*<sup>[103]</sup> showed a reduction in both QTc interval, and inflammatory markers, amongst patients with Ankylosing spondylitis (AS), following 6 mo of treatment with infliximab. Amongst patient with CIA, infliximab therapy duration has also been shown to be inversely and independently associated with QTc duration<sup>[59]</sup>. Conversely, DI Franco *et al*<sup>[104]</sup> found no significant difference in QTc interval duration amongst CIA patients treated with TNFi and rituximab. However, the authors did not report on disease activity and thus there may have been a large proportion of patients who did not achieve adequate disease control<sup>[105]</sup>. In the Diana study, 12 wk of treatment with combination synthetic DMARDs or biologics significantly improved cardiac autonomic dysfunction ( $P < 0.05$ ) in both RA and AS patients<sup>[106]</sup>. Inflammatory markers (ESR and CRP) correlated with variables of autonomic neuropathy before and after biologic treatment, suggesting that inflammatory markers may both predict the occurrence of autonomic neuropathy and response to treatment, especially with biologics<sup>[106]</sup>. Infliximab has also been associated with acute changes in HRV consistent with a decrease in sympathetic tone and shift towards relative vagal predominance<sup>[107]</sup>. Additionally, duration of treatment was also found to be correlated to increased HRV and improved cardiac autonomic function<sup>[59]</sup>.

However, the use of biologics is not without risk, and beyond the well-recognized risks of malignancy and infection, there have been reports of cardiac arrhythmias, in some cases life threatening, particularly following the use of anti-TNF monoclonal antibodies and rituximab<sup>[105]</sup>. Case reports have described ventricular arrhythmias<sup>[108,109]</sup>, supraventricular arrhythmias<sup>[110,111]</sup>, and various degrees of heart block<sup>[112-114]</sup>, associated with the use of infliximab, although in one case, the complete heart block did in fact resolve spontaneously<sup>[112]</sup>. It is thought that biologics and in particular TNF inhibiting monoclonal antibodies may be acutely unmasking the inflammation driven myocardial instability that characterizes RA, and other inflammatory conditions<sup>[105]</sup>. They could be doing this in one of three ways; firstly by worsening LV function, secondly by reducing coronary blood flow<sup>[115]</sup>, and thirdly, a mechanism which would be exclusive to monoclonal antibodies, *via* complement-mediated cytotoxic or inflammatory damage to the myocardium<sup>[105,116]</sup>. This is supported by two interesting studies in the literature.

The first, is a case report of 42-year-old AS patient who developed ventricular tachycardia requiring defibrillation following 3 doses of infliximab<sup>[117]</sup>. Despite this, the patient was retreated with infliximab given that there was no evidence of CAD on angiography and his inflammatory markers remained high. Over 2 mo a marked reduction in ventricular arrhythmias was noted with an associated attenuation of inflammatory response. The second study, a prospective, single-blind, crossover study of 75 patients with CIA, demonstrated that during acute infliximab infusion, there was 8% incidence of new-onset ventricular tachyarrhythmia vs 2.7% with placebo (OR = 3.17, 95%CI: 0.61-16.26)<sup>[107]</sup>. Although the difference was not statistically significant, the study was likely underpowered to detect this. Interestingly, those patients that experienced new onset ventricular arrhythmia showed baseline QTc and HRV values that were significantly prolonged and depressed, respectively, as compared to the patients who did not develop ventricular arrhythmia. Translating this into clinical practice, rituximab and monoclonal TNFi should be avoided in patients with significant CV risk factors, known structural heart disease or ECG abnormalities (conduction disease, QTc prolongation and HRV depression). If these drugs are still required, careful ECG monitoring should be performed in the early phases of administration, until disease activity is adequately controlled, to detect and treat any complications<sup>[105]</sup>.

## CONCLUSION

RA is a chronic inflammatory condition, which is associated with significant cardiovascular mortality and morbidity. Data suggests that RA patients are twice as likely to experience SCD compared to the general population<sup>[8]</sup>, a figure comparable to diabetics<sup>[9]</sup>. Whilst some of this excess risk can be explained by the higher rates of heart failure and IHD, thought to be partially triggered and mediated by inflammation, direct influence of inflammatory cytokines on electrophysiological parameters has been implicated in arrhythmogenesis leading to SCD in RA. Interest is growing in examining the interplay between QTc prolongation, autonomic dysfunction and the risk of SCD. Both autonomic dysfunction and QTc prolongation have been shown to be correlated to inflammation, with the best evidence in place for CRP<sup>[10]</sup>. The advent of DMARDs and biologics has improved cardiovascular morbidity and mortality<sup>[37,82]</sup>, with novel evidence demonstrating a direct normalisation effect on repolarization parameters such as QTc<sup>[62]</sup>, as well as improvement in parameters of autonomic dysfunction<sup>[106]</sup>. Randomised controlled trials assessing the impact of DMARDs and biologics on autonomic dysfunction and repolarization parameters, such as QTc or QT dispersion, are urgently required to demonstrate the potential for reduction of SCD in this patient population.

## Key messages

Patients with RA are twice as likely to experience SCD compared to the general population; This excess risk can be partially explained by the higher rates of heart failure and IHD, thought to be partially triggered and mediated by inflammation; Direct influence of inflammatory cytokines and autonomic dysfunction on electrophysiological parameters has been implicated in arrhythmogenesis in this patient group; Biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD by controlling inflammation.

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## Vascular complications of transcatheter aortic valve replacement: A concise literature review

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### Abstract

Transcatheter aortic valve replacement (TAVR) is a relatively newer therapeutic modality which offers a promising alternative to surgical aortic valve replacement

for patients with prohibitive, high and intermediate surgical risk. The increasing trend to pursue TAVR in these patients has also led to growing awareness of the associated potential vascular complications. The significant impact of these complications on eventual clinical outcome and mortality makes prompt recognition and timely management a critical factor in TAVR patients. We hereby present a concise review with emphasis on diverse vascular complications associated with TAVR and their effective management to improve overall clinical outcomes.

**Key words:** Vascular; Transcatheter; Aortic valve; Concise; Review

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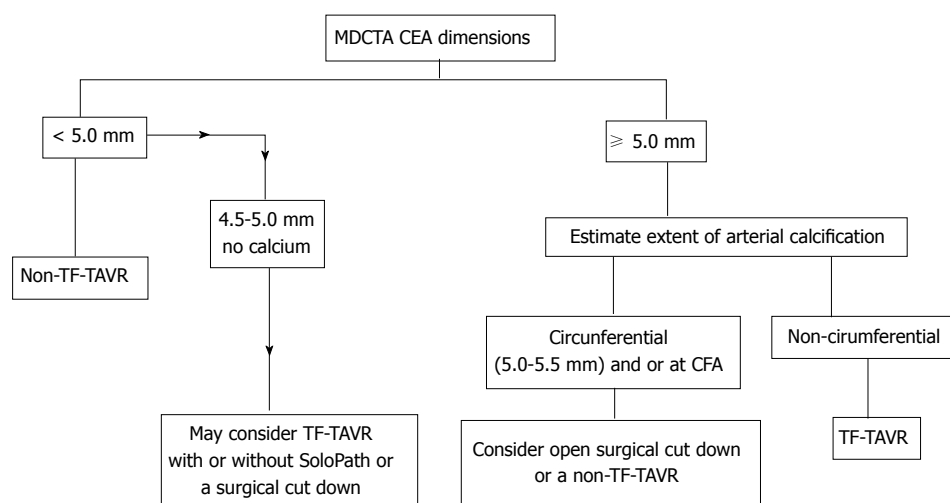
**Core tip:** Latest review of literature regarding vascular complications of transcatheter aortic valve replacement, optimum access techniques, key technical considerations and potential management strategies have been addressed.

Chaudhry MA, Sardar MR. Vascular complications of transcatheter aortic valve replacement: A concise literature review. *World J Cardiol* 2017; 9(7): 574-582 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/574.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.574>

### INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an evolving percutaneous valve replacement procedure especially with the new improved low profile sheaths. The most widely used approach for TAVR is retrograde access through a common femoral artery (CFA). Although there is a striking decrease in all-cause morta-





**Figure 1** Schematic representation of trans catheter aortic valve replacement access approach based on common femoral artery dimensions as seen on multidetector computed tomography angiography. TAVR: Transcatheter aortic valve replacement; CFA: Common femoral artery; MDCTA: Multidetector computed tomography angiography. Republished with permission of Sage from Sardar *et al.*<sup>[39]</sup>.

lity and cardiovascular outcomes between TAVR and standard therapy at 5 years in high risk patients<sup>[1]</sup>, there is a significant component of associated major vascular complications such as annular rupture, vessel dissection, major bleeding (16.7%)<sup>[2]</sup>. Analysis of the PARTNER trial showed the rate of major and minor complications as 15.3% and 11.9% respectively which was associated with a higher rate of 30 d and 1 year mortality especially among cohort B<sup>[3]</sup>. In comparison to this historic trend, newer temporal data from the STS/ACC TVT registry has shown a significant decrease in the annual rate of vascular complications to as low as 4.2%<sup>[4]</sup>. Effective management of vascular complications to improve outcomes is of paramount importance as recent studies have shown TAVR to be non-inferior to surgical aortic valve replacement in moderate risk patients<sup>[5]</sup> and that reflects a higher potential patient pool who could benefit from this procedure.

## RISK FACTORS FOR VASCULAR ACCESS

Risk factors associated with increased risk of vascular complications in TAVR include female gender, renal failure, peripheral vascular disease with significant calcification (especially when circumferential) and concomitant peripheral vascular disease. The sheath to femoral artery diameter ratio (SFAR) greater than 1.05 also compounds risk<sup>[6]</sup>. Newer delivery systems such as Edwards SAPIEN XT and S3 decrease the risk as does operator experience and skill<sup>[7]</sup>. The subclavian approach is comparable to transfemoral TAVR<sup>[8]</sup>. Most well-known complication of caval-aortic access is caval-aortic fistula but there is paucity of data regarding vascular complications as this approach is not used commonly.

## ACCESS TECHNIQUES

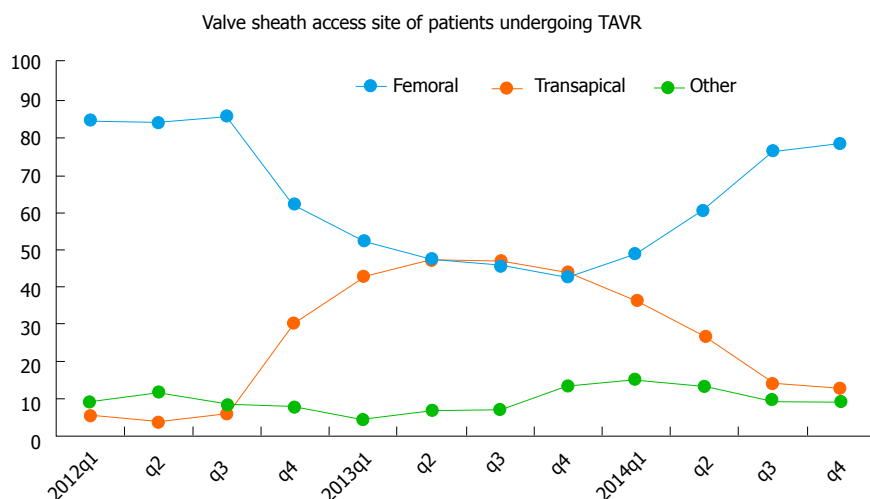
### Femoral

Pre-procedural multidetector computed tomography (MDCT) can help assess CFA calcification, determine the distance from skin to artery, and the vessel diameter, all of which can aid in selecting the optimal vessel entry site. A general schematic for femoral access based on MDCT is outlined in Figure 1. In recent times, there has been a significant surge in transfemoral approach as reflected by TVT registry results (Figure 2). In many centers, TF TAVR is performed using a micropuncture needle and 4 or 5 Fr sheath<sup>[9]</sup> but there is wide variability of approach dependent on an operator.

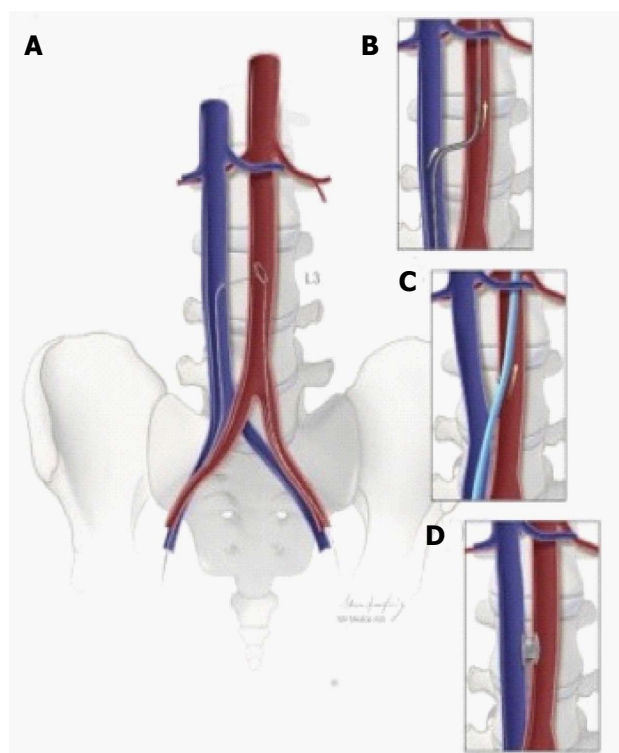
The micropuncture technique avoids potential large bore needle trauma at an unwanted CFA site (low, high or otherwise suboptimal), which may ultimately culminate in development of vascular complications. Fluoroscopy or ultrasound can be utilized to assist with identification of the appropriate site of entry, although the latter provides greater anatomic detail. A radio-opaque marker (*e.g.*, a hemostat) can be placed on the groin to mark the femoral head, facilitating guidance of needle entry under fluoroscopy. The level of sheath entry relative to the femoral head can be confirmed using fluoroscopy in an antero-posterior (AP) projection and its relation to the superficial-profunda femoral bifurcation ascertained using angiography performed from an ipsilateral oblique projection (*i.e.*, right or left anterior oblique for right- and left-sided access, respectively). B-mode ultrasound can be used as well and may result in less frequent vascular complications and higher first pass access success<sup>[10]</sup>.

Finally, needle puncture may be guided using real time digital subtraction angiography (DSA) or "road mapping" by using contralateral common femoral





**Figure 2** Transcatheter aortic valve replacement vascular access site in the transcatheter valve therapy Registry, 2012 to 2014. The changing valve sheath access site over time has resulted from multiple factors, including FDA instructions for use, and changing technology. TAVR: Transcatheter aortic valve replacement. Republished with permission of Elsevier, from Holmes DR, Nishimura RA, Holmes *et al*<sup>[4]</sup>.



**Figure 3** Schematic depiction of caval-aortic access. A: Using transfemoral venous access, a catheter directs a guidewire from the inferior vena cava toward a snare positioned in the adjacent abdominal aorta; B: The catheter is advanced over the guidewire into the aorta and used to introduce a more rigid guidewire; C: The valve introducer sheath is advanced from the vena cava into the aorta; D: After completion of transcatheter aortic valve replacement, the aorto-caval access tract is closed with a nitinol occluder. Republished with permission of Elsevier from A.B Greenbaum, *J Am Coll Cardiol* 2014; 63: 2795-2804.

access and placing a cross over sheath or catheter in the common or external iliac artery on the side to be accessed. Regardless of the method employed, after confirming appropriate CFA access, the micropuncture sheath can then be exchanged over guidewire to a

larger sheath as required.

### Subclavian

Subclavian access is an alternative option with a prerequisite vessel diameter of greater than 6 mm. Increased angulation, ectasia and calcification are all adverse risk factors. With history of coronary artery bypass grafting and a left internal mammary graft, subclavian vasculature diameter should be greater than 7 mm with no significant atherosclerotic disease and no ostial stenosis to consider it feasible for TAVR access. Surgical cut-down for proper visualization and ease of access is commonly used<sup>[11]</sup>.

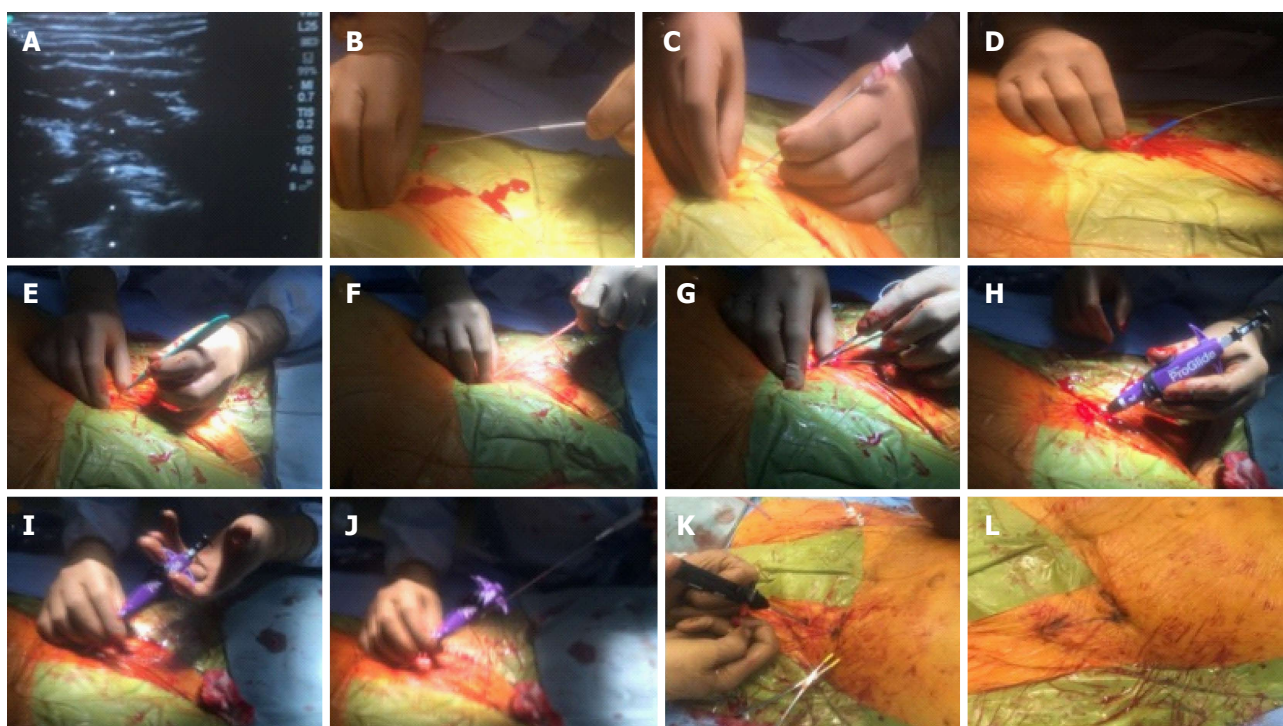
### Caval-aortic

This is an option for TAVR in patients with significant peripheral vascular disease in the femoral and iliac systems thereby limiting arterial access. The caliber and pliability of venous system provides advancement of the delivery system through the femoral vein into the inferior vena cava followed by puncture of the descending aorta and sealing the pathway with a nitinol plug on completion of the procedure<sup>[12]</sup>. A stepwise illustration is provided in Figure 3.

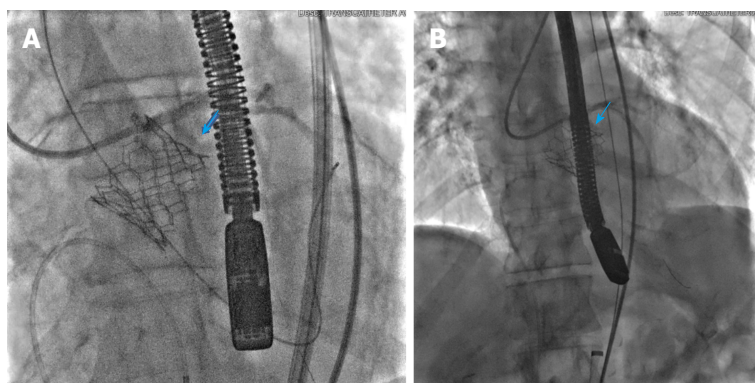
## HEMOSTASIS METHODS

Hemostasis following removal of the sheath is usually achieved with Prostar XL10F and Perclose ProGlide (Abbott Vascular Devices, Redwood City, CA, United States) in which the mechanism of action is a suture release and delivery. This method greatly decreases the incidence of access site complications<sup>[10]</sup>.

The Prostar XL and 6 Fr ProGlide are used for closure of upto 10F and 8F arteriotomies. If the devices are initially used at the time of initial access and sheath placement, hemostasis can be achieved in a more predictable and effective fashion. This is termed as the



**Figure 4** Pre-close hemostasis technique during a transcatheter aortic valve replacement procedure. A-C: A calcium-free zone is visualized using real time ultrasound and access is obtained using a micropuncture needle system; D-G: The micropuncture system is exchanged for a 180 cm 0.035 wire and the skin tract is sequentially dilated with scalpel, 7 F sheath dilator and later a forceps; H: A Proglide is advanced over the wire into the arterial lumen, and return of pulsatile blood flow confirmed; I and J: After ensuring stable Proglide position, two sequential sutures are deployed at 10 and 2 O'clock; K and L: After the removal of transcatheter aortic valve replacement sheath and guide wire, pre-close sutures are sequentially locked to ensure hemostasis.



**Figure 5** Annular rupture post transcatheter aortic valve deployment with the rupture site marked by blue arrows (A, B).

“Preclose” method and is illustrated in Figure 4. After TAVR completion, a 0.035” guidewire is always left in the artery while removing the sheath, to maintain continuous access in case an upstream perforation becomes apparent. Once sufficient hemostasis is achieved, the 0.035 wire can be removed and suture knots locked to ensure complete hemostasis. Occasionally a third Proglide or 8 Fr Angio-Seal (Abbott Vascular, Redwood City, California) can be used to adequately achieve hemostasis if required<sup>[13]</sup>.

Cross over balloon technique (CBOT) is an alternative method to achieve hemostasis. CBOT involves inflating a balloon above the access site prior to the

retrieval of TAVR sheath and closure of arteriotomy. CBOT can be performed over 0.018” or 0.035” guidewires, and the hemostasis balloon can be inflated at low pressure to ensure safe deployment of the suture-mediated closure device<sup>[14]</sup>.

## GUIDEWIRES

There are different guidewires with varying degrees of stiffness and flexibility which can be employed during the TAVR procedure. Wires used for TAVR delivery are usually 0.035” diameter and have an inner core with a tapered distal tip that is easily shapeable to

**Table 1** Traditionally used transcatheter aortic valve replacement guidewires (permission obtained)

Guidewire	Core material and coating	Wire guide diameter inch	Wire guide length (cm)	Taper length (cm)	Floppy tip length (cm)	Stiffness	Preshaped curve	Use
Amplatz Extra Stiff wire (Cook Medical Inc.)	PTFE-coated stainless steel	0.035	260	7	3	Least stiff	3 cm	TAVR device delivery Straightening of tortuous vessels Sheath insertion
Amplatz Super Stiff wire (Boston Scientific)	PTFE-Coated Stainless Steel	0.035	260	6	3	Stiffer than Extra stiff	1 and 3 cm	Straightening of tortuous vessels Sheath insertion
Lunderquist Extra Stiff wire (Cook Medical Inc.)	PTFE-Coated Stainless Steel	0.035	260 and 300	7.5	4	Stiffer than Amplatz extrastiff and superstiff	4 cm	Straightening of tortuous vessels Sheath insertion
Safari Guide wire (Boston Scientific)	LUBRIGREEN™ PTFE-Coated Stainless Steel	0.035	260 and 300			Stiffness equal to Amplatz extrastiff	Small curve - 16 cm distal grind and 1.7 inch/4.25 cm curve Large curve - 18 cm distal grind and 1.9 inch/4.90 cm curve	TAVR device delivery

TAVR: Transcatheter aortic valve replacement; PTFE: Polytetrafluoroethylene.

facilitate steerability. Length is usually in the range of 260 cm and some are coated to reduce resistance to minimize vessel trauma during catheter and device exchange in TAVR procedures. One should be wary of the fact that verbal description of guidewires does not co-relate with actual wire stiffness. Objective parameters such as “flexural modulus” co-relate well with wire stiffness and are more reliable as shown by Harrison et al in a retrospective analysis<sup>[15]</sup> rather than market terminology such as “super stiff” or “extra stiff”. If higher stiffness is required as in cases with significant vessel tortuosity, a pig tail curve is typically placed at the distal tip of the wire to prevent vascular or left ventricular trauma. Table 1 shows important characteristics of guidewires commonly used during TAVR.

## TAVR DEVICES

Balloon-expandable Edwards SAPIEN S3 and Edwards SAPIEN XT<sup>™</sup> valves (Edwards Lifesciences Inc., Irvine, CA) and the self-expanding Medtronic CoreValve<sup>®</sup> Evolut<sup>™</sup> R System valves (Medtronic, Minneapolis, MN) are United States Food and Drug Administration (FDA)-approved TAVR devices which are being used nowadays. Core Valve and Edwards Sapien S3 have a range of 23-32 mm and 20-29 mm valve size respectively with sheath size either 14 or 16 French. Currently there are two CE mark approved TAVR devices, the Lotus<sup>™</sup> valve system (Boston Scientific Corporation,) available in 23, 25 and 27 mm sizes and the Portico Valve (St. Jude Medical, Minneapolis, Minnesota), available in 27 and 29 mm sizes<sup>[16]</sup>.

## SHEATHS

The risk of vascular trauma increases with bigger sheath sizes and has shown a downward trend with the new generation TAVR delivery systems<sup>[17]</sup>.

Older generation Edwards SAPIEN and SAPIEN XT valves required up to 24 Fr and 20 Fr sheaths, respectively, while the first Medtronic CoreValve required up to a 25 Fr sheath. Newer generation valves require 14-16 Fr sheaths.

The SoloPath sheath (Terumo Medical Corporation, Irvine, CA, United States) is a balloon expandable and re-collapsible sheath, available in various internal diameters/outer diameters of 14/17, 16/19, 18/21, 19/22, 20/23 and 21/24 Fr, in working lengths of 25 and 35 cm, and balloon expandable lengths of 20 and 30 cm respectively. The sheath is inserted into the vessel in a folded state over a balloon-expandable dilator. Once the sheath is in the desired position, the dilator is inflated, the sheath expands, and later dilator is removed. Upon completion of the procedure, balloon is deflated and sheath returns to its original OD. The safety and efficacy of the 19F SoloPath sheath was investigated for TF-TAVR in a single arm study of 90 patients. When patients were dichotomized into those with a sheath to femoral artery ratio (SFAR) of  $\leq 1.05$  vs  $> 1.05$ , the 19 F Solopath sheath appeared feasible and safe even in patients with SFAR  $> 1.05$  (a traditional indicator of increased vascular risk) and there was no difference in technical or procedural success, total vascular complications, or total bleeding rates between groups<sup>[18]</sup>. The safety of the SoloPath access sheath was confirmed in a recent multicenter



**Table 2** Internal and external diameter of large percutaneous sheaths (permission obtained)

Manufacturer	Sheath	Sheath internal diameter (F)	Sheath outer diameter (mm)/ prosthesis size	Minimum vessel diameter (mm)
Edwards Lifesciences	RetroFlex 3 introducer sheath	22	8.4/23 Sapien	7.0
		24	9.2/26 Sapien	8.0
	NovaFlex introducer sheath	16	6.7/23 Sapien XT	6.0
		18	7.2/26 Sapien XT	6.5
		20	8.0/29 Sapien XT	7.0
	Expandable Sheath <sup>1</sup>	14	6.0/20	5.0
		14	6.0/23	5.5
		14	6.0/26	5.5
		16	6.7/29	6.0
Medtronic	InLine Sheath for Evolut R System <sup>1</sup>	14 F equivalent <sup>2</sup>	6.0	5.0
Gore medical	GORE® DrySeal Sheath <sup>1,3</sup>	14	5.5	5.0
		16	6.2	5.5
		18	6.8	6.0
		20	7.5	6.0
Terumo medical corporation	SoloPath sheath <sup>1,3</sup>	14 <sup>4</sup>	3.83 <sup>5</sup> /5.67 <sup>4</sup> (11.5-17F)	
		16 <sup>4</sup>	5.0 <sup>5</sup> /6.33 <sup>4</sup> (15-19F)	
		18 <sup>4</sup>	5.0 <sup>5</sup> /7.0 <sup>4</sup> (15-21F)	
		19 <sup>4</sup>	5.0 <sup>5</sup> /7.3 <sup>4</sup> (15-22F)	

<sup>1</sup>Currently used introducer or delivery sheath for TAVR. <sup>2</sup>Internal dimension is 14 Fr-equivalent systems with InLine™ Sheath. True outer diameter of the sheath is 18 Fr/6 mm. <sup>3</sup>Most commonly used sizes for TAVR. <sup>4</sup>Expanded internal and external dimensions of the sheath. <sup>5</sup>Unexpanded or folded SoloPath sheath dimension. TAVR: Transcatheter aortic valve replacement.

study of patients with  $\leq 5.0$  mm ilio-femoral access undergoing TF-TAVR using the CoreValve device<sup>[19]</sup>. A detailed list of different access sheaths used during TAVR is given in Table 2.

## ACCESS SITE INFECTION

There are variable reports of access site infection after TF-TAVR, ranging from 1.6% to 12.1% with 90% of access site infections encountered after surgical cut down with a 10% associated mortality<sup>[20]</sup>. In many practices, all patients undergoing TAVR are pretreated with broad spectrum antibiotics and the access site skin incision is closed with a topical skin adhesive. It provides a flexible microbial barrier with wound support that may prevent infection better than traditional wound dressings<sup>[21]</sup>.

## ACCESS SITE HEMATOMA

Hematomas at point of access can occur ranging from a few minutes to days following completion of TAVR procedure. Careful attention must be paid to the access site as the ideal point is the mid femoral head above the femoral bifurcation. Prolonged hospital stay as well as increased morbidity and mortality are potential associations<sup>[22]</sup>. The occurrence has continued to decrease due to enhanced center experience, operator skill and smaller delivery systems over the last few years. Manual pressure and anti-coagulation reversal is sufficient for successful management in majority of cases. In case of compressive symptoms or profound blood loss indicated by rapid drop in hemoglobin, contralateral femoral access with balloon tamponade

is usually employed. Viabahn covered stent placement (W.L. Gore and Associates, Newark, DE) has been shown to co- relate with an efficacy of 98%<sup>[23]</sup>.

## PSEUDOANEURYSMS

Pseudoaneurysm (PSA) is a contained rupture can occur with arterial puncture below the femoral bifurcation involving superficial or deep femoral arteries or the iliac system<sup>[24]</sup>. The frequency of pseudoaneurysm ranges from 2%-6%. PSA can thrombose spontaneously in upto 90% of cases at 3 wk if the size is less than 3 cm<sup>[25]</sup>. Size greater than 2 cm along with aggressive anticoagulation are potential predisposing risk factors and can lead to persistent discomfort and act as nidus of infection to increase risk of septic embolism<sup>[26]</sup>. Rupture can occur with devastating consequences with major bleeding and hypovolemic shock and diameter greater than 3 cm potentiates the possibility<sup>[27]</sup>.

Palpation of a pulsatile mass at the access site or the auscultation of a systolic bruit are suggestive of a possible PSA. For diagnostic purposes, doppler ultrasound has a 94% sensitivity and 97% specificity for PSA<sup>[28]</sup>.

Usually a 5-7 MHz frequency probe is used and the depth should be greater than 4 cm from the skin. Color Doppler shows a turbulent flow pattern in the PSA tract and pulse Doppler shows constant flow shift towards and away from the probe which is diagnostic. Ultrasound guided compression when used has a success rate of 30%-70%. Multiple attempts are mostly needed to obtain sustained compression and thrombosis with a mean time of 33 min<sup>[29,30]</sup>. Ultrasound guided thrombin injection is an effective treatment



modality with a 97% success rate. It facilitates the conversion of fibrinogen to fibrin<sup>[31]</sup>. Injections are usually given in incremental doses of 0.2-0.4 mL till no flow is observed on the pulse Doppler.

## ILEO-FEMORAL DISSECTION

Ileo-femoral dissection in transfemoral TAVR has an incidence of approximately 7% even in high volume centers. External iliac artery is the most commonly involved vessel and can occur during initial advancement of the delivery system or during sheath withdrawal.

Diagnosis can be made with careful review of DSA with either retrograde or contralateral antegrade contrast injections. Significant dissections can lead to lower limb ischemia which can be critical or subcritical depending on the spread of dissection and the vessel territory involved. This can predispose to thrombus formation and vessel occlusion or compression symptoms with blood extravasation.

Computed tomographic angiography (CTA) with distal runoff can be used to identify the focus of dissection.

Contained dissections can be managed by careful monitoring as mostly they resolve on their own with course of time. In case of extensive dissections, endovascular repair can be pursued. Ballooning alone with appropriate stent placement as needed is the preferred approach. Balloon inflation can tamponade the bleeding site and in addition maintenance stents are used for vessel patency. If the dissection is unable to be sealed with this modality, surgical repair is required. Follow up imaging with CTA as indicated can be used<sup>[32]</sup>.

## ILEO-FEMORAL RUPTURE

Ileo-femoral rupture is another feared complication of TAVR but the occurrence has decreased significantly with the use of smaller and compact delivery systems as compared to initial TAVR procedures when the frequency was roughly 4%. As long as the sheath is in place, pelvic vascular rupture is not evident but as soon as the sheath is withdrawn, the pressure seal is taken off and huge pelvic bleed can occur with rapid clinical deterioration and death<sup>[33]</sup>.

During the sheath withdrawal, the patient's clinical status should be monitored closely. Sudden hemodynamic compromise may be evident if there is a significant defect although small tears can extend and cause clinical instability within a few hours post procedure. Angiography prior to complete sheath removal is usually performed to assess for any focal dissection or to detect any extra-luminal contrast flow.

Management includes quick sheath reintroduction to seal the site of dissection while contralateral balloon delivery and inflation can be attempted. Massive fluid repletion, quick anticoagulation reversal and

covered stent placement is required although in cases of complex dissections, surgical intervention is indicated<sup>[34]</sup>.

## ARTERIAL AVULSION

In cases of extensive atheromatous and calcified vessels, vessel avulsion can rarely occur during sheath withdrawal. Urgent proximal occlusive balloon placement and prompt surgical intervention needed in this scenario<sup>[35]</sup>.

## ARTERIAL STENOSIS, THROMBOSIS AND OCCLUSION

CFA stenosis can occur following device closure of the arteriotomy site. If there is evidence of significant flow limitation, angioplasty can be done to reduce the stenosis. In cases of arterial thrombosis and occlusion, critical limb ischemia can occur and thrombectomy is needed to restore vessel patency.

## AORTIC DISSECTION

Aortic dissection is an uncommon but potentially fatal complication of TAVR procedure, Incidence has been reported in the range of 0.6%-1.9%<sup>[36]</sup>.

As the access approach varies from transfemoral and transapical to transaortic, any segment can be involved including the ascending or descending aorta. In a study of 412 patients reported by Lange *et al*<sup>[37]</sup> who were treated with transapical and transfemoral approach, annular and abdominal aortic rupture occurred in four patients. Generally, continuous transesophageal monitoring is done throughout the procedure, and Type A dissections can be diagnosed promptly. If aortic dissection is suspected post procedure, aortic angiography is pursued.

The clinical manifestation of aortic dissection may manifest at any time during or after the procedure. Symptoms vary from chest pain and abdominal pain to neurological deficits depending on the extent of involvement (mesenteric, renal, carotid arteries). Clinically, hypotension and pressure difference of greater than 20 mmHg between the arms can be suggestive. Imaging modalities such as computed tomography, magnetic resonance imaging and transesophageal echocardiography (TEE) can be used depending on availability and the complexity of the clinical scenario.

The management of aortic dissection depends on initial site of dissection, extent and vascular compromise. Strict blood pressure control with systolic less than 110 mmHg by using beta blocker with alpha blocking additive effect such as Labetalol or Carvedilol is preferred. Non-dihydropyridine calcium channel blockers can be used as well. In case of hypotension, volume repletion is done to maintain mean arterial

pressure of greater than 70 mmHg. Type A dissections should be treated with prompt surgical repair while Type B dissections are medically managed and uncommonly endovascular repair is considered<sup>[38]</sup>.

## AORTIC RUPTURE

Aortic rupture is a dreaded, rare complication with extremely poor prognosis. It has an incidence of less than 1%. Commonly the presentation is acute with rapid hemodynamic instability and circulatory shock. The rupture extends quickly along tissue planes and hemorrhagic tamponade can be seen on TEE quite frequently. Infrequently, there is a subacute clinical picture as the initial aortic tear takes time to extend and manifest clinically. The mechanisms includes trauma by the device catheter if it overshoots the guidewire or forceful attempts made to manoeuvre the catheter through vessels with steep angulation and tortuosity. It can be spotted on fluoroscopy at the time of valve deployment as shown in Figure 5. There should be an extremely low threshold of suspicion in TAVR patients with even mild hemodynamic instability as prompt intervention with open surgical or endovascular approach with covered stents is needed to stabilize or repair the ruptured focus. The overall prognosis is strikingly dismal even in skilled hands as rupture extension can take place exponentially with dramatic reduction in chances of recovery.

## CONCLUSION

TAVR has certainly evolved exponentially since its initial days. Improved device profiles, equipment design and operator expertise are major factors which have significantly improved success rates by reducing possible procedure complications. Nonetheless continuing awareness, meticulous technique, timely management and availability of even better delivery systems in the future would be the key to better clinical outcomes.

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## Peripheral interventions and antiplatelet therapy: Role in current practice

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### Abstract

Peripheral arterial disease (PAD) is a common disorder associated with a high risk of cardiovascular mortality and continues to be under-recognized. The major risk factors for PAD are similar to those for coronary and cerebrovascular disease. Management includes exercise program, pharmacologic therapy and revascularization including endovascular and surgical approach. The optimal revascularization strategy, endovascular or surgical intervention, is often debated due to the paucity of head to head randomized controlled studies. Despite significant advances in endovascular interventions resulting in increased utilization over surgical bypass, significant challenges still remain. Platelet activation and aggregation after percutaneous transluminal angioplasty of atherosclerotic arteries are important risk factors for re-occlusion/restenosis and life-threatening thrombosis following endovascular procedures. Antiplatelet agents are commonly prescribed to reduce the risk of myocardial infarction, stroke and death from cardiovascular causes in patients with PAD. Despite an abundance of data demonstrating efficacy of antiplatelet therapy in coronary artery disease and cerebrovascular disease, there is a paucity of clinical information, clinical guidelines and randomized controlled studies in the PAD population. Hence, data on antiplatelet therapy in coronary interventions is frequently extrapolated to peripheral interventions. The aim of this review article is to elucidate the current data on revascularization and



the role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

**Key words:** Peripheral arterial disease; Peripheral vascular disease; Antiplatelet therapy; Revascularization

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**Core tip:** Peripheral arterial disease (PAD) is nearly a pandemic disorder which carries a high morbidity and mortality. Treatment includes risk factor modification, revascularization whenever feasible and medical management including antiplatelet therapy being a crucial element. Despite improvements in endovascular techniques and equipment for revascularization in PAD patients, current data regarding antiplatelet therapy in this population is limited. Our objective is to consolidate the current data on role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

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## INTRODUCTION

Peripheral arterial disease (PAD) represents a major clinical problem affecting millions of people worldwide, which carries high morbidity and mortality and an increased risk of major adverse cardiovascular events including myocardial infarction (MI), stroke, premature death and impaired quality of life. The incidence of PAD is globally estimated to be between 3% and 12%<sup>[1-3]</sup>. This incidence has increased to as high as 29% in low to middle income areas, becoming one of the global problems of the 21<sup>st</sup> century<sup>[4]</sup>. Atherosclerosis in the peripheral arteries is a chronic, slowly developing disorder causing narrowing of the arteries. Depending on the degree of narrowing, clinical presentations vary from classic intermittent claudication, exercise limitations, or ischemic pain, to lower extremity ulceration or gangrene of the toes from chronic limb ischemia. Other patients found to have PAD from ankle brachial index (ABI) screening can remain asymptomatic throughout their life. Occasionally, acute events occur, frequently associated with thrombosis, embolism and/or major arterial occlusion.

Therapy for PAD includes both a pharmacologic and revascularization approach if possible. Antiplatelet therapy is the cornerstone of pharmacologic therapy in addition to risk factor reduction. The purpose of this paper is to discuss revascularization strategies and review clinical trial data for antiplatelet therapy in

patients with PAD.

## REVASCULARIZATION STRATEGY: ENDOVASCULAR THERAPY VS SURGICAL BYPASS

The optimal treatment strategy, endovascular or surgical intervention, is often debated due to the lack of head to head randomized controlled studies. Of the studies conducted, most are underpowered and lack uniform endpoint definitions making a direct comparison among studies difficult<sup>[5]</sup>.

Remarkable advancement in technology in the past decade has shifted the paradigm of revascularization strategies in PAD from an open surgical approach to percutaneous endovascular treatments including percutaneous atherectomy, percutaneous transluminal angioplasty (PTA) and stenting. Analysis conducted by Goodney *et al*<sup>[6]</sup>, provides statistical evidence based on Medicare claims between 1996 and 2006 that endovascular interventions are now performed more commonly than bypass surgery. The rate of major lower extremity amputation declined significantly more than 25% and endovascular interventions increased more than threefold [138 to 455 per 100000; relative risk (RR) = 3.30; 95%CI: 2.9-3.7], while surgery decreased by 42% (219 to 126 per 100000; RR = 0.58; 95%CI: 0.5-0.7)<sup>[6]</sup>. However, caution must be used to interpret this data as more research is warranted to determine if there is an association between lower extremity vascular procedures and improved rates of limb salvage in this population.

The BASIL trial was first published in 2005 followed by an intention-to-treat analysis published in 2010 evaluating amputation-free survival and overall survival. This was a prospective randomized controlled trial comparing the effectiveness of endovascular therapy vs open surgical approach in patients with severe limb ischemia due to infra-inguinal disease. Similar short term outcomes were found comparing both treatment modalities<sup>[7,8]</sup>. However, data also suggests that the results of angioplasty are less durable than that of surgical grafting. The primary patency rate after angioplasty is greatest for lesions in the common iliac artery and decreases distally. Additionally, the rates of patency are lower in cases with increasing lesion length, multiple and diffuse lesions, poor-quality run-off and in patients with concomitant diabetes and renal failure<sup>[9]</sup>.

The BEST-CLI trial is currently underway and designed to clarify this clinical conundrum for critical limb ischemia patients. This is a multi-center trial with a planned enrollment of 2100 patients that includes interventional cardiologists, interventional radiologists and vascular surgeons. The trial emphasizes a team based treatment approach and will compare patients eligible for both endovascular and open surgical bypass. All contemporary endovascular therapeutic modalities

**Table 1** Results of clinical trials initially designed for patients with coronary artery disease, with subgroup analysis in peripheral arterial disease

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
PEGASUS TIMI-54 subgroup analysis <sup>[40]</sup> (2016)	1143	CAD and concomitant PAD	Ticagrelor 90 mg BID + aspirin <i>vs</i> Ticagrelor 60 mg BID + aspirin <i>vs</i> Placebo + aspirin	Cardiovascular death, MI and stroke Acute limb ischemia and peripheral revascularization for ischemia	15.2% in ticagrelor (pooled group) and 19.3% in placebo. ARR 4.1% in ticagrelor (pooled group) 60 mg dose more beneficial (ARR of 5.2%) 0.46% in ticagrelor (pooled group) and 0.71% in placebo (HR 0.65; 95%CI: 0.44-0.95; <i>P</i> = 0.026)
PLATO-subgroup analysis <sup>[32]</sup> (2015)	1144	CAD and concomitant PAD	Ticagrelor <i>vs</i> clopidogrel	Cardiovascular death, MI and stroke	18% in ticagrelor group and 20.6% in clopidogrel group (HR: 0.85; 95%CI: 0.64-1.11; <i>P</i> = 0.99)
TRA 2P-TIMI 50 <sup>[35]</sup> (2012)	26449	Previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD	Vorapaxar <i>vs</i> placebo	Cardiovascular death, MI, and stroke	9.3% in vorapaxar group and 10.5% in placebo ( <i>P</i> < 0.001) Subgroup analysis in PAD patients showed no difference between groups for the primary endpoint Rate of intracranial hemorrhage (1% vorapaxar <i>vs</i> 0.5% placebo; <i>P</i> < 0.001)
CHARISMA <sup>[38]</sup> (2006)	15603	Patients with either clinically documented vascular disease or risk factors for atherothrombotic disease	Aspirin plus clopidogrel <i>vs</i> aspirin monotherapy	MI, stroke or cardiovascular death	6.8% in clopidogrel plus aspirin group and 7.3% in aspirin group ( <i>P</i> = 0.22) Subgroup analysis in PAD patients: no benefit was derived from dual antiplatelet therapy
CAPRIE <sup>[15]</sup> (1996)	19185	Recent MI, recent ischemic stroke or symptomatic PAD	Aspirin <i>vs</i> clopidogrel	MI, stroke and vascular death	RRR of 8.7% clopidogrel group ( <i>P</i> = 0.043; 95%CI: 0.3-16.5) Subgroup analysis in PAD patients: 23.8% RRR in clopidogrel over aspirin ( <i>P</i> = 0.0028; 95%CI: 8.9-36.2)

MI: Myocardial infarction; PAD: Peripheral arterial disease; ARR: Absolute risk reduction; RRR: Relative risk reduction.

and surgical bypass conduits will be compared and chosen by enrollment site and physician preference. The revascularization strategy will be selected for each case in a specialized vascular center in close cooperation with an endovascular specialist and a vascular surgeon<sup>[10]</sup>.

## ANTIPLATELET THERAPY

Platelets have a fundamental role in the development of atherothrombosis<sup>[11]</sup>. Although percutaneous revascularization therapies have evolved significantly with dramatic improvement in interventional devices and techniques, the most appropriate antiplatelet therapy regimen in PAD is understudied compared to the coronary artery disease (CAD) population. Multiple antiplatelet agents have been studied in the PAD population, including aspirin, the combination of aspirin and dipyridamole, clopidogrel, ticagrelor, cilostazol and vorapaxar. Results from randomized clinical trials in patients with CAD and subgroup analysis in the PAD population and PAD alone are summarized in Tables 1 and 2 respectively. Given the number of agents studied, there is a wide discrepancy in the management of patients with PAD. Meta-analysis conducted by the Antithrombotic Trialists Collaboration Group in 2002 evaluated 287 randomized studies, and concluded that antiplatelet therapy reduced the risk of

serious vascular events (non-fatal MI, non-fatal stroke, or vascular death) by about 23%, not just among the population with unstable angina, acute MI or stroke but also among patients with CAD, PAD, and those at high risk of embolism<sup>[12]</sup>.

## ASPIRIN

Aspirin is a commonly used antiplatelet agent, which irreversibly inhibits the cyclooxygenase-1 and 2 enzymes resulting in decreased formation of thromboxane A<sub>2</sub>, thus inhibiting platelet aggregation. However, compelling evidence to support a reduction in cardiovascular events in the setting of PAD is lacking<sup>[12]</sup>. In a meta-analysis published by Berger *et al.*<sup>[13]</sup> in 2009, 18 trials comprising 5269 participants with PAD were evaluated. Cardiovascular events occurred at a rate of 8.9% (251/2823 subjects) in the aspirin or aspirin plus dipyridamole group and 11% (269/2446 subjects) in the control group (95%CI: 0.76-1.04). This finding was a 12% relative risk reduction in non-fatal MI, non-fatal stroke and cardiovascular death with aspirin, but it failed to reach statistical difference<sup>[13]</sup>. Despite these results, aspirin (dose 75-325 mg) is given a class I recommendation in the 2016 AHA/ACC PAD guidelines for management of symptomatic patients largely due to benefit of aspirin in other vascular diseases<sup>[3,14]</sup>.

**Table 2** Results of clinical trials designed for patients with peripheral arterial disease

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
COMPASS <sup>[44,45]</sup> (2017)	27402	Peripheral arterial disease or coronary artery disease	Rivaroxaban plus aspirin or rivaroxaban alone <i>vs</i> aspirin alone	Myocardial infarction, stroke, CV death and the time from randomization to the first occurrence of major bleeding	Preliminary results: Trial stopped prematurely. One of rivaroxaban arms proved to be superior to aspirin alone No disclosed information on the primary bleeding endpoint or the regimen that showed superiority to aspirin alone
EUCLID <sup>[41]</sup> (2016)	13885	PAD (ABI $\leq$ 0.80 or prior (> 30 d) revascularization of the lower extremities)	Ticagrelor <i>vs</i> clopidogrel	CV death, MI, or ischemic stroke	10.8% in ticagrelor group <i>vs</i> 10.6% in clopidogrel group ( $P = 0.65$ )
MIRROR <sup>[39]</sup> (2012)	80	PAD treated with endovascular therapy	Dual antiplatelet therapy (aspirin plus clopidogrel) <i>vs</i> aspirin monotherapy	Local concentrations of platelet activation markers $\beta$ -thromboglobulin and CD40L	Reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group
Berger <i>et al</i> <sup>[13]</sup> (Meta-analysis-2009)	5269	PAD (patients with claudication, those undergoing percutaneous intervention or bypass surgery, and asymptomatic patients with an ABI of 0.99 or less)	Aspirin or combination of aspirin plus dipyridamole <i>vs</i> placebo	Composite end point of non-fatal MI, nonfatal stroke, and CV death	8.9% in aspirin or combination of aspirin and dipyridamole, 11% in placebo (95%CI: 0.76-1.04)
WAVE <sup>[43]</sup> (2007)	2161	PAD (atherosclerosis of the arteries of lower extremities, carotid arteries or subclavian arteries)	Antiplatelet agent plus oral anticoagulant <i>vs</i> antiplatelet therapy in patients with PAD	CV death, MI and stroke	12.2% in combination therapy group and 13.3% in antiplatelet therapy alone (95%CI: 0.73 to 1.16; $P = 0.48$ )
Thompson <i>et al</i> <sup>[29]</sup> (Meta-analysis-2002)	2702	PAD (stable, moderate to severe claudication)	Cilostazol <i>vs</i> placebo	MWD, pain free walking distance	MWD: 44% and 50% (cilostazol 50 mg and 100 mg respectively) and 21.4% in placebo ( $P < 0.05$ ) Pain-free walking distance: 60% and 67% (cilostazol 50 and 100 mg respectively) and 40% in placebo group ( $P < 0.05$ )
BOA <sup>[42]</sup> (2000)	2690	Patients undergone infra-inguinal bypass surgery	Warfarin <i>vs</i> aspirin	Graft occlusion	No observed difference in warfarin compared to aspirin (HR = 0.95; 95%CI: 0.82-1.11)

ABI: Ankle brachial index; CV: Cardiovascular; HR: Hazard ratio; MI: Myocardial infarction; MWD: Mean walking distance.

## CLOPIDOGREL

Clopidogrel is a thienopyridine derivative which inhibits platelet activation by adenosine diphosphate (ADP). There is data to support the effectiveness of clopidogrel as monotherapy in PAD. The first trial to establish this benefit was the CAPRIE trial, a randomized, blinded trial which compared the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in patients with high risk of ischemic events. It included 19185 subjects (recent MI, recent ischemic stroke or symptomatic PAD), followed over 1-3 years with mean follow up of 1.9 years. There was a statistically significant 8.7% relative risk reduction ( $P = 0.043$ ; 95%CI: 0.3-16.5) in the composite endpoint of MI, stroke and vascular death in the clopidogrel group. In a subgroup analysis of the PAD population from the CAPRIE trial, the average event rate per year was 3.71% in the clopidogrel arm compared to 4.86% in the

aspirin arm, resulting in a 23.8% relative risk reduction ( $P = 0.0028$ ; 95%CI: 8.9-36.2)<sup>[15]</sup>. This outcome provides support for the inclusion of clopidogrel as a class I recommended antiplatelet agent in the 2016 AHA/ACC guidelines for the management of PAD<sup>[3]</sup>.

We are currently in an era where individualized antiplatelet therapy is becoming an important concept due to the fact that significant major adverse cardiovascular events (MACE) still occur despite clopidogrel use<sup>[16]</sup>. It is possible that clopidogrel resistance due to poor metabolism may contribute to this problem<sup>[17,18]</sup>. Clopidogrel resistance has been demonstrated in populations of patients also identified to have risk factors for PAD, including diabetics<sup>[19]</sup>, smokers<sup>[20]</sup>, and chronic kidney disease patients<sup>[21]</sup>. Doubling the dose of clopidogrel in these patients has proved ineffective<sup>[22]</sup>. In these cases, a more potent P2Y<sub>12</sub> inhibitor such as prasugrel or ticagrelor should be considered as these agents have enhanced platelet inhibition<sup>[23,24]</sup>. This

concept has been validated by Spiliopoulos *et al.*<sup>[25]</sup>, who measured platelet reactivity after switching from clopidogrel to ticagrelor in clopidogrel resistant patients and found a significant response in platelet inhibition.

## DIPYRIDAMOLE AND ASPIRIN

The role of dipyridamole, an inhibitor of platelet adenosine uptake, in the management of PAD is debatable. Numerous small studies have shown benefit of combining dipyridamole and aspirin compared to aspirin alone<sup>[26,27]</sup>. The ESPRIT trial published in 2006 was a large randomized controlled trial which compared the efficacy of aspirin and dipyridamole combination therapy against aspirin alone to prevent vascular events within six months after ischemic stroke or TIA. The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding, which occurred at a rate of 13% in the aspirin and dipyridamole group and 16% aspirin alone group [hazard ratio (HR) = 0.80, 95%CI: 0.66-0.98; absolute risk reduction 1.0% per year, 95%CI: 0.1-1.8]<sup>[28]</sup>. However, it is uncertain if dipyridamole monotherapy would be superior to aspirin since there is no data available. Additionally, this study was not conducted in the PAD population.

## CILOSTAZOL

Cilostazol, a unique antiplatelet agent, is a phosphodiesterase III inhibitor which reversibly inhibits platelet aggregation and also possesses vasodilatory and antiproliferative properties. It has been widely studied in PAD. A meta-analysis of 8 randomized trials including 2702 PAD subjects with claudication found improvement in maximum and pain-free treadmill walking distance with cilostazol. The mean walking distance of patients taking cilostazol 50 and 100 mg twice daily increased by 44% and 50%, respectively compared to 21.4% in placebo ( $P < 0.05$ ). The pain-free walking distance increased by 60% and 67% in the cilostazol 50 and 100 mg twice daily groups respectively, compared to 40% in the placebo group ( $P < 0.05$ )<sup>[29]</sup>. Hence cilostazol has class IA recommendation to improve symptoms and walking distance in patients with claudication<sup>[3]</sup>. There are some available studies that support an additional value of cilostazol in reducing restenosis and repeat revascularization following endovascular therapy, although these studies are very small and thus hypothesis generating<sup>[30,31]</sup>.

## TICAGRELOR

Ticagrelor is a cyclopentyltriazolopyrimidine which reversibly binds to the platelet ADP P2Y<sub>12</sub> receptor, unlike the thienopyridines. Ticagrelor is metabolized by Cytochrome P450 3A4/5. Its metabolite AR-C124910XX is equally active and potent, reversibly interacting with the platelet P2Y<sub>12</sub> ADP receptor, resulting in the

inhibition of platelet aggregation. Ticagrelor has been reported to have a faster onset of action compared to clopidogrel and, like prasugrel, results in greater platelet inhibition than clopidogrel.

The PLATO trial established the benefit of ticagrelor over clopidogrel in the ACS population. In this study, 18624 ACS patients with or without ST-segment elevation were randomized to receive ticagrelor (180 mg loading dose, then 90 mg twice daily) or clopidogrel (300-600 mg loading dose, then 75 mg daily). All patients received low dose aspirin (75-100 mg daily), although 325 mg was permitted for 6 mo following PCI with stenting. There was a significant reduction in the rate of death from vascular causes, MI, or stroke with ticagrelor compared to clopidogrel (9.8% vs 11.7%,  $P < 0.001$ ), although the rate of non-CABG related major bleeding was higher (4.5% vs 3.8%,  $P = 0.03$ )<sup>[23]</sup>. An analysis of the PLATO population ( $n = 1144$ ) with concomitant PAD, found similar results to the overall trial although it did not reach statistical significance. It also showed a significantly higher rate of the primary endpoint compared to patients without PAD<sup>[32]</sup>.

The recently published EUCLID trial is a direct comparison of ticagrelor and clopidogrel in the PAD population. This is a large, multicenter, randomized, parallel blinded study that enrolled 13885 patients 50 years or older with PAD defined as ABI  $\leq 0.80$  or prior ( $> 30$  d) revascularization of the lower extremities. Patients were randomized to ticagrelor 90 mg twice daily ( $n = 6930$ ) or clopidogrel 75 mg daily ( $n = 6955$ ) and followed for 30 mo. The primary outcome of the study was the incidence of cardiovascular death, MI, or ischemic stroke, which occurred at a rate of 10.8% of the ticagrelor group and 10.6% of the clopidogrel group ( $P = 0.65$ ). There was also no noted difference in secondary outcomes including acute limb ischemia and major bleeding between the two groups. Not surprisingly, there was a higher rate of medication discontinuation in the ticagrelor group due to dyspnea. In summary, among patients with symptomatic PAD, ticagrelor was not superior to clopidogrel in preventing MACE<sup>[33]</sup>.

The THEMIS Study (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) is another ongoing trial which is evaluating the efficacy of ticagrelor vs placebo, in addition to standard care including aspirin, for the long-term prevention of major vascular events in patients with type 2 diabetes and coronary atherosclerosis<sup>[34]</sup>.

## VORAPAXAR

Vorapaxar is a protease activator receptor-1 (PAR-1) antagonist, inhibiting the interaction of thrombin with the PAR-1 receptor, thus inhibiting platelet aggregation. The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic events-Thrombolysis in Myocardial Infarction 50 (TRA



2P-TIMI 50) trial published was a double blinded placebo controlled trial which evaluated vorapaxar for the secondary prevention of atherothrombosis. It included 26449 subjects with a previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD, randomized to either vorapaxar 2.5 mg daily or placebo. Concomitant antiplatelet therapy was permitted. The primary endpoint included a composite of cardiovascular death, MI and stroke. Results revealed that the composite endpoint occurred in 9.3% of patients receiving vorapaxar vs 10.5% of patients receiving placebo (HR = 0.87; 95%CI: 0.80-0.94;  $P < 0.001$ ). Subgroup analysis in the PAD population showed no difference in the primary endpoint, however the vorapaxar group showed a significant reduction in limb ischemic events (vorapaxar 2.3% vs placebo 3.9%; HR = 0.58; 95%CI: 0.39-0.86;  $P = 0.006$ ) and the need for peripheral artery revascularization (vorapaxar 18.4% vs placebo 22.2%; HR = 0.84; 95%CI: 0.73-0.97;  $P = 0.017$ ). However, the clinical benefit offered by vorapaxar was offset by a significant increase in the rate of intracranial hemorrhage (vorapaxar 1% vs placebo 0.5%,  $P < 0.001$ )<sup>[35]</sup>.

## DUAL VS MONO ANTIPLATELET THERAPY

Data behind optimal antiplatelet therapy following peripheral endovascular treatment is limited. A recent meta-analysis reviewed dual vs mono antiplatelet therapy trials after endovascular therapy in coronary, carotid and peripheral vascular territories. The authors did not find conclusive data proving superiority of dual antiplatelet therapy over monotherapy in peripheral vascular interventions, however they did note the paucity of data in this regard<sup>[36]</sup>.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial compared the effect of combination aspirin and clopidogrel vs aspirin monotherapy in patients with either clinically documented vascular disease or risk factors for atherothrombotic disease. It included 15603 patients randomized to either clopidogrel (75 mg/d) plus low dose aspirin (75-162 mg) or placebo plus low dose aspirin for a mean follow up of 28 mo. Dual antiplatelet therapy did not significantly reduce the rate of MI, stroke or cardiovascular death (6.8% in clopidogrel plus aspirin group and 7.3% in aspirin monotherapy group,  $P = 0.22$ )<sup>[37]</sup>. In a subgroup analysis of patients with symptomatic PAD, no benefit was derived from dual antiplatelet therapy<sup>[38]</sup>.

The MIRROR study was a randomized double blinded trial, enrolling only 80 patients, which assessed the influence of dual antiplatelet therapy with aspirin and clopidogrel vs aspirin alone on local platelet activation in patients with PAD treated with endovascular therapy. Primary endpoints were local concentrations of platelet activation markers  $\beta$ -throm-

boglobulin and CD40L and the rate of clopidogrel resistance. Secondary endpoints included the clinical development of target lesion revascularization (TLR), stenosis, ABI, adverse events and days spent in hospital because of TLR, 6 mo after the intervention. The duration of therapy was 6 mo post intervention and results showed reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group. The median peri-interventional concentration of  $\beta$ -TG was 224.5 vs 365.5 ( $P = 0.03$ ) in the clopidogrel and placebo group respectively. The concentration of CD40L was 127 in the clopidogrel group and 206.5 in the placebo group ( $P = 0.05$ )<sup>[39]</sup>.

Finally, the combination of ticagrelor and aspirin was studied against aspirin alone in the PEGASUS-TIMI 54 trial to evaluate the benefit of prolonged treatment with dual antiplatelet therapy. A total of 21162 patients with a history of myocardial infarction 1 to 3 years prior, were randomized to receive placebo or two different regimens of ticagrelor, 60 mg twice daily or 90 mg twice daily. All patients were recommended to take aspirin, with 97% taking aspirin 75-100 mg daily. The trial continued for a median of 33 mo with a primary composite endpoint of cardiovascular death, MI or stroke. The rate of the primary endpoint was 9.04% in the placebo (aspirin only) arm, 7.77% in the ticagrelor 60 mg arm and 7.85% in the ticagrelor 90 mg arm ( $P = 0.004$  ticagrelor 60 mg vs placebo;  $P = 0.008$  ticagrelor 90 mg vs placebo). This benefit was counterbalanced by a significant increase in TIMI major bleeding with both ticagrelor groups compared to placebo<sup>[40]</sup>.

The symptomatic PAD population from this trial included 1143 patients and was separately analyzed. As expected, the PAD population had a higher rate of major cardiovascular events compared to the population without PAD (19.3% vs 8.4%,  $P < 0.001$ ). Both ticagrelor groups had a lower incidence of the primary endpoint compared to placebo, but only the 60 mg arm had a statistically significant reduction. There was no difference in the rates of major bleeding between the three groups, although the numbers of patients in each group were small<sup>[41]</sup>.

## ROLE OF ANTICOAGULANT THERAPY

### Vitamin K antagonists

There is limited information describing the role of oral anticoagulation, with or without antiplatelet therapy, in patients with PAD. Warfarin and acenocoumarol, both vitamin K antagonists, have been studied in a few PAD population based studies. The Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial evaluated anticoagulation with warfarin (INR goal 3.0-4.5) compared to aspirin 80 mg daily in 2690 patients undergoing infra-inguinal bypass surgery. There was no observed difference in the patency rates with warfarin

compared to aspirin, respectively (HR = 0.95; 95%CI: 0.82-1.11). Subgroup analysis revealed that patients with vein grafts benefited from lower rates of graft occlusion (HR = 0.69; 95%CI: 0.54-0.88) in the warfarin group. However, patients with prosthetic grafts experienced higher rates of graft occlusion on warfarin (HR = 1.26; 95%CI: 0.82-1.11). As predicted, the warfarin population experienced an increased number of major bleeding episodes compared to aspirin (HR = 1.96; 95%CI: 1.42-2.71). The BOA trial reiterated that only selected patients with PAD stand to benefit from chronic warfarin therapy, particularly patients undergoing lower extremity bypass with vein grafts<sup>[42]</sup>.

The WAVE trial compared the efficacy and safety of combination therapy with an antiplatelet agent (aspirin 81-325 mg, ticlopidine or clopidogrel) and a vitamin K antagonist (warfarin or acenocoumarol) (target INR, 2.0 to 3.0) to antiplatelet therapy (aspirin, ticlopidine or clopidogrel) alone in patients with PAD. Results showed that the use of combination therapy did not prevent major cardiovascular complications to a greater extent than antiplatelet therapy alone (combination therapy group 12.2% and antiplatelet therapy alone 13.3%; 95%CI: 0.73-1.16;  $P = 0.48$ ). Instead, combination therapy was associated with a significantly higher incidence of life-threatening bleeding (4.0% vs 1.2%; 95%CI: 1.84-6.35;  $P < 0.001$ ) and moderate bleeding (2.9% vs 1.0%; 95%CI: 1.43-5.58;  $P = 0.002$ )<sup>[43]</sup>. Due to lack of evidence to support any benefit of the addition of warfarin to antiplatelet therapy in the reduction of thrombotic events in patients with PAD, oral anticoagulant therapy is highlighted as a class III (no benefit and possible harm) recommendation in the most recent AHA/ACC guidelines<sup>[3]</sup>.

## DIRECT ACTING ORAL ANTICOAGULANT AGENTS

Studies are currently ongoing to investigate the potential role of direct acting oral anticoagulant agents (DOAC) (dabigatran, rivaroxaban, apixaban and edoxaban) therapy in the PAD population. Apixaban, edoxaban and rivaroxaban are all factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. Preliminary results from the Cardiovascular Outcomes for People using Anticoagulation Strategies trial have recently been released, following early termination due to clinical benefit. In this study, 27402 patients with documented atherosclerosis (coronary and/or peripheral) were randomized to either 2.5 mg of rivaroxaban twice-daily plus aspirin 100 mg daily, 5 mg rivaroxaban twice-daily monotherapy or aspirin 100 mg once daily monotherapy. Primary endpoints were defined as the time from randomization to the first occurrence of either myocardial infarction, stroke or cardiovascular death and the time from randomization to the first occurrence of major bleeding. The primary efficacy outcome data was not released, but the

company stated that the trial reached its prespecified criteria for superiority in at least one of the rivaroxaban-based arms compared to aspirin alone. Bleeding information was not disclosed, although the company release mentioned "confirmation of the existing safety profile"<sup>[44,45]</sup>. In a similar trial, edoxaban, a once-daily factor Xa inhibitor is being evaluated in a randomized multicenter study in patients with PAD to assess the efficacy of its addition to aspirin compared to a clopidogrel plus aspirin regimen in preventing stenosis or occlusion in patients undergoing femoro-popliteal endovascular intervention<sup>[46]</sup>.

## ANTIPLATELET THERAPY AND PATENCY POST PERIPHERAL ENDOVASCULAR TREATMENT

Restenosis after percutaneous transluminal angioplasty is a major limitation for favorable outcomes, and is influenced by a number of factors such as vascular inflammation, platelet activation and aggregation. Data on post endovascular intervention duration of treatment with antiplatelet therapy is insufficient. There is high rate of re-occlusion and target lesion stenosis post angioplasty. Patency rate after PTA is impacted by variables; such as length of diseased segments, severity of the disease in run-off arteries, the number of lesions treated and presence of cardiovascular risk factors<sup>[1,47]</sup>.

The ideal antiplatelet regimen and appropriate duration of treatment has not been well validated in clinical trials. The combination of aspirin and dipyridamole trended toward a superior impact on patency after femoro-popliteal angioplasty compared with vitamin K antagonists at 3, 6, and 12 mo. Aspirin 50 to 300 mg, with or without dipyridamole, given before femoro-popliteal endovascular treatment, reduced the incidence of re-occlusion at 6 and 12 mo without any safety concerns when compared with no therapy or vitamin K antagonists<sup>[48]</sup>. The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization study which was designed to assess the efficacy and safety of this regimen after femoro-popliteal PTA was stopped prematurely because of insufficient randomization numbers. Off-label use of dual antiplatelet therapy in many patients led to its failure. The combination of clopidogrel and aspirin showed higher inhibition of platelets before and after angioplasty in patients undergoing endovascular intervention for claudication<sup>[49]</sup>. As mentioned previously, in the MIRROR study, treatment with clopidogrel and aspirin reduced target lesion revascularization improving the patency of treated lesions and decrease the need for revascularization<sup>[39]</sup>.

Lower extremity bypass is another important treatment for patients with symptomatic PAD when less-invasive endovascular procedures are not an

**Table 3** Current available guidelines addressing antiplatelet therapy for peripheral arterial disease

Class of recommendation	Guidelines
Class Ia	Aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg/d is recommended to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD
Class IIa	Antiplatelet therapy is reasonable to manage asymptomatic individuals with an ABI less than or equal to 0.90 to reduce the risk of MI, stroke, or vascular death
Class IIb	Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization

PAD: Peripheral arterial disease; MI: Myocardial infarction.

option because of anatomic or technical considerations. Graft failure is related to multiple factors including type of graft material, site of anastomosis, rate of stenosis, type of antiplatelet used post procedure and duration of medical treatment post intervention. Prosthetic grafts with anastomosis to the tibial arteries seem to have highest rate of failures. Most grafts fail in the first two years, mainly attributed to graft stenosis<sup>[50]</sup>.

Antiplatelet therapy with aspirin improves grafts patency and limb salvage. Patients receiving a prosthetic graft were more likely to benefit from administration of antiplatelet agents than those treated with a venous graft<sup>[51]</sup>. Risk of graft occlusion while on single antiplatelet therapy; typically aspirin, still remains high. Incidence reported to be 15% per year when a vein is used and 20% with synthetic material (polytetrafluoroethylene) rising to 45% and 75%, respectively, for below-knee grafts<sup>[52,53]</sup>. In the CASPAR trial, combination of aspirin and clopidogrel showed statistically significant decrease in prosthetic graft failure with decreasing rate of occlusion and amputation to levels similar to those seen with venous grafts<sup>[54]</sup>.

compared to those seen in the coronary realm. This translates to more extensive endothelial damage and subsequent re-endothelialization which would make longer duration of dual antiplatelet therapy appear intuitive.

### Current guidelines

The recently updated AHA/ACC guidelines for the management of patients with PAD, recommend either aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg per day as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD (class Ia). A Class IIa recommendation is given for considering antiplatelet therapy to manage asymptomatic individuals with an ABI less than or equal to 0.90. Dual antiplatelet therapy with aspirin and clopidogrel may be reasonable after lower extremity revascularization (class IIb), due to the lack of well designed, large clinical trials<sup>[3]</sup>. A summary of the current AHA/ACC Guideline recommendations for antiplatelet therapy in PAD is provided in Table 3.

## DISCUSSION

### Current practice

Dual antiplatelet therapy is often used in patients undergoing infra-inguinal angioplasty and stenting as mentioned in a survey by Allemang *et al.*<sup>[55]</sup> from the vascular surgery community itself, which revealed that the most common antiplatelet therapy after lower extremity endo-luminal therapy was a combination of aspirin and clopidogrel. Duration of therapy also varied, with 1 to 3 mo as the most common time frame. Therapy use increased with distal endovascular treatment and with the placement of stents and there was no consensus over the duration of therapy<sup>[55]</sup>. However, there is no robust data to support such practice. Rationale for shorter duration of antiplatelet therapy post endovascular interventions in patients with PAD is primarily drawn from the fact that there is endothelial damage from balloon angioplasty and stenting is generally reserved as a last resort for treating flow limiting localized complications. However, in the current era, peripheral vascular intervention invariably involves atherectomy and significantly longer length of lesions

## CONCLUSION

There have been significant advances in open surgical and endovascular modalities for the treatment of peripheral vascular disease. Long term patency rates for either modality continue to improve, however, randomized controlled trial data comparing the two options head to head are lacking. There appears to be a consensus emerging that endovascular therapy when feasible should be attempted first, although robust randomized data is still needed to support this approach. With contemporary atherectomy techniques, drug coated balloons and stents, a bigger armamentarium is available for immediate and long term success of endovascular therapy. Similarly there is lack of data regarding post intervention medical therapy. Although dual antiplatelet therapy with aspirin and clopidogrel is commonly used, the duration of such therapy is highly variable without a strong recommendation in practice guidelines. Practice patterns for dual antiplatelet therapy are influenced and extrapolated from data available for PCI. It is apparent that there is paucity of clinical trial data for the treatment of peripheral vascular disease

and subsequent care. Additional data is warranted from large scale multicenter randomized controlled trials and observational studies to assess the optimal medical treatment and duration of medical therapy across the spectrum of PAD.

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## Is Entresto good for the brain?

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### Abstract

The main stay pharmacotherapy for heart failure (HF) is targeted towards rennin-angiotensin-aldosterone (RAAS) and neprilysin pathways (NP). Both therapeutic strategies decreases morbidity and mortality but also

carry considerable adverse effects. This review of the literature highlights the new generation of HF drug, sacubitril-valsartan (SV), trade name Entresto (researched as LCZ696, Novartis) which simultaneously blocks RAAS and NP. This dual action of angiotensin receptors blocker and neprilysin inhibitor (NPI) has improved HF prognosis and it is an evolution in the management of HF. Although the initial follow-up of patients treated with SV has yielded promising results, there are concerns regarding potential side effects especially an increase in the risk of Alzheimer's disease (AD) and young onset of AD. NPI interferes with the breakdown and clearing of beta-amyloid peptides, the plaques seen in AD, raising concern for AD in SV patients. On the other hand, hypertension and cardiovascular diseases are established risk factors for AD which can be decreased by SV therapy. It is therefore essential that SV treated patients are followed up over an extended period of time to detect any adverse cognitive changes.

**Key words:** Heart failure; Sacubitril-valsartan; Entresto; LCZ696; Neprilysin inhibitor; Alzheimer's disease

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**Core tip:** We are discussing an innovative and exciting new treatment for heart failure (HF). This advance in pharmacotherapy has shown promising results and is rapidly incorporating into standard medical therapy for HF. There is, however, a theoretical concern for cognitive dysfunction and early onset Alzheimer's disease particularly in the young. This review informs clinicians of the mechanism and potential for cognitive dysfunction, thereby increasing awareness and promoting informed prescribing.

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## INTRODUCTION

Heart failure (HF) is typified by the reduced ability of the heart to deliver an adequate supply of blood and oxygen to the tissues. Its causes are numerous including ischemic heart disease, diabetes, hypertension, cigarette smoking, obesity and valvular heart disease<sup>[1]</sup>. Over 5 million individuals worldwide suffer from HF and its incidence is rising with 550000 new diagnoses annually<sup>[1,2]</sup>. With a steadily aging population, HF incidence is projected to increase to 46% by the year 2030<sup>[1,2]</sup>. HF is associated with increased morbidity, mortality and cost<sup>[1,3]</sup>.

HF occurring due to depressed left ventricular function [ejection fraction (EF)  $\leq$  40%] is known as HF with reduced EF (HFrEF)<sup>[4]</sup>. Pharmacological intervention for HF largely depended on angiotensin inhibitors such as angiotensin receptor blockers (ARBs) and angiotensin converter enzyme inhibitors (ACEi). Recently, a new strategy using a Neprilysin inhibition (NIs) and recombinant natriuretic peptides was proven as a therapeutic option to target HF pathophysiology<sup>[5]</sup>. The new generation of HF pharmacotherapy entails the simultaneous inhibition of both the angiotensin and Neprilysin pathways, the latest version of which is Entresto® - the combination of sacubitril and valsartan (SV) (researched as LCZ696)<sup>[6,7]</sup>. In this concise review, we highlight the mechanisms of SV activity, the results of the successful clinical trial and the potential adverse effects, highlighting those on cognitive function.

## METHODS

The search for the relevant articles was conducted on Medline. The following terms "Entresto", "neprilysin inhibitors", "angiotensin inhibitors", "dementia" and "Alzheimer's Disease" "cognitive impairment" were searched in different combinations. The search was limited to articles in English language but no search filters were used for timeline and subjects.

## INCLUSION CRITERIA

Articles that met our following inclusion criteria were included in this review: (1) discussed pathophysiology of HF and target pharmacotherapy mechanism; (2) discussed pathophysiology of development of AD; (3) ongoing trials of Entresto; (4) reported link between neprilysin inhibitors and development of AD; and (5) articles that were published full and in English language.

## PATHOPHYSIOLOGY OF HF

The pathophysiology of HFrEF results mainly from the activation of the renin-angiotensin-aldosterone (RAAS) neuro-hormonal compensatory mechanism. Although the peripheral vasoconstriction initiated by the RAAS mechanism maintains blood pressure and cardiac output for a short time, sustained activation of

RAAS leads to ventricular hypertrophy, hypertension and angioedema, ultimately worsening myocardial dysfunction<sup>[8,9]</sup>. A second compensatory mechanism, the natriuretic peptide (NP) system, counteracts the vasoconstrictive and sodium/water retentive effects of the RAAS system<sup>[10]</sup>.

## GOALS OF PHARMACOTHERAPY

The initial HF pharmacotherapy targeted the RAAS circuit using ARBs<sup>[11]</sup>, ACEi<sup>[12]</sup>, beta-blockers<sup>[13]</sup>, diuretics<sup>[14]</sup> and aldosterone inhibitors<sup>[15]</sup>. All of these drugs have proven to be effective in lowering the morbidity and mortality in HFrEF. The NP system consists of four related peptides (Atrial, Brain, C-Type, and Dendroaspis NP) and a membrane bound peptidase called Neprilysin that degrades these vasoactive peptides<sup>[16]</sup>. NP system targeting drugs have included a recombinant form of BNP (Nesiritide)<sup>[17]</sup> as well as NIs, *e.g.*, candoxatril, recedodotril, *etc*<sup>[18,19]</sup>. HF pharmacotherapy targeting the NP system and the respective clinical trials are summarized in Table 1<sup>[20-32]</sup>. Although strategies blocking either of these two pathways have reduced mortality and morbidity in HF<sup>[12,28,32]</sup>, the prognosis still remains poor due to long term ineffectiveness of the drugs as well as adverse physiological effects<sup>[5]</sup>.

The newest strategy in HFrEF pharmaco-intervention is the combination of ARB and NI (ARNI) that causes a dual inhibition of the RAAS pathway and Neprilysin: The prototype drug was LCZ696<sup>[6,7]</sup> which is made up of 1:1 ratio of the ARB valsartan<sup>[33]</sup> and the NI sacubitril (AHU 377)<sup>[34]</sup>. The action of SV is multimodal. Sacubitril is a pro-drug which is activated to Sacubitrilat (LBQ657), the active metabolite that inhibits NP while valsartan simultaneously blocks the angiotensin receptor. The dual action of Sacubitril and valsartan augment the beneficial actions of the NPs and inhibits the deleterious effects of the RAAS system<sup>[7]</sup>. The PARADIGM-HF trial was conducted by McMurray *et al*<sup>[31]</sup> to determine the efficacy of SV compared to the ACE inhibitor Enalapril<sup>[35,36]</sup>, which improves mortality and morbidity. The median follow-up duration was 27 mo and SV reduced HF related symptoms and overall survival by 20%<sup>[31]</sup>. Additionally, the ARNI approach avoids the common side-effects of ACEi such as cough and angioedema that result from impaired degradation and elevated levels of bradykinin<sup>[37]</sup>. In the ONTARGET trial, ARBs were documented to result in a lower rate of cough and angioedema compared to ACEi: Therefore, combination therapy prefers ARBs over ACEi<sup>[38]</sup>.

The United States Food and Drug Administration had approved SV for clinical use and at present it is produced under the name of Entresto® by Novartis<sup>[39]</sup>. The recommended dose of Entresto is 49 mg sacubitril/51 mg valsartan twice daily increased to 97 mg sacubitril/103 mg valsartan after 2-4 wk. It is contraindicated in patients with history of angioedema, hypotension, hyperkalemia or renal dysfunction and in pregnant women due to fetal toxicity<sup>[40]</sup>. In the



**Table 1 Overview of drugs targeting the neprilysin pathways and its pathways**

Drug	Mechanism	Clinical trials and year	Results on HF symptoms
Nesiritide	Increasing natriuretic peptide activity	VMAC, 2000 <sup>[20]</sup> PRECEDENT, 2002 <sup>[21]</sup> ASCENT-HF, 2009 <sup>[22]</sup>	Improved BP and dyspnea Less cardiac arrhythmias More hypotension
Candoxatril	NPi	Single-centered investigation with only a limited number of patients <sup>[23-25]</sup>	More exercise tolerance Increase in vascular resistance
Omapatrilat	NPi	IMPRESS, 2000 <sup>[26]</sup> OVERTURE, 2002 <sup>[27]</sup> OCTAVE, 2004 <sup>[28]</sup>	More exercise tolerance Increase in angioedema Reduction in BP
LCZ696	NPi	PARAMOUNT, 2012 <sup>[29]</sup> PARADIGM, 2014 <sup>[30,31]</sup> PARAGON, ongoing <sup>[32]</sup>	Lower mortality Reduction in BP Improved ejection fraction Lower mortality No change in angioedema

BP: Blood pressure; HF: Heart failure; NPi: Neprilysin inhibitors.

PARADIGM-HF trial, 10.7% of the patients reported at least one of the following adverse effects hypotension, renal failure, hyperkalemia, fatigue and dizziness<sup>[31]</sup>.

In clinical practice, approximately 50% of the HF patients have a preserved left ventricular ejection fraction (HFpEF) and present with similar morbidity and mortality as seen in patients with HFrEF<sup>[2-4]</sup>. Sacubitril/valsartan is validated in HFrEF but is being evaluated for HFpEF in the PARAMOUNT-HF (The Prospective comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial. Patients who treated with sacubitril/valsartan showed a reduction in NYHA class and left atrial volumes<sup>[29]</sup>. At present, the PARAGON-HF trial is ongoing comparing the effects of sacubitril/valsartan versus valsartan in the HFpEF patients<sup>[32]</sup>.

## NEPRILYSIN INHIBITORS AND ALZHEIMER'S DISEASE

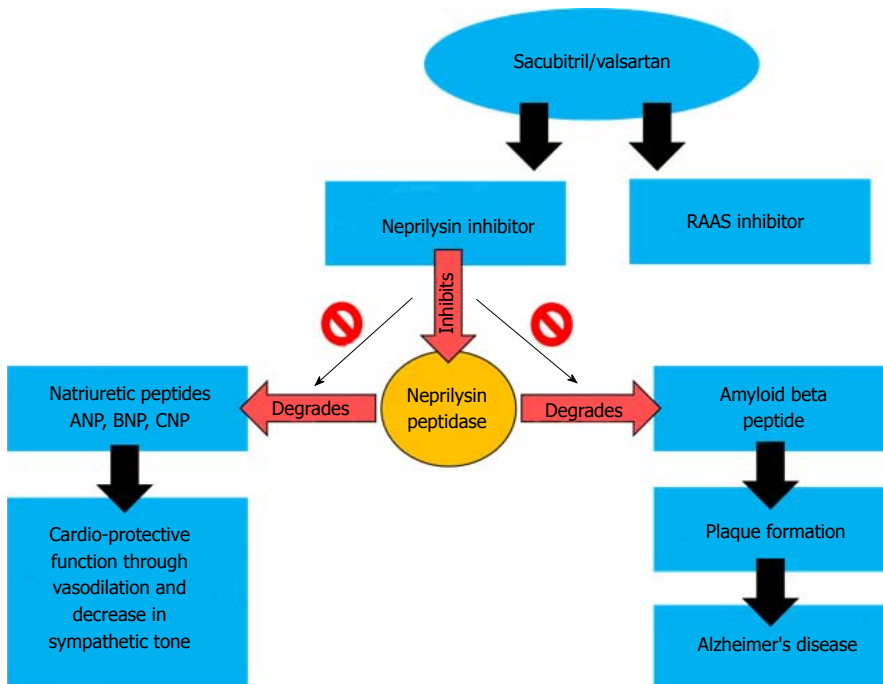
An interesting facet of the use of NIs in the treatment of cardiovascular diseases is their potential role in the development or progression of Alzheimer's disease (AD), as there is considerable overlap between the populations suffering from HF and AD<sup>[41]</sup>. The hallmark of AD is the accumulation of beta amyloid ( $\beta$ A) peptide in the brain causing neurotoxic plaques that are supposedly responsible for the pathology of AD<sup>[42]</sup>. Under normal physiological conditions, the  $\beta$ A peptide is degraded by proteases such as ACE, NP and insulin degrading enzyme<sup>[43]</sup>. NP has a broad range of substrates apart from the NPs such as bradykinin, enkephalins as well as the  $\beta$ A peptide<sup>[44]</sup>. Additionally, patients with AD have lower expression of NP compared to healthy subjects<sup>[45]</sup>, and NP deficient mice develop the murine form of AD<sup>[46]</sup>. This possible correlation was further highlighted when intracerebral infusion of NPi lead to the development of AD-like lesions in rabbits<sup>[47]</sup>. Lastly, certain polymorphisms in the NP gene (NEP) were associated with a higher propensity

for AD in a Finnish cohort<sup>[48]</sup>. Therefore, NP is as much a pharmaceutical target for the treatment of AD as for HF, except that the strategies are opposite for both pathologies (Figure 1). Indeed, NP centered therapies have been developed independently for AD and tested at the pre-clinical levels. CNS targeted recombinant human NP was able to reduce  $\beta$ A peptide toxicity in the mouse model of AD<sup>[49,50]</sup>.

## ENTRESTO® AND ALZHEIMER'S DISEASE

Clinicians should be aware of the possible inhibitory action of SV in the clearing of  $\beta$ A peptide while considering it for HF treatment. In patients who are at the risk of developing AD, whether due to age or genetic predisposition, the chronic exposure to SV may accelerate the clinical onset of the disease. Critical to this hypothesis is the ability of SV to cross the blood brain barrier (BBB) in order to block brain NP. There is evidence that certain NIs like S-acetylthiorphan can cross the BBB<sup>[51]</sup> while some like candoxatril cannot<sup>[52]</sup>. Both Sacubitril and its active metabolite LBQ657<sup>[7]</sup> are under the threshold size of 400 kD which makes them fit to cross the BBB<sup>[53,54]</sup>. It is noteworthy that the PARADIGM-HF trial<sup>[31]</sup> had excluded patients with AD and did not include any cognitive function tests to evaluate drug safety. McMurray *et al.*<sup>[55]</sup> have confirmed some correlation between EN treatment and  $\beta$ A peptide levels in a recent review article. While cynomolgus monkeys treated with SV had increased levels of  $\beta$ A peptide in the CSF, the healthy volunteers treated with EN for two weeks had no change in  $\beta$ A peptide levels. McMurray *et al.*<sup>[31]</sup> showed that the dementia and cognitive defects were not increased in the EN treated patients during the trial. However, it should be noted that the earliest symptoms of AD can take as long as 8-10 years to manifest<sup>[56]</sup>. If there is a correlation between EN therapy and AD, one would predict an earlier onset of symptoms.

It is therefore imperative that patients on SV are followed up for cognitive abilities and potentially



**Figure 1** Schematic representation of the contradictory effects of angiotensin receptor and neprilysin inhibitors on cerebrovascular disease and Alzheimer's disease. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide.

evaluated for AD. One can consider cerebrospinal fluid (CSF) analysis for  $\beta$ A peptide levels and amyloid plaques through PET scans if early signs of dementia ensue<sup>[57]</sup>. In the ongoing PARAGON-HF<sup>[32]</sup> trial, AD patients have not been excluded and serial cognitive tests have also been included as part of initial follow-up.

Another concern is that the proportion of HF patients younger than 40 years old is increasing<sup>[58]</sup>. Younger patients receiving SV have the potential for a longer term exposure and the consequent potential for increased risk of young onset Alzheimer's disease (YOAD) is noteworthy. YOAD is described in subjects less than 65 years of age and has a more rapid progression than the typical late onset Alzheimer's<sup>[59]</sup>.

Interestingly, one can also describe SV as having protective effect against AD since hypertension and cardiovascular diseases are established risk factors for AD<sup>[60]</sup>, is decreased by SV therapy. ACEi or ARBs have also been shown to decrease in dementia and other symptoms of AD through reducing hypertension and cardiovascular disease<sup>[61]</sup>. It will be interesting to follow the neuro-cognitive outcomes from PARAGON-HF trial.

## CONCLUSION

Clinicians should be aware of the potential adverse effects of SV and make informed decisions in prescribing SV, particularly to patients with existing neuro-degenerative diseases or the very young. As there are no definitive answers yet about the long term effects of SV, we await the results from PARAGON-HF and reports to follow with interest. Patients who are currently

receiving SV treatment should be well monitored for potential adverse events with particular attention to dementia. A low threshold for testing for AD if/when dementia symptoms occur seems warranted. More study on the implications for young HF patients is warranted.

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## Cardiac and pericardial tumors: A potential application of positron emission tomography-magnetic resonance imaging

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### Abstract

Cardiac and pericardial masses may be neoplastic, benign and malignant, non-neoplastic such as thrombus or simple pericardial cysts, or normal variants cardiac

structure can also be a diagnostic challenge. Currently, there are several imaging modalities for diagnosis of cardiac masses; each technique has its inherent advantages and disadvantages. Echocardiography, is typically the initial test utilizes in such cases, Echocardiography is considered the test of choice for evaluation and detection of cardiac mass, it is widely available, portable, with no ionizing radiation and provides comprehensive evaluation of cardiac function and valves, however, echocardiography is not very helpful in many cases such as evaluation of extracardiac extension of mass, poor tissue characterization, and it is non diagnostic in some cases. Cross sectional imaging with cardiac computed tomography provides a three dimensional data set with excellent spatial resolution but utilizes ionizing radiation, intravenous iodinated contrast and relatively limited functional evaluation of the heart. Cardiac magnetic resonance imaging (CMR) has excellent contrast resolution that allows superior soft tissue characterization. CMR offers comprehensive evaluation of morphology, function, tissue characterization. The great benefits of CMR make CMR a highly useful tool in the assessment of cardiac masses. (Fluorine 18) fluorodeoxyglucose (FDG) positron emission tomography (PET) has become a corner stone in several oncological application such as tumor staging, restaging, treatment efficiency, FDG is a very useful imaging modality in evaluation of cardiac masses. A recent advance in the imaging technology has been the development of integrated PET-MRI system that utilizes the advantages of PET and MRI in a single examination. FDG PET-MRI provides complementary information on evaluation of cardiac masses. The purpose of this review is to provide several clinical scenarios on the incremental value of PET and MRI in the evaluation of cardiac masses.

**Key words:** Cardiac; Pericardial tumors; Echocardiography

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**Core tip:** With the commercial availability of positron emission tomography- magnetic resonance imaging (PET-MRI) true simultaneous PET and MRI in a single study is real. Several studies have demonstrated the feasibility and incremental value of combined PET and MRI in many clinical applications. A combination of PET and MRI can provide incremental information in many cardiovascular scenarios. Evaluation of cardiac tumors may be most straightforward application for PET-MRI because it offers a unique opportunity to evaluate the tumor morphology, characterization, infiltration to adjacent structures, local and M staging and comprehensive cardiac evaluation in a single study. The purpose of this review is to provide several clinical scenarios on the incremental value of PET and MRI in the evaluation of cardiac masses.

Fathala A, Abouzied M, AlSugair AA. Cardiac and pericardial tumors: A potential application of positron emission tomography-magnetic resonance imaging. *World J Cardiol* 2017; 9(7): 600-608 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/600.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.600>

## INTRODUCTION

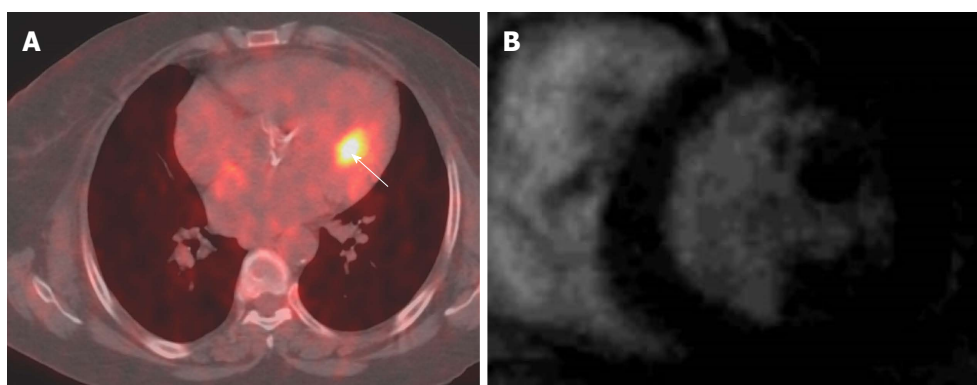
Primary cardiac tumors, Benign and Malignant, are rare with an estimated prevalence of 0.002%-0.3% at autopsy<sup>[1]</sup>. The primary benign cardiac tumors are common and include myxomas, fibromas, rhabdomyomas, lipoma, fibroelastomas, hemangioma, and paragangliomas. The primary malignant cardiac neoplasm is generally sarcomas, mesotheliomas, or lymphoma. Cardiac metastases involving the heart and pericardium (secondary cardiac tumors) from direct invasion or hematological spread are 20%-40% more common than primary cardiac tumors and usually associated with poor prognosis primary related to advanced stage of primary malignancy<sup>[2]</sup>. However, the most common type of cardiac mass is in fact pseudotumors or tumors like structures such as intracardiac thrombus, pericardial cyst, valvular vegetation, perivalvular abscess, or normal cardiac variant such as crista terminalis.

Patients with primary cardiac tumors may present with a range of symptoms that can simulate cardiac disease. The clinical presentation is determined mostly by location, size, and texture, the rate of growth and invasiveness of the tumor. For example, patients with mechanical obstruction related to cardiac mass in outflow tract may present with heart failure or valvular disease, systolic dysfunction or diastolic dysfunction related to impaired contractility. Pericardial disease may present as pericardial effusion, pericardial tamponade, or pericardial thickening and nodularities.

Several imaging modalities are used in the evaluation of cardiac and Pericardial tumors with their inherent advantages and disadvantages. Transthoracic

echocardiography is widely available and is considered the procedure of choice for diagnosis of intracardiac tumors. It provides information on the size, mobility, shape and location of the cardiac mass but limited information on mass tissue characterization. In certain patients, such as obese patients or patients with chronic obstructive lung disease trans esophageal echocardiography offers a diagnostic alternative<sup>[3]</sup>. Cardiac computed tomography (CT) is a noninvasive technique which offers a high spatial resolution and sufficient temporal resolution. Both cardiac and intracardiac mass can be very clearly depicted as well as their degree of myocardial and pericardial involvement; however, radiation and iodinated contrast injection are some of CT imaging<sup>[4]</sup>. Cardiac magnetic resonance (CMR) has several advantages in the diagnosis of patients with cardiac tumors. The greatest advantages of CMR over various imaging modalities, is that CMR have a unique ability to characterize tissue composition based on the inherent T1 and T2 relaxation of different tissue; in addition CMR provides excellent temporal and spatial resolution, multiplanar 3D imaging capabilities, large field of view, evaluating adjacent vascular structures, lymph nodes involvement and mediastinum<sup>[5,6]</sup>. Positron emissions tomography (PET) offers an accurate evaluation of the metabolic activity of the tumors via utilizing (fluorine 18) fluorodeoxyglucose (FDG). FDG PET is very helpful for staging malignancies, optimizing biopsy location, radiation therapy planning and detection of tumors recurrence and response to therapy. In cases of cardiac metastases FDG pet can detect both primary lesions such as lung cancer and cardiac metastases. The extent of FDG uptake by tumors is useful for differentiation between benign and malignant tumors<sup>[7]</sup>.

Positron emission tomography-magnetic resonance imaging (PET-MRI) hybrid scanners are a newly developed type of clinical imaging system. PET-MRI benefits from the advantages of both PET and MRI. MRI provides tumors tissue characterization with T1 and T2, and different pulse sequence with and without gadolinium injection, extent of the tumors invasion and local metastasis, in addition, CMR offers a comprehensive examination of the heart and any complication related to the tumors such as pericardial effusion or valvular dysfunction. PET assesses the metabolic evaluation of the tumors, and evaluation of the primary extracardiac tumors or other distant metastases. Integrated PET-MRI systems provide improved spatial and temporal alignment, CMR image based motion correction is also improved, artefacts such as motion and partial volume effect in PET scanning. Integrated PET-MRI system significantly reduces time of imaging acquisition compared to performing two separate examinations, improve throughput and also reduce patient's discomfort<sup>[8,9]</sup>. In this review, we will discuss several clinical scenarios in which CMR and PET provides additive information, these illustrated cases performed as sequential examinations, not



**Figure 1** Localization of abnormal fluorodeoxyglucose activity in the heart. A: Axial fused PET-CT image shows focal intense FDG uptake in the heart (arrow) in patient with melanoma that thought represents cardiac metastases; B: Selected delayed enhancement short axis image of the same patient with other images (not shown) shows no abnormal enhancement or tissue infiltration, the FDG uptake was corresponding to hypertrophic papillary muscle, follow PET-CT was normal. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.

on integrated PET-MRI scan, these includes: (1) characterization and Localization of abnormal FDG uptake in the heart; (2) characterization and Localization of abnormal FDG uptake adjacent to the heart; (3) differentiation between tumoral thrombus from bland thrombus; (4) distant Metastasis (M staging); (5) evaluation of aggressiveness of the lesion and assessment of cardiac involvement; and (6) other potential indications.

## CHARACTERIZATION AND LOCALIZATION OF ABNORMAL FDG UPTAKE IN THE HEART

The patterns and distribution of FDG in the normal myocardium may be classified into three types; no to faint uptake, regional uptake, and diffuse uptake. There is no specific pattern myocardial FDG uptake<sup>[10]</sup>. Furthermore, myocardial FDG uptake in the same individual is neither stable nor reproducible unless under the same fasting condition. The PM has a characteristic location on axial and coronal images. PM uptake can occasionally be seen without myocardial uptake, this appearance can mimic an intraventricular thrombus or tumor<sup>[11]</sup>. Focal intense FDG uptake is frequently observed in the basal septal region in patients with active cardiac sarcoidosis<sup>[12]</sup>. Several reports describing FDG patterns in cardiac tumors have been published<sup>[13,14]</sup>. However, the usefulness of FDG in the differentiation between benign (including thrombus) and malignant tumors.

Different imaging modalities are often necessary for approaching final diagnosis of primary or metastatic cardiac tumors. The differential diagnosis can be narrowed down by clinical history, signs and symptoms of the clinical presentation, history of primary neoplasm. Normal cardiac variants and variable myocardial uptake of FDG may raise the suspicion of cardiac metastasis in some PET-CT studies in patients with cancer. In such clinical circumstances, CMR is very

useful (Figures 1 and 2).

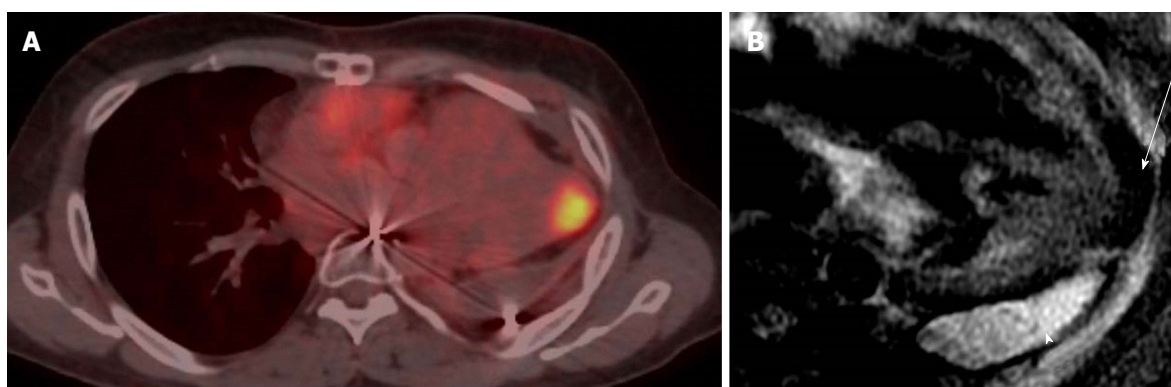
## CHARACTERIZATION AND LOCALIZATION OF ABNORMAL FDG UPTAKE ADJACENT TO THE HEART

One of the most and frequent artefact in PET-CT is due to respiratory motion during scanning. It typically creates mismatch between a specific stage of breath cycle during the CT and average of many breath cycles of the PET images. The diaphragm that is visualized in a single position during fast CT acquisition is different from mean position of PET images or in case of respiratory motion. misregistration of CT and PET images disrupts images fusion of normal organ and may cause erroneous localization of FDG avid lesion in the liver, upper abdomen, base of the lung, or adjacent to the heart. The best way to correct for respiratory motion between CT and PET images would be acquired gated images to discriminate different interval for a breath cycle<sup>[15]</sup>. There are some techniques in integrated PET-MRI that correct for motion artifact, motion can be derived from MR data without the need for navigators, an approach called self-navigation, and these techniques require that K-space be sampled in a motion sensitive scanner<sup>[16]</sup>. The motion control and gating approaches will continue to be used in integrated PET-MRI scanner, the field will likely move towards data-derived approaches<sup>[17]</sup>. Oncologic PET-CT scans may reveal abnormal focus of hypermetabolism in the chest, either in or adjacent to the heart. It is often not possible to accurately localize this lesion using PET or the corresponding low-dose CT scan. In such situations, MRI can provide additional information in localizing and characterizing these masses (Figures 3 and 4).

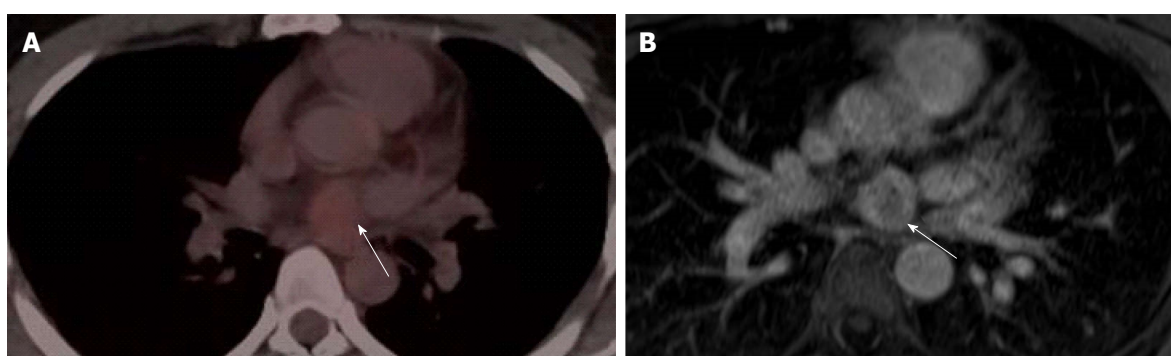
## DIFFERENTIATION BETWEEN TUMORAL THROMBUS FROM BLAND THROMBUS

Tumor thrombosis is often clinically asymptomatic,

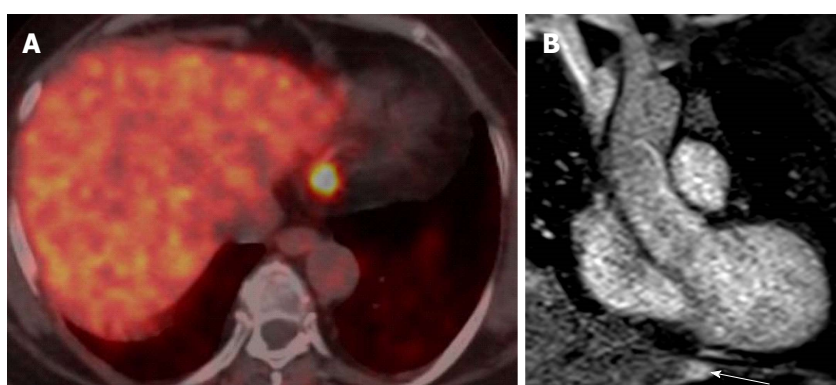




**Figure 2** Localization and characterization of abnormal fluorodeoxyglucose activity in the heart. A: Axial PET-CT images in patient with history of invasive thymoma underwent surgical resection shows intense FDG focal uptake in the cardiac apex highly suspicious for cardiac metastases, review CT component of PET-CT shows area of and soft tissue; B: Four-chamber DE image with triple inversion recovery shows complete fat suppression of the apical activity in keeping with brown fat (arrow), with high signal fluid intensity consistent with post-operative lobulated fluid collection (arrowhead). PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.



**Figure 3** Localization and characterization of abnormal fluorodeoxyglucose activity adjacent to the heart. A: Localization and characterization of abnormal FDG activity adjacent to the heart. Axial PET-CT image of the heart shows a non-FDG avid nodule near the base of the heart (arrow), PET-CT was performed for incidentally discovered nodule mass on Echocardiography. The study was otherwise unremarkable; B: Axial first pass perfusion image shows highly vascular intrapericardial tumors with no evidence of tissue invasion (arrow); this lesion was surgically removed and pathologically proven schwannoma. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.

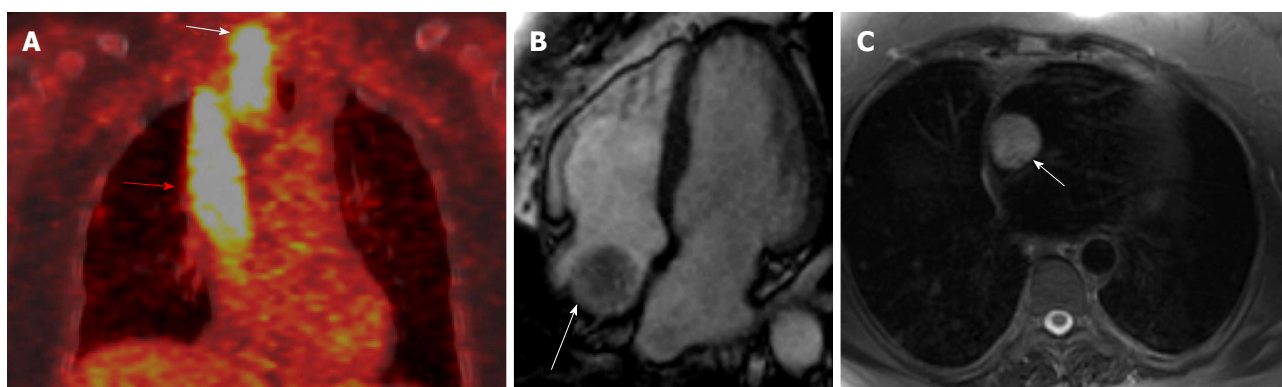


**Figure 4** Localization and characterization of abnormal fluorodeoxyglucose activity adjacent to the heart. A: Axial Ga-68 DOTATATE PET/CT shows a focal intense radiotracer uptake adjacent to the heart with difficulty to accurately localize; patient is known to have history of ileocecal area carcinoid and underwent surgery; B: Coronal first pass perfusion images show highly vascular lesion in the tip of the left lobe of the liver corresponding to abnormal radiotracer uptake, this location is very common for PET-CT misregistration and there was no focal lesion identified in CT component of PET-CT. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.

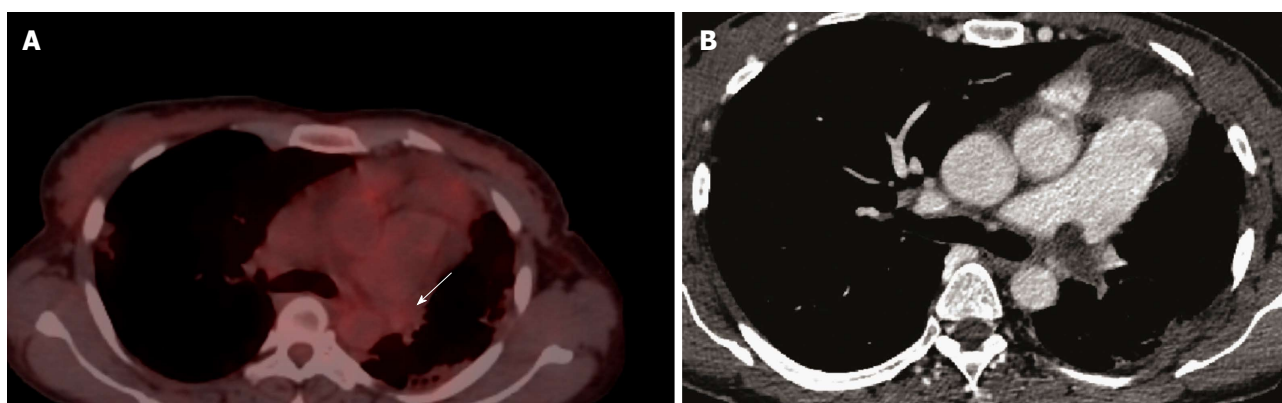
the diagnosis of tumoral thrombus is usually made incidentally, discrimination between benign, and tumor thrombus can have significant implications in patient's management. In general, tumor thrombus

is a rare complication of solid cancers, with occult inferior vena cava tumor thrombosis having a reported incidence of 0.11%. Few case reports have described the diagnosis of tumor thrombus by PET-CT in





**Figure 5** Differtiation between tumoral thrombus from bland thrombus. A: Differtiation between tumoral thrombus from bland thrombus in patient with history of thyroid cancer treated with total thyroidectomy presented with neck mass. Coronal fused FDG-PET image shows intense linear FDG uptake from in the thyroid bed (white arrow) and spreading through SCV to the right atrium (red arrow); B: Four chamber cine image shows irregularly defined mass in the right atrium (arrow), the rest of cardiac examination was unremarkable; C: Axial HASTE at the junction of superior vena cava and right atrium shows a high signal intensity mass (arrow). PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.



**Figure 6** Differtiation between tumoral thrombus from bland thrombus. A: Differtiation between tumoral thrombus from bland thrombus in female patient with history ovarian cancer, patient was known to have chronic pulmonary embolism, there was a bland thrombus almost occluding the left pulmonary artery was no FDG uptake (arrow); B: Axial CT image shows a left pulmonary artery thrombus. CT: Computed tomography; FDG: Fluorodeoxyglucose.

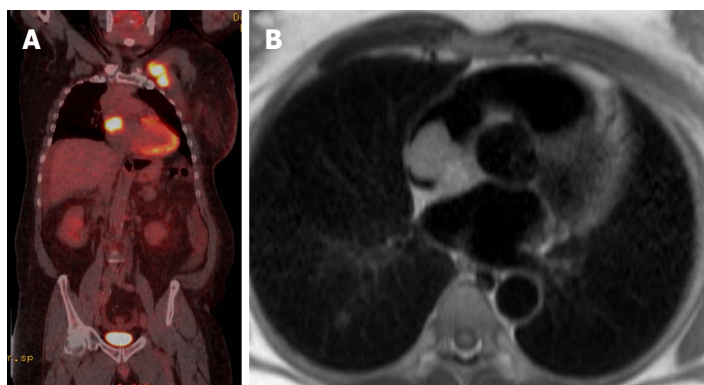
various cancer including pancreatic, colon, renal cell cancer and adrenocortical cancer. In contrast, venous thromboembolism (VTE) is relatively common than tumor thrombosis in patients with cancer. Cancer has been associated with 18% of all cases of incidental VTE. Across all patients with cancer, the risk for VTE has elevated seven folds, in certain malignances the risk for VTE may increase up to 28-folds<sup>[18]</sup>.

Tumor thrombosis is composed mainly of viable tumor cells and usually has high metabolic neoplastic activity<sup>[19]</sup> with subsequent high FDG uptake. FDG uptake in malignant cells is mediated through glucose transporters receptors. In contrast, benign thrombus is composed of activated of platelets, macrophages and fibrin. Therefore, benign thrombus is none metabolically active, simple, non-infected thrombus called bland thrombus. On PET-CT images, bland thrombus appear as intravascular filling defect without FDG uptake and can be found in veins of any size and location.

Distinguishing between benign thrombus and tumor thrombus on basis of presence or absence of FDG uptake may be difficult, it is quite reasonable for

inflammatory or infectious thrombus to demonstrate some degree of FDG uptake. It is reported that inflammatory cells cause significant increase in FDG uptake in presence of platelet-aggregation factors and cytokines including growth factors<sup>[20]</sup>. In addition, expression of the glucose transporter is also increased in activated granulocytes and macrophages<sup>[21]</sup>. The differential diagnosis can be narrowed down by correlating clinical presentation, distinctive clinical features, demographics, and relevant laboratory findings in association with imaging characterization of the thrombus.

Different imaging modalities are available for distinguishing between benign and malignant thrombus. PET-CT offers comprehensive anatomical and metabolic evaluation of the thrombus, particularly, if CT component performed with IV iodinated contrast. On MRI, the signal intensity of the thrombus may vary depending on the age of the thrombus. Gadolinium contrast is useful for differentiating thrombus from tumor, Thrombus typically does not enhance but tumors usually enhance on delayed imaging<sup>[22]</sup>. One



**Figure 7 M staging.** A: M staging: Coronal PET-CT image of patient with lymphoma with unexpected cardiac involvement; B: Axial T1-weighted image at the level of interatrial septum shows well defined mass attached to the atrial septum and nearly fills the right atrium and was proved to be lymphoma. PET: Positron emission tomography; CT: Computed tomography.

study reported, diffusion weighted (DW) imaging enables differentiation between portal vein tumoral thrombus from bland thrombus in patients with hepatocellular carcinoma (HCC), when apparent diffusion coefficient (ADC) of the thrombus to ADC of HCC is less than 2 and when the thrombus showed signal intensity similar to HCC, DW imaging may be very helpful in certain patients, such as patients with contraindication for contrast material injection and/or history of previous reaction to contrast media<sup>[23]</sup> (Figures 5 and 6).

## M STAGING

CMR is a very helpful imaging technique for diagnosis of cardiac tumors which enables evaluation of anatomy, function, tissue type, and vascularity and relationship to adjacent structures. It also allows searching for primary tumors in case of cardiac metastases and detection for metastases in the thorax and liver/abdomen. However, CMR is not adequate for M staging, PET-CT is useful technique for M staging of wide varieties of cancers, several studies reported that PET-CT is more accurate than other conventional imaging staging in several cancer such as several types of lymphoma, solid cancer such as breast, lung, ovary, and head and neck cancers. The newer MRI technique, whole body diffusion weighted imaging is used for tumors detection, characterization, therapy monitoring. In certain with low FDG, uptakes such as neuroendocrine tumors, thyroid cancer and several low malignancy lymphomas, whole body DW is additive for PET-CT for tumors detection, staging, and assessment for response for therapy<sup>[24,25]</sup> (Figure 7).

## EVALUATION OF AGGRESSIVENESS OF THE LESION AND ASSESSMENT OF CARDIAC INVOLVEMENT

FDG PET uptake reflects the metabolic glycolysis in tumors and supplies additional information to mor-

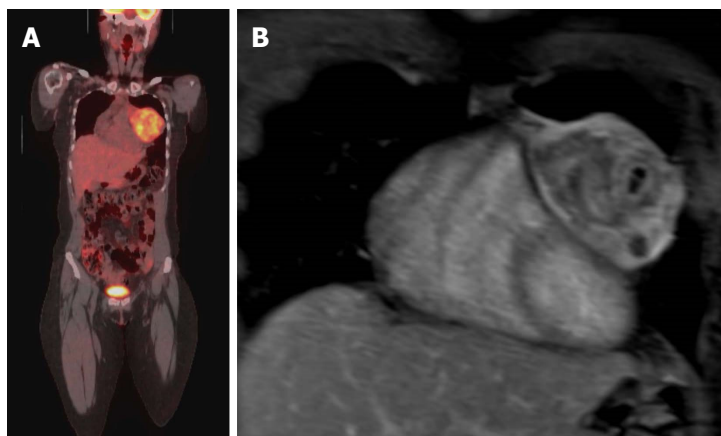
phological imaging. Generally, there is correlation between glucose accumulation in tumors tissue and degree of malignancy, with some exceptions<sup>[26,27]</sup>. However, PET has not yet systematically evaluated for characterization of cardiac tumors, furthermore, PET imaging can assess the local extent of the tumors and tumor infiltration to adjacent tissue. In addition, it is not often possible to accurately localize the lesion using low dose CT component of PET-CT. Contrast-enhanced CT visualizes several morphological features of cardiac tumors and helps to discriminate between benign and malignant tumors. CT high sensitive markers for malignancy includes location of the tumors outside the heart, tissue inhomogeneity and contrast enhancement. The presence of pericardial effusion is a high specific feature for malignancy, but tumors size is neither specific nor sensitive for malignancy<sup>[28]</sup>. A well-defined tumor without infiltration to adjacent structures is highly suggestive for benignity. CMR may have benefit over CT in the assessment of local tumor extension because MRI provides high soft tissue contrast<sup>[29,30]</sup>. Therefore PET-MRI can have role in the detection of T-stage and assessment of local invasion and infiltration (Figures 8 and 9).

## OTHER POTENTIAL INTEGRATED PET-MRI APPLICATIONS RELATED TO CARDIAC TUMORS

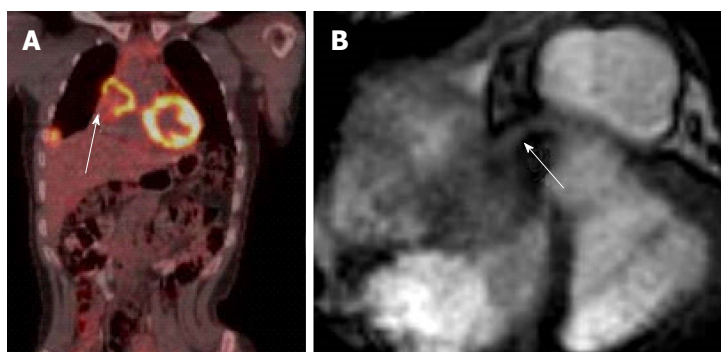
PET-MRI with optimal coregistration is essential to differentiate between residual scar tissue and tumors relapse, integrated PET-MRI imaging obviously combines the advantage of both methods in a single examination. FDG PET- and MRI-imaging yielded 100% sensitivity and 92% specificity in detecting tumors malignancy, but combined PET-MR yielded 100% sensitivity and specificity in one small study, one of the limitations of this study was small sample size<sup>[31]</sup>. In addition, in integrated PET-MRI, MRI component can assess the cardiac function, volume, morphology, and metabolism, and accurately assess tumors infiltration to



**Figure 8** Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement. A: Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement; whole body PET-CT image of patient with extensive Ewing sarcoma of the left hemithorax, PET-CT images are not sufficient to evaluate local extension of the tumor to the heart; B: Axial delayed enhancement image shows large necrotic mass occupying the left hemithorax with direct left ventricle (upper arrow) the arrow without circle and left atrial invasion (lower arrow). PET: Positron emission tomography; CT: Computed tomography.



**Figure 9** Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement. A: Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement; Coronal PET-CT image in a patient with Ewing sarcoma of the left chest wall with direct compression of the left side of the heart; B: Coronal Post contrast T1-weighted image of the heart shows no evidence of cardiac invasion with clear separation of the mass from the heart, the mass was surgically removed and there was no evidence of cardiac invasion. PET: Positron emission tomography; CT: Computed tomography.



**Figure 10** Evaluation of coronary artery involvement by the tumor. A: Coronal PET-CT image in a female patient with history of breast cancer with mediastinal and lung metastasis and recurrent chest pain; B: Axial cine image at the base of the heart shows metastatic lesion invading the heart causing mechanical obstruction of the right coronary artery (arrow). PET: Positron emission tomography; CT: Computed tomography.

various cardiac struts such as valves, papillary muscle, or coronary artery (Figure 10).

## CONCLUSION

With the commercial availability of PET-MRI true

simultaneous PET and MRI in a single study is real. Several studies have demonstrated the feasibility and incremental value of combined PET and MRI in many clinical applications. A combination of PET and MRI can provide incremental information in many cardiovascular scenarios. Evaluation of cardiac tumors may be most



straightforward application for PET-MRI because it offers a unique opportunity to evaluate the tumor morphology, characterization, infiltration to adjacent structures, local and M staging and comprehensive cardiac evaluation in a single study.

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## Hand dysfunction after transradial artery catheterization for coronary procedures

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### Abstract

#### AIM

To synthesize the available literature on hand dysfunction after transradial catheterization.

#### METHODS

We searched MEDLINE and EMBASE. The search results were reviewed by two independent judicators for studies that met the inclusion criteria and relevant reviews. We included studies that evaluated any transradial procedure and evaluated hand function outcomes post transradial procedure. There were no restrictions based on sample size. There was no restriction on method of assessing hand function which included disability, nerve damage, motor or sensory loss. There was no restriction based on language of study. Data was extracted, these results were narratively synthesized.

#### RESULTS

Out of 555 total studies 13 studies were finally included in review. A total of 3815 participants with mean age of 62.5 years were included in this review. A variety of methods were used to assess sensory and motor dysfunction of hand. Out of 13 studies included, only 3 studies reported nerve damage with a combined incidence of 0.16%, 5 studies reported sensory loss, tingling and numbness with a pooled incidence of 1.52%. Pain after transradial access was the most common form of hand dysfunction (6.67%) reported in 3 studies. The incidence of hand dysfunction defined as disability, grip strength change, power loss or any other hand complication was incredibly low at 0.26%. Although radial artery occlusion was not our primary end point for

this review, it was observed in 2.41% of the participants in total of five studies included.

## CONCLUSION

Hand dysfunction may occur post transradial catheterisation and majority of symptoms resolve without any clinical sequel.

**Key words:** Transradial access; Transfemoral access; Hand dysfunction

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**Core tip:** Transradial access (TRA) is default access site in many countries to perform coronary procedures. Hand function may occur post TRA, however our review shows that its incidence is exceedingly low and most symptoms resolve without any clinical sequel.

Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction after transradial artery catheterization for coronary procedures. *World J Cardiol* 2017; 9(7): 609-619 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/609.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.609>

## INTRODUCTION

Coronary angiography is the current gold standard in providing anatomical information regarding the extent and severity of coronary artery disease<sup>[1,2]</sup>. Access site practice has changed in a number of European and Asian countries from mainly being transfemoral (TFA) to transradial (TRA)<sup>[3,4]</sup> in view of less access site related bleeding complications, mortality and shorter hospital stay associated with TRA<sup>[5-11]</sup>. For instance, in the United Kingdom use of radial access has increased from 14% to 80% between 2005 and 2014 in patients undergoing percutaneous coronary intervention (PCI) and it is estimated that this practice change has saved an estimated 450 lives nationally<sup>[12]</sup>. In the most recent European Society of Cardiology guidelines for management of non-ST elevation myocardial infarction (NSTEMI), TRA received class 1A indication for invasive management of NSTEMI with PCI<sup>[2]</sup>. Furthermore national bodies have formulated recommendations to prevent and minimize procedure related complications of TRA such as reducing the risk of radial artery occlusion (RAO), minimizing patient and operator radiation exposure and transitioning to TRA for primary PCI<sup>[13,14]</sup>.

Nevertheless, despite of its clear advantages over TFA, TRA is not without limitations and is associated with longer operator learning curve<sup>[15,16]</sup>, increased radiation exposure in individual operators at the start of their learning curves<sup>[17,18]</sup> and higher case radial proportion to translate the better results of randomized trials into clinical practice<sup>[11,19,20]</sup>. Moreover, vas-

cular complications such as RAO<sup>[21]</sup> and radial artery spasm<sup>[22]</sup> are not uncommon and very recently concerns have been raised that patients undergoing TRA PCI may encounter hand dysfunction<sup>[23]</sup>.

Whether access site related complications can lead to hand dysfunction is unclear and studies have reported inconsistent results. A study by van Leeuwen *et al*<sup>[24]</sup> investigated the impact of TRA on limb function at long term follow up, reported 9% and 11% of the patients develop temporary or permanent hand dysfunction respectively. Whereas Zwaan *et al*<sup>[25]</sup> reported a pooled incidence of 0.32% in 14 studies evaluating hand dysfunction post TRA.

Considering that the TRA is the predominant access site for cardiac catheterization procedures in many countries, there is little data around hand dysfunction post procedure. In view of the limited published data we conducted a systematic review to evaluate the hand dysfunction post TRA.

## MATERIALS AND METHODS

We searched MEDLINE and EMBASE on 23 August 2016 using the search terms: [(radial or transradial or radial artery) AND (catheterisation or catheterization or angiography or angiogram or angioplasty or percutaneous coronary intervention or PCI)] AND (hand function or grip strength or disability or dysfunction or sensation or paraesthesia or paralysis). The search results were reviewed by two independent adjudicators (MAU, CWW) for studies that met the inclusion criteria and relevant reviews. The bibliographies of included studies and relevant reviewers were screened for additional studies.

We included studies with patients undergoing transradial procedure and evaluated hand function outcomes post procedure. No control group was required so studies could be single arm. There were no restrictions based on language, sample size or method of assessing hand function which included disability, nerve damage, motor or sensory loss. These results were then narratively synthesized.

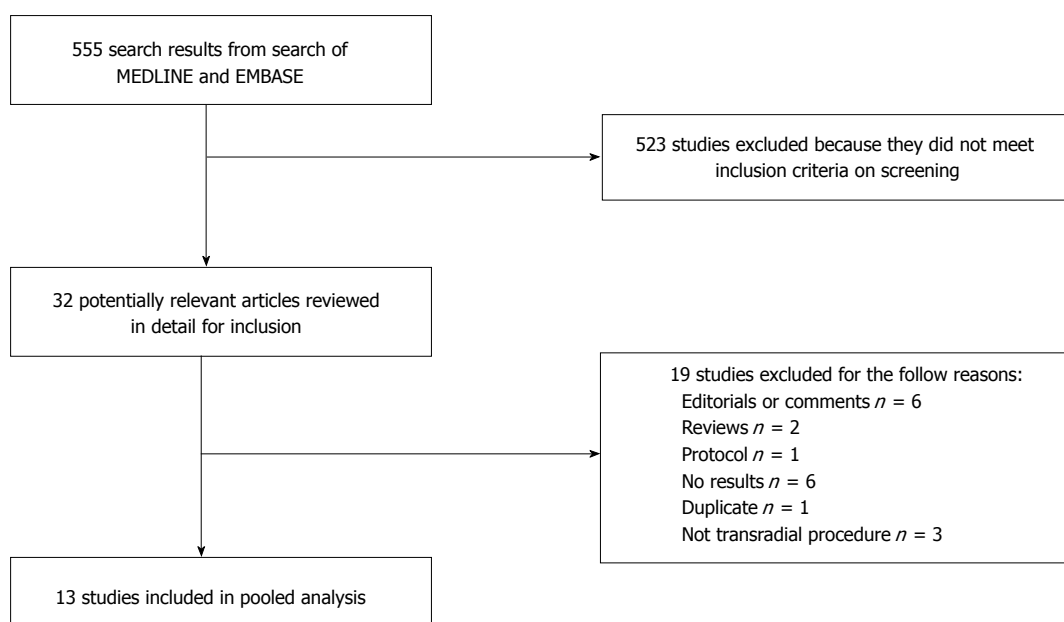
## RESULTS

Our search yielded 555 related studies out of which after screening and reviewing the full manuscripts, 13<sup>[24,26-38]</sup> studies were included in the final review. Detail process of inclusion and exclusion is illustrated in Figure 1.

Table 1 provides the description of studies, year of study, percentage of males and number of participants. A total of 3815 participants with mean age of 62.5 years were included in the studies. Table 2 describes the various methods of assessment employed to assess hand dysfunction, follow up time and results. We observed significant heterogeneity in the methods of assessment hand function and follow

**Table 1 Study design and participant characteristics**

Ref.	Study design/country/ year	No. of participants	Mean age	% male	Participant inclusion criteria and procedural details
Benit <i>et al</i> <sup>[26]</sup>	Randomized trial; Belgium; 1994-1995	50	57.7	100%	Participants had transradial coronary angioplasty with 6-Fr catheters and Palmaz-Schatz stent
Campeau <i>et al</i> <sup>[27]</sup>	Cohort study; Canada; Unclear	100	58 (median)	90%	Participants had transradial coronary angiogram with 5-Fr, 6-Fr and 7-Fr sheath
Chatelain <i>et al</i> <sup>[28]</sup>	Cohort study; Switzerland; 1995-1997	159	60	82%	Participants had transradial diagnostic and interventional cardiac procedures with 4-Fr, 5-Fr or 6-Fr introducer sheath and guide catheters with RadiStop radial compression system
De Belder <i>et al</i> <sup>[29]</sup>	Cohort study; United Kingdom; Unclear	75	Unclear	69%	Participants had transradial coronary angiography and intervention and severe peripheral vascular disease with 5-Fr or 6-Fr sheath and 6-Fr guide catheter
Kiemeneij <i>et al</i> <sup>[30]</sup>	Cohort study; The Netherlands; 1992-1993	100	62	77%	Participants had transradial coronary angiography with 6-Fr introducer and 6-Fr-guide catheters
Lotan <i>et al</i> <sup>[31]</sup>	Cohort study; Israel; 1994	100	61	79%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer and 6-Fr guide catheters
Prull <i>et al</i> <sup>[32]</sup>	Cohort study; Germany; Unclear	93	62.5	80.6%	Participants had transradial diagnostic cardiac catheterization with 5-Fr or 6-Fr sheath or transradial coronary intervention with 7-Fr sheath
Sciahbasi <i>et al</i> <sup>[33]</sup>	Prospective cohort study; Italy; Unclear	99	65	72%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer sheath
Tharmaratnam <i>et al</i> <sup>[35]</sup>	Retrospective case control study; United Kingdom; 2005-2006	1283	65.5	79%	Participants had transradial coronary angiography and angioplasty
Valgimigli <i>et al</i> <sup>[39]</sup>	Prospective cohort study; The Netherlands, Italy; 2014	942	70	73%	Participants had transradial coronary angiography and angioplasty
Van Leeuwen <i>et al</i> <sup>[24]</sup>	Prospective cohort study; The Netherlands; 2015	286	64	72%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer sheath
Wu <i>et al</i> <sup>[37]</sup>	Cohort study; United States; 1996-1998	40	65	88%	Participants underwent 6-Fr and 8-Fr transradial procedure
Zankl <i>et al</i> <sup>[34]</sup>	Prospective cohort study; Germany; 2010	488	Unclear	Unclear	Participants had transradial coronary angiography and angioplasty with 5- and 6-Fr introducer, 4-, 5- and 6-Fr catheters


**Figure 1 Flow diagram of study inclusion/ exclusion.**

up time. For instance, the follow up of assessment varied from anytime between the day procedure was undertaken up to a year post TRA. Similarly, an array

of methods were employed to assess the sensory and motor component of hand function such as questionnaire based surveys in the form of Disabilities



**Table 2 Results of studies**

Ref.	Measure of hand function and vascular complications	Follow up post procedure	Results
Benit <i>et al</i> <sup>[26]</sup>	Local complications assessed in clinic by history and EMG	1 mo	Nerve damage documented by EMG: 0/50 Local pain: 0/50
Campeau <i>et al</i> <sup>[27]</sup>	Patients were re-examined or questioned over telephone about local complications	1 to 3 mo	No nerve injury: 0/100
Chatelain <i>et al</i> <sup>[28]</sup>	Physicians assessed for any clinical events	Assessment prior to discharge	Paraesthesia of right thumb during exercise: 1/159
De Belder <i>et al</i> <sup>[29]</sup>	Clinical evaluation	4-6 wk	Haematoma and paraesthesia post procedure: 1/75 Hand sensation and function at 4-6 wk: 0/75
Kiemeneij <i>et al</i> <sup>[30]</sup>	Examination and ultrasound study performed if radial artery pulsations or flow were absent	1 to 3 mo	Functional disability of the hand: 0/100
Lotan <i>et al</i> <sup>[31]</sup>	Assessment methods unclear	1 mo follow up	Small hematoma in wrist: 3/100 Small pseudoaneurysm: 2/100 Numbness of the thumb and index finger: 1/100 No flow on Doppler: 2/100
Prull <i>et al</i> <sup>[32]</sup>	Clinical evaluation with ultrasound	Post-procedure assessment	Vascular complication: 9/93 Motor skills, coordination or force reduction of hand after procedure: 0/93
Sciahbasi <i>et al</i> <sup>[33]</sup>	Radial artery occlusion by ultrasound test. Handgrip strength by Jamar Plus dynamometer. Thumb and forefinger pinch test by Jamar Plus electronic pinch gauge	Day of procedure and at least 30 d follow up	No pseudoaneurysm: 0/93 Radial artery occlusion: 9/99 Hand grip strength change at follow up: 0/99 Thumb and forefinger pinch test change at follow up: 0/99
Tharmaratnam <i>et al</i> <sup>[35]</sup>	Questionnaire posted to address and clinical notes for significant clinical events	Unclear	Problem with radial access site: 166/1283 (12.9%) Pain at puncture site: 95/1283 (7.4%) Swelling: 46/1283 (3.6%) Bruising: 30/1283 (2.3%) Non-specific sensory abnormalities either pain or paraesthesia in hand: 22/1283 (1.71%)
Valgimigli <i>et al</i> <sup>[39]</sup>	Radial artery occlusion by duplex echocardiographic examination. Hand grip strength test with dynamometer	Just after procedure, 1 d, 30 d and 1 yr	Radial artery occlusions at day 1: 5/942 Radial artery occlusions at 1 year: 3/942 Change in handgrip strength test: 0/942
Van Leeuwen <i>et al</i> <sup>[24]</sup>	Quick DASH questionnaire and CISS questionnaire. Patients were asked to describe any procedure-related extremity complaints or loss of function at 1 mo	Pre, 30 d and 1 yr post procedure	Ischemic vascular or bleeding complications: 0/942 Temporary upper limb complaint (< 30 d): 26/286 (9%) Persisting upper limb complaint (> 30 d): 31/286 (11%) Pain: 13/286 Numbness: 2/286 Tingling: 3/286 Stiffness: 2/286 Less power: 2/286
Wu <i>et al</i> <sup>[37]</sup>	Ultrasound assessment for radial artery occlusion, aneurysm or dissection. Grip strength based on dynamometer results. Palmar pinch, key pinch and tip pinch strength tests were assessed by dynamic endurance test	Late follow up 315 d	Upper limb function by QuickDASH at 30 d: No change over time, baseline 4.55 (IQR 0-13.64), follow up 2.27 (IQR 0-9.32) Upper limb function by CISS at 30 d: No change over time Upper limb function by QuickDASH at 1 yr: no change over time, baseline 2.39 (IQR 0-13.64), follow up 0 (0-11.02) Cold intolerance was not associated with access route at 1 yr Hand complication in hospital: 0/40 Radial occlusion: 1/40 Late radial occlusions: 5/34 Radial artery aneurysm: 0/40 Radial artery dissection 0/40 Grip strength: Baseline 68 ± 34, post-catheterization 69 ± 35 Palmar pinch: Baseline 18 ± 10, post-catheterization 17 ± 6 Key pinch: Baseline 19 ± 7, post-catheterization 19 ± 6 Tip pinch: Baseline 14 ± 6, post-catheterization 14 ± 4 Endurance: Median for 6 Fr and 8 Fr is 78 (IQR 53, 108) and 58 (IQR 32, 68) respectively, post-catheterization 58 (IQR 47, 84) and 56 (IQR 38, 80), respectively
Zankl <i>et al</i> <sup>[34]</sup>	Assessment with ultrasound	4 wk follow up	Radial artery occlusion at 1 d: 51/488 Persistent radial artery occlusion at 4 wk: 21/488 Radial nerve paralysis: 1/488

CISS: Cold intolerance symptom severity; EMG: Electromyography.

**Table 3 Summary of pooled results for hand dysfunction or vascular complications post transradial procedure**

Hand dysfunction or vascular complication	No. of studies	No of events	No of participants	Percentage of events
Nerve damage	3 <sup>[26,27,34]</sup>	1	638	0.16%
Sensory loss, tingling and numbness	5 <sup>[24,28,29,31,35]</sup>	29	1903	1.52%
Pain	3 <sup>[24,26,35]</sup>	108	1619	6.67%
Hand function, disability, grip strength change, stiffness, power loss and hand complications	6 <sup>[24,30,32,33,37,39]</sup>	4	1560	0.26%
Vascular complications including occlusions, hematoma, pseudoaneurysm and dissection	6 <sup>[29,31,32,35,37,39]</sup>	54	1762	3.06%
Radial artery occlusion	5 <sup>[31,33,34,37,39]</sup>	40	1663	2.41%

**Table 4 Disabilities of Arm, Shoulder and Hand (QuickDASH) Questionnaire**

	No difficulty	Mild difficulty	Moderate difficulty	Severe difficulty	Unable
1 Open a tight or new jar	1	2	3	4	5
2 Do heavy house hold chores eg. Wash walls, floors	1	2	3	4	5
3 Carry a shopping bag or briefcase	1	2	3	4	5
4 Wash your back	1	2	3	4	5
5 Use a knife to cut food	1	2	3	4	5
6 Recreational activities in which you take some force or impact through your arm shoulder or hand	1	2	3	4	5
7 During the past week to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbors or groups?	1	2	3	4	5
8 During the past week, were you limited in your work or other daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5
9 Arm, shoulder or hand pain	1	2	3	4	5
10 Tingling	1	2	3	4	5
11 Sleep	1	2	3	4	5

of Arm, Shoulder and Hand (Quick DASH) or Cold Intolerance and Symptom Severity (CISS) or postal surveys, electromyography (EMG), dynamometer and forefinger pinch grip tests.

Table 3 presents pooled results of various form of limb dysfunction described by the studies. Out of 13 studies included, only 3 studies reported nerve damage<sup>[26,27,34]</sup> with a combined incidence of 0.16%, 5 studies reported sensory loss, tingling and numbness<sup>[24,28,29,31,35]</sup> with a pooled incidence of 1.52%. Pain after TRA was the most common form of hand dysfunction (6.67%) reported in 3 studies<sup>[24,26,35]</sup>. The incidence of hand dysfunction defined as disability, grip strength change, power loss or any other hand complication was incredibly low at 0.26%<sup>[24,30,32,33,37,39]</sup>. Although RAO was not our primary end point for this review, it was observed in 2.41% of the participants in total of five studies included<sup>[31,33,34,37,39]</sup>.

In one the very early studies from pre-stent era, Campeau *et al.*<sup>[27]</sup> assessed the neurological damage to hand following TRA using 5 Fr, 6 Fr or 7 Fr sheath. Patients were assessed at 1 and 3 mo either clinically or *via* telephone reported no nerve injury. It is not clear how the nerve damage was assessed in patients reviewed by telephone. Another study employing a more subjective assessment of nerve function using EMG in 150 patients receiving TRA using a 6

Fr sheath reported no damage to the median nerve at 1 mo follow up. In a large retrospective analysis of 1283 patients undergoing TRA using hydrophilic sheaths, 13.2% patients reported non-specific sensory symptoms post procedure<sup>[35]</sup>. However, the results were dependent on a questionnaire based postal survey and no objective method was used to assess for the sensory loss. Similarly two other studies<sup>[28,29]</sup> assessing the neurological dysfunction post TRA, reported only 1 case of paraesthesia of right thumb and 1 case of forearm haematoma resulting in some sensory disturbance of hand but no loss of function. More importantly, both cases made full recovery without any clinical sequel.

In a prospective study of 203 patients after TRA, Valgimigli *et al.*<sup>[39]</sup> assessed the motor component of hand function by performing handgrip strength tests using a dynamometer at 30 d and 1 year, maximal isometric strength on handgrip test did not change over time. Van Leeuwen *et al.*<sup>[24]</sup> conducted a randomised study of 338 patients to evaluate motor component of upper limb function using self-reported shortened version of Disabilities of Arm, Shoulder and Hand (Quick DASH, Table 4) and sensory component using Cold Intolerance and Symptom Severity (CISS, Table 5) questionnaires at baseline and 30 d. There was no statistically significant change in Quick DASH score at baseline to follow up in patients undergoing

**Table 5 Cold Intolerance symptoms severity Questionnaire**

Questions	Score
Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold? Pain, numbness, stiffness, weakness, aching, skin colour change (white/bluish white/blue)	
How often do you experience these symptoms? (Please tick)	
Continuously/all the time	
Several times a day	
Once a day	
Once a week	
Once a month or less	
Never	
When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved? (Please tick)	
Not applicably	
Within a few minutes	
Within 30 min	
After more than 30 min	
What do you do to ease or prevent your symptoms occurring? (Please tick)	
Take no special action	
Keep hand in pocket	
Wear gloves in cold weather	
Wear gloves all the time	
Avoid cold weather/stay indoors	
Other (please specify)	
How much does cold bother your injured hand in the following situations? (Please score 0-10)	
Holding a glass of ice water	
Holding a frozen package from the freezer	
Washing in cold water	
When you get out of a hot bath/shower with air room temperature	
During cold wintry weather	
Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4)	
Domestic chores	
Hobbies and interests	
Dressing and undressing	
Tying your	

TRA (baseline 4.55; IQR: 0.00 to 13.64; follow-up 2.27 IQR: 0.00 to 9.32,  $P = 0.06$ ). Similarly there was no change in the CISS score over time. An important feature of the study was they included patients undergoing TFA to make a comparison between the two access sites. More recently, HANGAR (HAND Grip test After tRansradial percutaneous coronary procedures) study investigated 108 patients with stable angina undergoing PCI using 6Fr sheath with a primary endpoint of variation in hand grip strength measured with the Jamar Plus dynamometer after the procedure<sup>[33]</sup>. The secondary endpoints of interest were thumb and forefinger pinch measured using key pinch and electronic pinch gauge respectively. Out of 99 patients, 9 patients developed radial artery occlusion after the procedure, the patients were then divided in two groups according to the radial patency (group 1) or occlusion (group 2) The hand grip test values were significantly reduced compared with baseline values ( $40 \pm 11$  kg in group 1,  $P < 0.0001$  and  $37 \pm 17$  kg in group 2,  $P = 0.007$ ) after the procedure but returned back to baseline at follow up. Interestingly thumb and finger pinch function was unaffected at baseline, after the procedure and follow up. Finally ARCUS (Effects of transradial percutaneous coronary intervention on upper extremity function) is an ongoing trial assessing

the effects of TRA on hand function by taking various measurement such as Echo Doppler for radial artery occlusion, Questionnaires testing including Quick DASH (Table 4), Boston Carpal Tunnel Questionnaire (BCTQ, Table 6) and Visual Analogue Scale (VAS), volumetry of hand and forearm, sensibility of fingertips, key and palmar grips and isometric strength of wrist and elbow<sup>[40]</sup>. The interim results were published recently suggesting that 143 of 191 (74.9%) patients had some form of upper limb dysfunction defined as a compiled binary score of various measurements taken<sup>[38]</sup>. Furthermore, RAO was 9.8% in upper limb dysfunction group as compared to 0% RAO in non-upper limb dysfunction group.

## DISCUSSION

In the current review, we synthesize the evidence on the incidence and clinical impact of hand dysfunction after TRA. We observe a very low incidence of hand dysfunction in limited literature and importantly, we observe significant heterogeneity in the definition and method of assessment of hand dysfunction amongst the studies, with no internationally accepted measure of hand dysfunction that can be used as the gold standard for such studies. Many of these studies are

**Table 6 Boston Carpal Tunnel Syndrome Questionnaire**

	1	2	3	4	5
A: Symptom severity scale (11 items)					
1 How severe is the hand or wrist pain that you have at night?	Normal	Slight	Medium	Serious	Very serious
2 How often did hand or wrist pain wake you up during a typical night in the past two weeks?	Normal	Once	2-3	4-5	> 5
3 Do you typically have pain in your hand or wrist during the daytime?	No Pain	Slight	Medium	Serious	Very Serious
4 How often do you have hand or wrist pain during daytime?	Normal	1-2 times/d	1 times/d	> 5 times/d	Continued
5 How long on average does an episode of pain last during the daytime?	Normal	< 10 min	10-60 continued	> 60 min	Continued
6 Do you have numbness (loss of sensation) in your hand?	Normal	Slight	Medium	Severe	Very Serious
7 Do you have weakness in your hand or wrist?	Normal	Slight	Medium	Severe	Very Serious
8 Do you have tingling sensations in your hand?	Normal	Slight	Medium	Severe	Very Serious
9 How severe is numbness (loss of sensation) or tingling at night?	Normal	Slight	Medium	Severe	Very Serious
10 How often did hand numbness or tingling wake you up during a typical night during the past two weeks?	Normal	Once	2-3 times	4-5 times	> 5
11 Do you have difficulty with the grasping and use of small objects such as keys or pens?	Without difficulty	Little difficulty	Moderate difficulty	Very difficulty	Very difficult
B: Functional status scale (8 items)					
Writing					
Buttoning of cloths					
Holding a book while reading					
Gripping of a telephone handle					
Opening of jars					
House hold chores					
Carrying of grocery basket					
Bathing and dressing					

poorly conducted and subjective reports of sensory/hand dysfunction with only few studies quantifying any changes in a robust manner. Finally, we find no evidence of widespread clinically significant hand dysfunction post TRA and the potential benefits of TRA in reducing major bleeding, access site related complications and mortality outweigh such rare events.

The majority of studies that reported cases of neurological deficits following TRA were underpowered<sup>[26,29,37]</sup>. In most circumstances, studies relied on subjective reporting of symptoms by patients, rather than quantifying the neurologic deficit with proper neurophysiological or other robust objective testing<sup>[24,27-31,34,35]</sup>. Benit *et al*<sup>[26]</sup> assessed nerve damage clinically and quantified this using EMG. Valgimigli *et al*<sup>[39]</sup> and Sciahbasi *et al*<sup>[33]</sup> used dynamometer to assess hand grip function whereas only Sciahbasi *et al*<sup>[33]</sup> used electronic pinch gauge to check for thumb and finger pinch tests. Van Leeuwen *et al*<sup>[24]</sup> used QuickDASH questionnaire and Cold Intolerance Symptom Severity (CISS) questionnaire based assessment of hand function post TRA.

The clinical significance of neurological and motor injuries leading to hand dysfunction must be con-

sidered. Many neurological injuries are known to be transient and resolve over time. For instance, van Leeuwen *et al*<sup>[24]</sup> reported that almost 20% patients developed subjective neurological complications in the form of numbness, tingling, stiffness and less power, more importantly nearly 50% resolved by 30 d at follow up. Similarly, pain is commonly reported by patients regardless of the access site practice but long term sequel of such symptoms is unclear. In addition, there is no consensus on the optimal method of assessing hand function and studies so far have used various methods such VAS, BCTQ, Disabilities of Arm, Shoulder and Hand (QuickDASH) and CISS (Tables 4-6).

Visual analogue scale is measure of pain intensity on a continuous scale anchored by pain descriptor ranging from "no pain (0 score)" to worst pain (score 10)<sup>[41]</sup>. BCTQ questionnaire comprises of a symptom severity scale and a functional status scale (Table 6). The symptom severity scale has 11 questions scored from 1 point (mildest) to 5 points (most severe). Likewise, functional status scale has eight questions scored from 1 point (no difficulty with activity) to 5 points (cannot perform the activity at all)<sup>[42]</sup>. Similarly,



CISS score is usually employed to detect cold intolerance. It consists of 6 questions and based on response, patient with a score of 30 or higher is said to have pathological CISS score<sup>[43,44]</sup>. There is a need of internationally agreed, sensitive method of assessing hand function amongst the radial community to evaluate and monitor for such complications.

The mechanisms that may underlie hand dysfunction after TRA remains unclear though there are several possible explanations. For instance, Flexor Carpi Radialis, Flexor Pollicis Longus tendons and Median nerve lies next to radial artery at wrist from lateral to medial respectively. Neurological deficits may occur from direct damage to these structures during cannulation of the radial artery. There also may be indirect extrinsic compression of these structures due to haematomas which may result in motor or sensory deficit of the hand. Endothelial dysfunction, intimal hyperplasia and medial dissections resulting in radial artery stenosis and occlusion are well known complications associated with TRA<sup>[45,46]</sup>. Haematoma or pseudoaneurysm is another relatively rare complications encountered after TRA. There is a possibility that such vascular complications may lead to transient or permanent ischemia of the nervous supply of hand leading to sensory deficit or directly cause motor dysfunction of small muscles of hand. Additionally, there are anatomic variations of neurovascular bundles of hand<sup>[47]</sup> which might be injured during the puncture leading to hand dysfunction such as sensory or motor symptoms. There are isolated case reports that describe this mechanism of nerve damage<sup>[48-50]</sup>. RAO may occur post TRA<sup>[21]</sup>, however it is usually asymptomatic and rarely causes ischemia due to the excellent collateral supply of hand from ulnar and intermediate artery<sup>[45,51]</sup>. Notably, recent results of ACRUS trial suggested that hand dysfunction was very common in patients developing RAO compared to the ones with a patent radial artery post procedure<sup>[38]</sup>. However, in the study conducted by Valgimigli *et al.*<sup>[39]</sup> across whole spectrum of Allen test, there were no differences in serial lactate measurement after the procedure suggesting that it is unlikely such mechanism can lead to clinically significant hand dysfunction.

It is unclear what factors are associated with hand dysfunction after TRA. It could very well be that certain patient factors, such as baseline hand muscle strength, history of musculoskeletal disorders, gender, atypical anatomy may be a risk factor but no studies have evaluated such predictors. Another important point how minor changes in hand function may impact on a patient's life. For example individuals that require very fine manual dexterity for their profession such as watchmakers, pianists, and surgeons may notice very minor changes in hand function whilst in other patient groups this may be less relevant. Finally, the way in which complications are managed may also affect hand function such as how quickly a haematoma

is identified and compressed. Future studies should be focused in assessing both patient and procedure related factors which may lead to development of hand dysfunction with clinically relevant end points. Finally, current literature does not provide an insight around the prevalence and significance of lower limb function in patients undergoing transfemoral access. Adequately powered randomized trial with a control group is required to better understand the incidence and mechanisms involved in the development of hand dysfunction post TRA.

In conclusion, hand dysfunction is an exceedingly rare complication post TRA. There is significant heterogeneity in the methodology and reporting of the studies investigating hand function after TRA. Patients may develop non-specific sensory symptoms or muscle weakness but majority of these symptoms resolve over time. Future studies should be focused around assessing such complications using robust methodology and more importantly reporting on the clinical relevance of hand function. Given the reductions in mortality, MACE and major bleeding complications associated with use of TRA in high risk groups undergoing PCI, TRA should remain the default access site for PCI in such high risk groups of patients at risk of bleeding complications, in line with international guidelines and consensus statements.

## COMMENTS

### Background

The uptake of transradial access (TRA) for cardiac procedures is growing with both observational and randomized controlled trial data showing decreases in mortality and access site related bleeding complications across the whole spectrum of acute coronary syndromes compared to procedures undertaken through the femoral approach.

### Research frontiers

Recently, concerns have been raised around hand dysfunction following transradial procedures.

### Innovations and breakthroughs

The review of the literature suggests that hand dysfunction after TRA has been reported in several studies and case reports. The quality of the evidence describing these complications is poor as many studies are underpowered and do not report any events. These complications appear to be rare and of uncertain clinical impact in most cases. Isolated case reports have reported rare complications such as compartment syndrome requiring emergency surgery or complex regional pain syndrome which can be disabling due to chronic pain.

### Applications

The current literature is limited as there is no standardized method of assessment of hand function with very few studies that provide mechanistic insight. Higher quality studies with clinically relevant endpoints are needed to better understand the incidence and clinical significance of the hand dysfunction following TRA.

### Terminology

TRA: Transradial access; TFA: Transfemoral access; PCI: Percutaneous coronary intervention; UED: Upper Extremity dysfunction.

## Peer-review

It is an excellent review.

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## Infective endocarditis and thoracic aortic disease: A review on forgotten psychological aspects

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### Abstract

#### AIM

To summarize the current evidence on psychological issues in thoracic aortic disease (TAD) and infective endocarditis (IE) setting.

#### METHODS

We performed a narrative review about psychological issues in adults with IE and TAD. Through the electronic databases, PubMed and PsycINFO, we searched full manuscripts in English and published until September 1, 2014.

#### RESULTS

We found sixteen studies exploring psychological issues in patients with IE (six studies) and in TAD (ten papers). Psychological issues assessed were quality of life, depression, anxiety and posttraumatic stress disorder. Quality of life was explored in IE (four papers) and in TAD (eight papers). Depression and anxiety were analyzed in TAD only (five papers). Post-traumatic stress disorder was assessed in IE (one study). Quality of life was found impaired in three of four studies about IE and in three of eight studies about TAD. Posttraumatic stress disorder was present in 11% and was associated with lower levels of quality of life in IE patients. In TAD patients, anxiety and depression levels after different invasive interventions did not differ.

#### CONCLUSION

Sixteen studies report about psychological issues in IE and TAD. Most of them explore quality of life and to a less extent anxiety and depression.

**Key words:** Infective endocarditis; Thoracic aortic disease; Psychology; Depression; Anxiety; Quality of life; Posttraumatic stress disorder

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**Core tip:** Some papers and guidelines have recently reported that psychosocial factors such as depression, anxiety and other mental disorders like personality disorders and post-traumatic stress disorder are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies. However, other cardiovascular diseases are poorly or not yet studied from a psychological point of view, including infective endocarditis and thoracic aortic disease. The study of psychological issues in these severe diseases could bring us information about specific needs to cover with psychological interventions and to design specialized care training and practice.

Suárez Bagnasco M, Núñez-Gil JJ. Infective endocarditis and thoracic aortic disease: A review on forgotten psychological aspects. *World J Cardiol* 2017; 9(7): 620-628 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/620.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.620>

## INTRODUCTION

Infective endocarditis (IE) is an inflammatory disease of the heart, an infection of the endocardium that usually involves valves and adjacent structures. The incidence of IE ranges from one country to another within 3-10 episodes/100000 person-years. It is higher in patients with underlying valvular heart diseases, prosthesis and those with intravenous drug abuse. IE with positive blood cultures represents 85% of all IE. Causative microorganisms are most often staphylococci, streptococci, and enterococci<sup>[1-7]</sup>. This disorder presents in a variety of clinical forms according to the initial clinical manifestation, underlying cardiac disease, microorganism involved, prosthesis presence, and development of complications. It may present as an acute and rapidly progressive infection or as sub-acute with low-grade fever and non-specific symptoms. With a modern combination of antimicrobial therapy and heart valve surgery, the in-hospital mortality rate of patients with or chronic disease IE varies from 9.6 to more than 26% (1-8)<sup>[1-8]</sup>. Psychological factors such as depression, anxiety and some personality traits could negative influence IE development and prognosis.

On the other hand, thoracic aortic diseases (TAD) include a wide spectrum of degenerative, structural, acquired, genetic-based, and traumatic disease states and presentations. The overall global death rate from aortic aneurysms and aortic dissection increased from 2.49 per 100000, to 2.79 per 100000 inhabitants between 1990 and 2010. TAD may be diagnosed after a long period of subclinical development or after an acute presentation such as acute aortic syndromes. Acute aortic syndromes are often the first sign of the disease, requiring rapid diagnosis and decision-making to improve prognosis. Medical therapy aims to reduce

shear stress on the diseased segment of the aorta by reducing blood pressure and cardiac contractibility. Further management options include endovascular therapy and surgery<sup>[9,10]</sup>. Psychological factors such as anxiety, depression and personality, could promote subclinical development and could negatively influence medical outcome after surgery and endovascular therapy, as well.

The aim of this review is to summarize the current evidence on psychological issues in TAD and IE setting. Thus, we performed a narrative review about psychological issues in adults with both TAD and IE.

## MATERIALS AND METHODS

Through the electronic databases PubMed and PsycINFO we searched all full manuscripts published in English until September 1, 2014.

The main data search terms were: Infective endocarditis + psychology, infective endocarditis + psychiatry, infective endocarditis + depression, infective endocarditis + anxiety, infective endocarditis + quality of life, infective endocarditis + personality, infective endocarditis + illness perception, infective endocarditis + therapeutic adherence, infective endocarditis + coping, thoracic aortic disease + psychology, thoracic aortic disease + psychiatry, thoracic aortic disease + depression, thoracic aortic disease + anxiety, thoracic aortic disease + personality, thoracic aortic disease + quality of life, thoracic aortic disease + therapeutic adherence, thoracic aortic disease + illness perception, thoracic aortic disease + coping.

## RESULTS

We found sixteen studies exploring psychological issues in patients with IE and TAD: Six about IE and ten about TAD. Main results are summarized in Tables 1 (IE) and 2 (TAD). Psychological issues assessed were mainly quality of life, depression, anxiety and post-traumatic stress disorder.

Quality of life was reviewed in 4 papers for IE and for TAD in 8 papers using Short Form 36 Health Survey questionnaire (SF-36) or EuroQol five dimensions questionnaire (EQ-5D).

Post-traumatic stress disorder was assessed in IE (one study) using the Post-traumatic stress disorder questionnaire. Depression and anxiety were analyzed in TAD (five papers) using Hospital Anxiety and Depression Scale (HADS).

### IE

We included six manuscripts about psychological issues in IE, all published in the last 5 years. Two papers used a qualitative method and four studies used a quantitative prospective design.

**Quantitative studies:** Quantitative studies assessed quality of life using standardized questionnaires.

**Table 1** Scheme of main findings about infective endocarditis

Ref.	Methods and materials	Main results
Verhagen <i>et al</i> <sup>[11]</sup> , 2009	Prospective, 67 treated for left-sided native valve endocarditis complete Short Form 36 Health Survey questionnaire and Posttraumatic Stress Disorder questionnaire	Quality of life was significantly impaired in IE patients, compared with an age- and sex-matched population. Posttraumatic stress disorder 11%
Perrotta <i>et al</i> <sup>[12]</sup> , 2010	Prospective, 40 infective prosthetic valve endocarditis or native endocarditis with abscess operated with homograft replacement. Short Form 36 Health Survey questionnaire	Statistically significant differences in quality of life were found between IE patients and an age-matched and gender-matched general population
Berg <i>et al</i> <sup>[15]</sup> , 2010	Qualitative, 10 patients. Semi-structured interview	Patients explain that a sudden unexpected physical change occurred that is difficult to understand and interpret. During the hospital admission, time is spent thinking about choices and lost possibilities before admission. They talk about investing their energy and attention on getting well
Yeates <i>et al</i> <sup>[13]</sup> , 2010	Prospective, 9 active native left sided valve endocarditis and cerebrovascular complications. EuroQol five dimensions questionnaire	6 reported some problems with mobility, 5 reported some problems with usual activities and 5 pain or discomfort
Nayak <i>et al</i> <sup>[14]</sup> , 2011	Prospective, 85 active endocarditis, native valve endocarditis or prosthetic valve endocarditis. EuroQol five dimensions questionnaire	Quality of life was not impaired
Rasmussen <i>et al</i> <sup>[16]</sup> , 2014	Qualitative, 11 patients. Semi-structured interview	Patients felt physically weak and mentally imbalanced to a varying degree. Uncertainty of recovery trajectory and future capacity was considered stressful

Three of four studies reported quality of life impaired in IE patients. One study reported the presence of a posttraumatic stress disorder in 11% of the cases.

In 2009, a prospective and multicenter follow-up study was performed aiming to assess quality of life and posttraumatic stress disorder of adults treated because a left-sided native valve endocarditis. Twelve months after the end of the antimicrobial treatment 67 adults completed both the SF-36 and the Post-traumatic stress disorder questionnaires. The quality of life was significantly impaired in IE patients, compared with an age- and sex-matched population. A posttraumatic stress disorder was present in 11% of the cases. The type of infecting microorganism, the length of hospitalization, type of cardiac surgery, and infective complications did not affect the result of the quality of life scores<sup>[11]</sup>.

In 2010, another study reported the outcomes and quality of life after homograft replacement for IE. After a mean follow-up of  $37 \pm 11$  mo, the quality of life was assessed using a SF-36 form. Forty five patients completed a specific questionnaire.

Statistically significant differences between patients operated with homograft and an age-matched and gender-matched general population were depicted in four subscales: Role-physical, general health, vitality, mental health<sup>[12]</sup>.

In the same year, Yeates *et al*<sup>[13]</sup> assessed the quality of life of IE patients who suffered cerebrovascular complications using the EQ-5D questionnaire. After a mean follow-up of 37.2 mo, 9 adults responded EQ-5D questionnaire by telephone: 7 reported no problems with self-care, 6 reported some problems with mobility, 5 reported some problems with usual

activities and 5 pain or discomfort.

In 2011, another study evaluated the early and mid-term outcomes, mortality and morbidity and quality of life of patients operated for IE. After a mean follow-up time of 37.2 mo, 85 patients answered a EQ-5D questionnaire. In that study, the patient's quality of life was not impaired<sup>[14]</sup>.

**Qualitative studies:** Qualitative studies review patient's experiences after IE diagnoses. Berg *et al*<sup>[15]</sup> described in 2010 IE experiences before and during hospital admission, including experience of physical symptoms and expectations for future health. Ten patients were included just before or after discharge, after a mean of 51.5 d of hospital admission. IE was perceived as an "intermezzo in life": Presage and appearance of IE, reaction to IE, living through IE, the little life with IE, body change and loved ones at distance.

The patients explained that perceived a sudden unexpected physical change, difficult to understand and interpret. This happens after a very long hospital admission, far different from one's normal way of life. During the hospital admission, they spent some time thinking about choices and lost possibilities before admission. They mentioned the idea of investing their energy and attention on getting well. Patients felt like not being able to interpret their body's signals, or that they did not receive clear signals whatsoever from the body that there is something wrong. Symptoms of IE are similar to and are often misinterpreted as a common infection or virus, such as a lung infection or influenza. Another important idea reported was that the disease does not only affect the patients, but can

Table 2 Scheme of main findings about thoracic aortic disease

Ref.	Methods and materials	Main results
Immer <i>et al</i> <sup>[22]</sup> , 2004	Prospective, 363 patients. 176 acute type A dissections, 187 aortic aneurysms. Antegrade cerebral perfusion 41 cases. Short Form 36 Health Survey questionnaire	Averaged quality life score was higher with the use of antegrade cerebral perfusion, independently of the duration of deep hypothermic circulatory arrest
Stalder <i>et al</i> <sup>[23]</sup> , 2007	Prospective, 244 patients. 76 isolated replacement of the ascending aorta, 42 separate aortic valve replacement and supracoronary replacement of the ascending aorta, 86 mechanical composite graft, 40 biologic composite graft. Short Form 36 Health Survey questionnaire	No difference in quality of life between groups was found
Dick <i>et al</i> <sup>[17]</sup> , 2008	Post hoc analysis, 122 patients. 52 thoracic endovascular aortic repair, 70 open aortic repair. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	Anxiety and depression scores were not significantly different between group No statistical differences in quality life scores
Immer <i>et al</i> <sup>[26]</sup> , 2008	Prospective, 567 patients. 387 deep hypothermic circulatory arrest with pharmacologic protection with pentothal only, 91 selective antegrade cerebral perfusion and pentothal, 89 continuous cerebral perfusion through the right subclavian artery and pentothal. Short Form 36 Health Survey questionnaire	Average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than selective antegrade cerebral perfusion
Krähenbühl <i>et al</i> <sup>[24]</sup> , 2008	Prospective, 907 patients. 219 acute aortic dissection type A, 617 aortic aneurysm. Transient neurological dysfunction 89 cases. Short Form 36 Health Survey questionnaire	Patients with transient neurological dysfunction showed a significantly impaired quality of life
Dick <i>et al</i> <sup>[18]</sup> , 2009	Post hoc analysis, 52 patients. 27 treated electively, 25 emergency indications. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	Anxiety and depression scores were in normal range and not increased after emergency situations No statistical differences between groups in quality of life were found
Lohse <i>et al</i> <sup>[25]</sup> , 2009	Prospective, 124 patients. 45 supracoronary replacement of the ascending aorta, 59 Wheat procedure, 15 David procedure, 12 Bentall-De Bono procedure, 3 Cabrol procedure. Short Form 36 Health Survey questionnaire	Different surgical techniques had no statistically significant influence on postoperative quality of life
Aicher <i>et al</i> <sup>[19]</sup> , 2011	Prospective, 166 patients. 86 aortic valve repair, 41 valve replacement with mechanical prosthesis, 39 valve replacement with pulmonary autograft. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	No differences were found in anxiety or depression scores between groups Patients after aortic valve repair <i>vs</i> replacement with pulmonary autograft revealed similar quality of life scores
Lehr <i>et al</i> <sup>[20]</sup> , 2011	Prospective, 144 patients. 51 mechanical conduit, 93 biological valve conduit. Hospital Anxiety and Depression Scale	No significant differences were found between groups for either anxiety and depression
Okamoto <i>et al</i> <sup>[21]</sup> , 2013	Prospective, 128 patients. 49 aortic surgery, 79 coronary artery bypass. Hospital Anxiety and Depression Scale	No statistical differences were found in depression or anxiety scores

also have a great impact on the life of their families<sup>[15]</sup>.

In 2014, a qualitative study described patient experiences during recovery after IE. Eleven patients were interviewed 3 to 6 mo after discharge. Patients talked of IE as an unpredictable disease. They described a phase of adaptation to a new life situation, which some perceived as manageable and temporary, whereas others found it extremely distressing and prolonged. Most of them experienced a persisting weakness and felt frustrated about the prolonged recovery phase. Patients felt physically weak and mentally imbalanced to a varying degree. They described a time of emotional instability and different psychological reactions, ranging from mild mood swings to severe anxiety. Uncertainty of recovery trajectory and future capacity was considered stressful. They worried about sources of infections; open wounds and they recognized that even a hemorrhoid could become a cause for concern. Most of them described how significant the support from family and friends had been during hospital admission and recovery. Some also described feeling concerned and guilty; being the cause of the stress and strain their loved ones had been through<sup>[16]</sup>.

## TAD

We found ten suitable manuscripts that studied psychological issues using standardized questionnaires in TAD patients, after surgery or endovascular therapy and a variable follow up period.

**Depression and anxiety:** Five papers studied depression and anxiety in patients treated with surgery or endovascular therapy. No statistical differences were found in anxiety and depression scores after aortic valve repair using mechanical replacement *vs* after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery *vs* after coronary artery bypass grafting; after thoracic endovascular aortic repair *vs* after open aortic repair or after thoracic endovascular aortic repair which indication was done electively *vs* emergency.

In 2008, a study assessed anxiety and depression on diseases of descending thoracic aorta, in patients treated either by thoracic endovascular aortic repair or open aortic repair. After mean follow-up of  $34 \pm 18$  mo, 75 adults fulfilled a HADS form. Although depression and anxiety scores tended to be more elevated in patients that underwent thoracic endovascular aortic



repair than in patients that underwent open aortic repair patients, statistical significances were not found<sup>[17]</sup>.

In 2009, Dick *et al.*<sup>[18]</sup> studied the impact of urgency procedures on quality of life in patients with descending thoracic aorta disease. Twenty seven patients completed the HADS after mean follow-up of  $29 \pm 16$  mo. Anxiety and depression scores were in normal range and did not increase after emergency situations.

In 2011, a study was conducted to assess and compare anxiety and depression after aortic valve repair using two replacement alternatives: Mechanical valve and pulmonary autograft. After a follow up interval that ranged between 3 and 7 years, 166 subjects responded the HADS questionnaire. No differences were found regarding anxiety or depression scores between groups<sup>[19]</sup>.

In the same year, anxiety and depression over a group of patients who underwent aortic root replacement with mechanical and biological conduits were assessed and compared by Lehr *et al.*<sup>[20]</sup>. Seventy four patients completed a HADS form after a median follow-up of 40 mo. Anxiety and depression scores were not significantly different between groups.

In 2013, other study compared anxiety and depression in patients undergoing thoracic aortic surgery with another cohort of patients undergoing coronary artery bypass grafting. Hospital anxiety and depression scale was complete at 1-5 years postoperatively by 98 patients. Twenty-eight percent of thoracic aortic surgery patients had depression and 14% anxiety. Twenty percent of coronary bypass patients had depression and 16% anxiety. No statistical differences were found in depression or anxiety scores either in this study<sup>[21]</sup>.

**Quality of life:** Over ten, eight studies analyzed the impact of different surgical procedures and endovascular therapy on the quality of life of patients with diseases of aortic root and aortic valve, ascending aorta, aortic arch, and descending aorta.

One study assessed the quality of life after aortic valve replacement comparing two replacement alternatives: Mechanical and pulmonary autograft. Over a follow-up interval between 3 and 7 years, 166 subjects completed a SF-36 questionnaire. Patients who had undergone aortic valve repair and replacement with pulmonary autograft depicted similar quality of life scores, but this matter was better in patients after replacement with mechanical prosthesis regarding physical functioning, general health, and mental health<sup>[19]</sup>.

**Ascending aorta:** Four papers studied the quality of life of patients with diseases of ascending aorta.

In 2004 a study analyzed the impact of the duration of the deep hypothermic circulatory arrest and the potential effects of antegrade cerebral perfusion

on quality of life in patients undergoing surgery of the thoracic aorta. Two hundred and ninety adults completed the SF-36 questionnaire after mean follow up of  $2.4 \pm 1.2$  years. Averaged quality life score was significantly better with the use of antegrade cerebral perfusion, independently of the duration of deep hypothermic circulatory arrest<sup>[22]</sup>.

In 2007 another manuscript analyzed the impact of different surgical procedures on quality of life in patients with ascending aorta diseases. Patients were divided according to the operative procedure: Isolated replacement of the ascending aorta, separate aortic valve replacement and supracoronary replacement of the ascending aorta, mechanical composite graft, and biologic composite graft. After mean follow-up of  $26.6 \pm 8.8$  mo, 176 patients completed a SF-36 questionnaire. No difference in quality of life between groups was found<sup>[23]</sup>.

Krähenbühl *et al.*<sup>[24]</sup>, in 2008, assessed the influence of transient neurological dysfunction (defined as a Glasgow coma scale value  $< 13$ ) on the quality of life of patients undergoing surgery of ascending aorta and proximal aortic arch. Over a mean follow-up interval of  $27 \pm 14$  mo, 79 subjects completed a SF-36 questionnaire. Patients with transient neurological dysfunction showed a significantly impaired quality of life except for bodily pain.

In 2009, a study assessed the quality of life among patients who underwent replacement of a dilated ascending aorta. Patients were divided according to the operative procedure. Operative procedures consisted of supracoronary replacement of the ascending aorta, the Wheat procedure, the David procedure, the Bentall-De Bono procedure, and the Cabrol procedure. One hundred and twenty two patients completed a SF-36 questionnaire after mean follow-up of  $36.4 \pm 15.5$  mo. Different surgical techniques had no statistically significant influence on postoperative quality of life. However, many subscales of SF-36 were below the norm when compared with a standard population, in particular physical pain and physical function<sup>[25]</sup>.

**Aortic arch:** Two studies assessed quality of life of patients with diseases of aortic arch.

Immer *et al.*<sup>[26]</sup> published (2008) a study assessing the impact of continuous cerebral perfusion through the right subclavian artery on quality of life. With a mean follow-up of  $2.4 \pm 1.2$  years, 453 adults respond SF-36 questionnaire. Interestingly, the average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than when selective antegrade cerebral perfusion was used.

As we mentioned previously, in 2008, Krähenbühl *et al.*<sup>[24]</sup> assessed the influence of transient neurological dysfunction on quality of life of patients undergoing surgery of proximal aortic arch and ascending aorta, showing that patients with transient neurological

dysfunction showed a significantly impaired quality of life later.

**Descending aorta:** Two studies explored quality of life of patients with diseases of descending aorta. Dick *et al.*<sup>[17]</sup>, in 2008 analyzed quality of life in patients treated either by thoracic endovascular aortic repair or by open aortic repair for diseases of the descending thoracic aorta. Seventy-five adults completed the SF-36 questionnaire after a mean follow-up of  $34 \pm 18$  mo. Quality of life scores of open aortic repair in the patients included in this study ranged from 63 to 110; the median was 93. Quality of life scores of thoracic endovascular aortic repair ranged from 60 to 112, with a median of 83. Thus, the authors concluded that after thoracic aortic repair the quality of life was reduced.

One year later, Dick *et al.*<sup>[18]</sup>, published another paper regarding the impact of urgency procedures on quality of life in patients with descending thoracic aorta disease. After a mean follow-up of  $29 \pm 16$  mo, 27 adults responded the SF-36 questionnaire. Quality of life scores after emergency range between 58 and 124, with a median of 72. Quality of life scores after elective endovascular aortic repair range between 61 and 105, median: 85. No statistical differences between groups in quality of life were found.

## DISCUSSION

We summarize the results of a small number of studies dealing with psychological issues in IE and TAD. Despite the high impact that psychological conditions might cause in these severe diseases, we could verify that there is not much information available on these matters. Thus, we aimed to review the available evidence on this context.

Some papers<sup>[27-29]</sup> and guidelines<sup>[30-33]</sup> previously reported that psychosocial factors such as depression, anxiety and other mental disorders such as personality disorders and post-traumatic stress disorders are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies in that setting. Otherwise, other cardiovascular diseases are poorly or not studied from a psychological point of view, such as IE and TAD. We found four studies comparing anxiety and depression scores in patients with TAD after treatment and only one paper assessing post-traumatic stress disorder after IE treatment.

When specialists choose a specific type of invasive intervention, psychological aspects are usually ignored. The identification of interventions that increase anxiety and/or depression could be of interest from a medical point of view because anxiety and/or depression might negatively influence patient recuperation after the intervention. In TAD patients, anxiety and depression levels after different invasive interventions did not differ. No statistical differences were found in anxiety

and depression scores: After aortic valve repair using mechanical replacement vs after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery vs after coronary artery bypass grafting; after thoracic endovascular aortic repair vs after open aortic repair, after thoracic endovascular aortic repair which indication was done electively vs emergency. Moreover, baseline anxiety and depression scores had not been reported. Depression or/and anxiety before invasive intervention, might negatively influence coping and recuperation after intervention.

A posttraumatic stress disorder was present in 11% and was associated with lower levels of quality of life in IE patients. IE patients with posttraumatic stress disorder reported feeling nervousness and depressive, having problems with work or other daily activities and having frequent interference with social activities due to physical or emotional problems. Although the percentage of posttraumatic stress disorder in IE might be considered low, IE patients with posttraumatic stress disorder need specialized mental health care and interventions to improve their quality of life.

Most of the studies assessed IE and TAD quality of life after treatment. Quality of life was reported to be impaired in three of four studies about infectious endocarditis and in three of eight studies about TAD. However, recent clinical guidelines about infectious endocarditis did not mention quality of life and recent guidelines about TAD did not make the slightest reference to quality of life either.

Most of quantitative studies about IE reported that after 12 or 37 mo after IE diagnosis, quality of life was clearly impaired. Only one study explored the possible influence of the causal microorganism, length of hospitalization, type of cardiac surgery, and infective complications in quality of life scores. The authors concluded that those issues did not clearly affect quality of life scores. In two studies, the patients evaluated their personal health as poor mentioning that it was likely to get worse. In one study, patients reported feeling tired, worn out all, nervousness and depressive. Since depression was not assessed, we can not know if those IE patients had depression, although this is a possibility. Moreover, elevated pro-inflammatory cytokines in IE could promote psychological alterations such as depression, especially in vulnerable patients, and this might compromise prognosis and the ability to cope the disease.

The cerebral perfusion technique used in invasive intervention of TAD patients might have neurological consequences and could influence the perceived quality of life as well. After a surgery of thoracic aorta, patients might postoperatively develop confusion, agitation and delirium, also named "temporary neurological dysfunction". Although resolution of these symptoms usually occur before hospital discharge, patients with temporary neurological dysfunction had lower scores in quality of life than patients without temporary neurological dysfunction. Patients with temporary

neurological dysfunction evaluate their personal health as poor and believe that it is likely to get worse. This way, they reported feeling nervousness, depressive, and having problems with work or other daily activities. The incidence of neurological complications might be decreased using selective antegrade cerebral perfusion. A study reported that the average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than selective antegrade cerebral perfusion. One important limitation was that all the studies revised did not include assessment before treatment or a proper control group. In addition, detailed medical records about patients that answered these mentioned questionnaires used to assess psychological issues are frequently not available.

Sixteen studies have been published about psychological issues in IE and TAD. Most of them explored quality of life and to a less extent anxiety and depression. Papers reviewed were heterogeneous in patients and procedures; they included few participants, they did not include control groups and they did not evaluate patients before treatment. Thus, we feel that more studies are needed, especially with a prospective design. The study of psychological issues is relevant and could bring us information about specific needs to be covered by psychological interventions and to design specialized care training and practice.

## COMMENTS

### Background

Some papers and guidelines reported that psychosocial factors such as depression, anxiety and other mental disorders such as personality disorders and post-traumatic stress disorder are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies. Otherwise, other cardiovascular diseases are poorly or not yet studied from a psychological point of view, such as infective endocarditis (IE) and thoracic aortic disease (TAD). The study of psychological issues in these severe diseases could bring people valuable information about specific needs to cover with psychological interventions and to design specialized care training and practice. The aim of this review is to summarize the current evidence on psychological issues in TAD and IE setting. The authors performed a narrative review about psychological issues in adults with both TAD and IE.

### Research frontiers

From the health-psychology standpoint, both IE and TAD are almost forgotten research subjects. Patients with medical disorders usually require specialized medical attention and psychological care. It might be expected that patients with severe cardiovascular diseases will not be the exception, especially in the cases of IE and TAD, which generally require several invasive interventions. This area of interest is pretty new. All the papers revised in this research were published in the present century. Nevertheless, precise data on the psychological disorders that could be associated with IE and TAD is still lacking.

### Innovations and breakthroughs

Sixteen studies have been published about psychological issues in IE (six studies) and TAD (ten papers). Psychological issues assessed were quality of life, depression, anxiety and posttraumatic stress disorder. Quality of life was reported impaired in three of four studies about infectious endocarditis and in three of eight studies about TAD. However, recent clinical guidelines about infectious endocarditis did not mention quality of life and recent guidelines

about TAD made slightest reference to quality of life. Depression and anxiety were analyzed in TAD only (five papers). Anxiety and depression levels after different invasive interventions did not differ. No statistical differences were found in anxiety and depression scores: After aortic valve repair using mechanical replacement vs after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery vs after coronary artery bypass grafting; after thoracic endovascular aortic repair vs after open aortic repair, after thoracic endovascular aortic repair which indication was done electively vs emergency. Moreover, baseline anxiety and depression scores had not been reported. Depression or/and anxiety before invasive intervention, might negatively influence patient recuperation after intervention. Regarding to IE, since depression was not properly assessed in the published manuscripts we do not have precise data. However, elevated pro-inflammatory cytokines in IE could promote psychological alterations such as depression, especially, in vulnerable patients, and this might compromise prognosis and coping disease. Post-traumatic stress disorder was assessed in IE (one study). It was present in 11% and was associated with lower levels of quality of life in IE patients. Although percentage of posttraumatic stress disorder in IE might be considered low, IE patients with posttraumatic stress disorder need specialized mental health care and interventions to improve quality of life.

### Applications

Despite the high impact that psychological conditions might cause in these severe diseases, the authors could verify that there is not much information available. It would be desirable that future studies used prospective designs, included control group and completed psychological assessment before and after treatments/interventions.

### Terminology

Psychological aspects revised in this paper include depression, anxiety, personality, coping, therapeutic adherence, illness perception and quality of life.

### Peer-review

The focus on IE is very timely and important, and the author presents the data in a very meaningful and useful manner.

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## Endovascular treatment of paravisceral mycotic aneurysm: Chimmeny endovascular sealing the end of de road

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### Abstract

Open surgery is the elective treatment for mycotic aneurysms of the aorta. This surgery consists of resection of the aneurysm, debridement and revascularization with an *in situ* or extra-anatomic bypass. Even when surgery has been successful, the morbidity is raised and the endovascular treatment has become an alternative for specific patients. When mycotic aneurysms involved the visceral arteries, more complex techniques are necessary such as fenestrated endovascular aortic repair or chimney endovascular aortic repair and the most frequent complications of this are endoleaks and occlusion the visceral arteries. We present a case of a patient with a paravisceral abdominal mycotic aneurysms that was result with 2 chimney technique (in the right renal and superior mesenteric arteries) and a single Nellix EVAS (Endologix, Irvine, Calif) of 12 cm long without evidence of endoleaks in the follow-up.

**Key words:** Mycotic aneurysms; Endovascular repair; Aorta; Endoleaks; Para visceral aneurysms

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**Core tip:** The interesting of the case that we present is the resolution of the mycotic aneurysms throw a new techniques calls chimney endovascular sealing (Ch-EVAS). This case it would be the first case treated with Ch-EVAS that has been reported since in the

bibliographical review that we made we do not find cases of paravisceral abdominal mycotic aneurysms treated with this technology.

Rabellino M, Moltini PN, Di Caro VG, Chas JG, Marenchino R, Garcia-Monaco RD. Endovascular treatment of paravisceral mycotic aneurysm: Chimney endovascular sealing the end of de road. *World J Cardiol* 2017; 9(7): 629-633 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/629.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.629>

## INTRODUCTION

Open surgery is the elective treatment for mycotic aneurysms of the aorta. This surgery consists of resection of the aneurysm, debridement and revascularization with an *in situ* or extra-anatomic bypass<sup>[1]</sup>. Even when surgery has been successful, the morbi-mortality is raised and the endovascular treatment has become an alternative for specific patients<sup>[2]</sup>.

The main problem of this kind of pseudoaneurysms is the location. When the mycotic aneurysm is in the descending aorta or infrarenal aorta without compromising the supra-aortic trunks or the visceral arteries, endovascular treatment is possible with a successful outcome<sup>[2]</sup>. Nevertheless, it has not been well described in the literature this type of procedure for paravisceral abdominal aortic aneurysm.

When mycotic aneurysms involved the visceral arteries, more complex techniques are necessary such as Fenestrated endovascular aortic repair (f-EVAR) or chimney endovascular aortic repair (Ch-EVAR) and the most frequent complications of this are endoleaks and occlusion the visceral arteries<sup>[3,4]</sup>.

We present a case of a patient with a paravisceral abdominal mycotic aneurysms with absolute contraindication for open surgery with two unsuccessful endovascular treatments, that was result with chimney technique and Nellix (Endologix, Irvine, Calif) chimney endovascular sealing (Ch-EVAS).

## CASE REPORT

A 72-year-old woman was admitted in the emergency department presented with acute abdominal pain. She had a medical history of former smoker, multiple coronary by-pass with dehiscence of the chest wound, pulmonary embolism treated with anticoagulants and respiratory failure (SpO<sub>2</sub> 82%).

To the physical examination, the patient was presenting an acute abdominal pain with rigidity, guarding and peritoneal irritation so an AngioCT scan was performed and showed gastrointestinal perforation and a 4.9 cm paravisceral abdominal aneurysms with intraluminal thrombus (Figure 1A). Small bowel resection and jejunostomy was done.

Anatomopathology showed miliary tuberculosis with intestinal involvement and peritoneal implants.

With this result and the presence of the aortic aneurysms we made the diagnosis of tuberculous mycotic aneurysm with compromise of the four visceral branches. Although, the endovascular treatment was decided because of the clinical situation of the patient, the endovascular options have not been simple because of the location of the aneurysms. The options were a f-EVAR, which was impossible for the time confection or a Ch-EVAR with the risk of endoleaks in the pseudoaneurysms that needs 4 chimney.

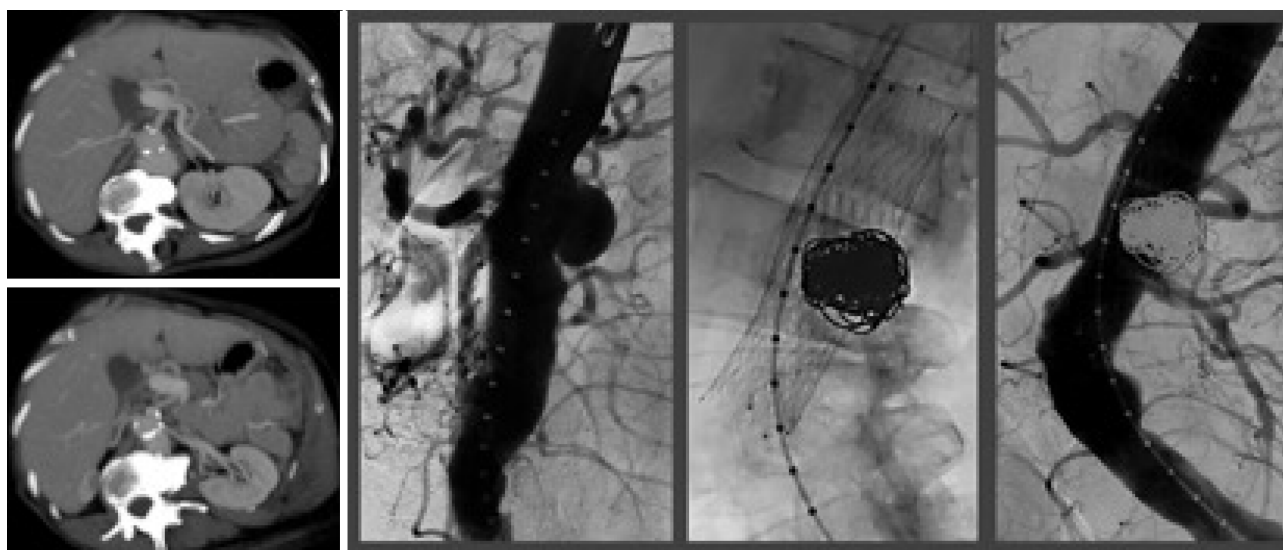
Another therapeutic option was Ch-EVAS which was not available in our country. Base on the foregoing, and knowing that it was not a definitive treatment, the decision was to perform stent assisted coil embolization technique of the aneurysms.

In the procedure, for a femoral access a Sinus XL stent (OptiMed, Ettlingen, Germany) was placed in the aortic visceral topography and across it embolization of the pseudoaneurysm with coils was performed with a successful initial first result (Figure 1B and D) and without complications. The patient was discharged 48 h later with parenteral nutrition, aspirin 100 mg/d and antibiotics therapy for tuberculosis.

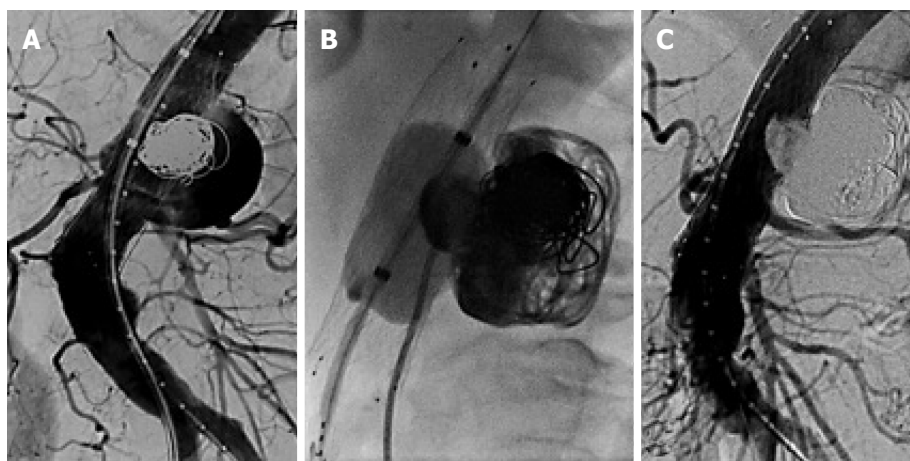
Four month later, an AngioCT scan revealed that the mycotic aneurysm had grown and a for a percutaneous femoral access a balloon-assisted coils and n-butyl 2-cyanoacrylate embolization was performed with good angiographic outcomes (Figure 2). The patient was still undergoing treatment for her infection disease and was discharged 24 h later without complications. Bowel transit and abdominal wall reconstruction was made a month later. Two month after surgery, the patient was admitted with low back pain and the CT angiogram showed an endoleak with aneurysm sac enlargement and extravasation of the embolic agents used previously that indicated rupture, so an endovascular treatment with Ch-EVAS was decided, because it was already available in our country.

Under general anesthesia a percutaneous femoral access was done for the introduction of a single Nellix EVAS of 12 cm long (the aortic diameter was normal and it was not necessary to spread up to the iliac arteries) and a open left subclavian access to place the chimneys for the right renal and superior mesenteric arteries. Both chimneys were performed with a Viabahn covered stent (Gore and Associates, Flagstaff, AZ) of 7 mm × 100 mm for the right renal artery and 8 mm × 100 mm for the superior mesenteric artery. Inside the chimneys a nitinol self-expanding stent was placed to give them a greater radial force strength and to avoid the chimney collapse by the polymer (Figure 3).

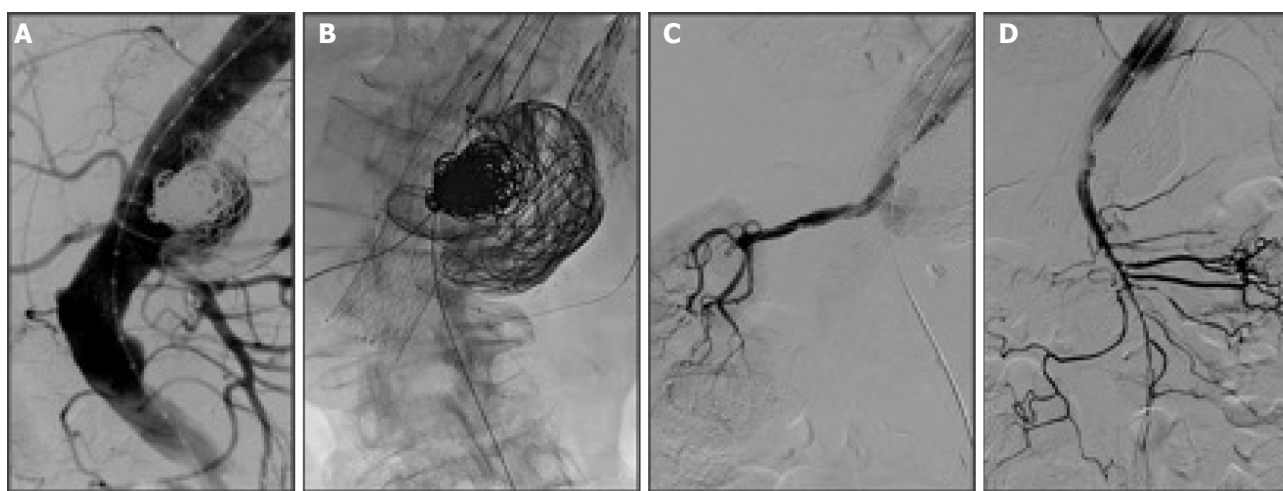
The left renal artery was catheterized but it was not possible to advance a catheter across the strut of the Sinus stent, so an angioplasty with a 6-mm low-profile coronary balloon was performed. Despite these, it was not possible to introduce a 4 Fr diagnostic catheter



**Figure 1** AngioCT scan and digital subtraction angiography. Mycotic aneurysm and the relation with the visceral branches, stent assisted coil embolization of aneurysms with a Sinus XL stent and complete embolization of the mycotic aneurysms without evidence of flow inside the sac.

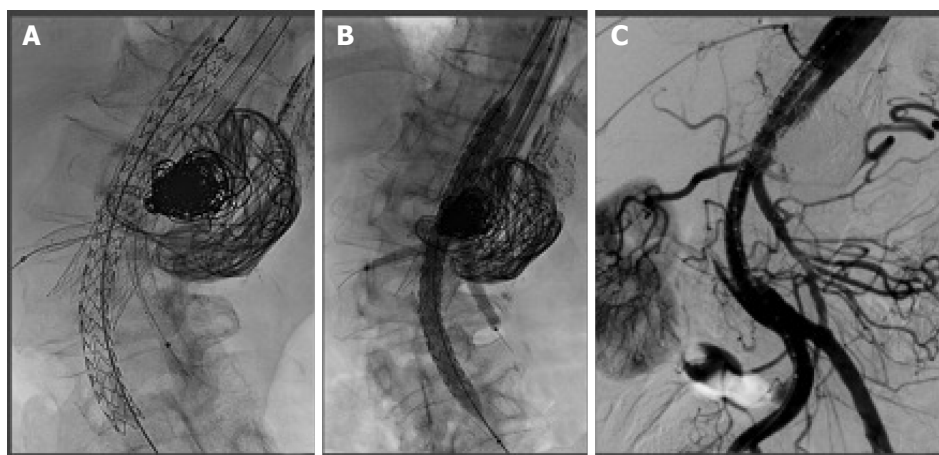


**Figure 2** Digital subtraction angiography (A-C). Flow in the mycotic aneurysms an increased de diameter of the sac. Coils and n-butyl 2-cyanoacrylate embolization performed with the balloon-assisted technique and final angiographic control shows absence of flow in the interior of the aneurysms.



**Figure 3** Digital subtraction angiography. Rechanneling of the pseudoaneurysms. Renals and superior mesenteric arteries catheterization (the left renal artery with a coronary balloon angioplasty) and the presence of n- butyl 2-cyanoacrylate out of the pseudoaneurysms. Chimney in the right renal artery and superior mesenteric artery.





**Figure 4** Single Nellix endovascular sealing and the chimneys (A-C). Fluoroscopy of the balloons inflated during the filling of the bag of the Nellix EVAS with the polymer. Permeability of the endograft, both chimneys and the celiac trunk without evidence of endoleaks.

so it was decided to abandon the left renal artery. It was decided not to be catheterized the celtrunk for the idea that it would be compensated for the superior mesenteric artery, as it happened.

The final angiographic control showed the exclusion of the mycotic aneurysms with permeability of the right renal artery and superior mesenteric artery which supply the celiac trunk and its branches (Figure 4). After the procedure, the patient was discharged 5 d later without complications, normal renal function, clopidogrel 75 mg, aspirin 100 mg a day and antibiotic therapy. AngioCT scan follow-up at 3 mo, showed absence of endoleaks and permeability of the right renal artery, superior mesenteric artery and the celiac trunk.

## DISCUSSION

Open surgery is the elective treatment for mycotic aneurysms of the aorta, however in patient with absolute contraindication for surgery, the endovascular treatment become an important alternative for this patients that have been well described in the multicentric European study which concluded that endovascular treatment it is a feasible and lasting option in most patients<sup>[2]</sup>. Nevertheless, in this study of all treated aneurysms only in the 7% of them it was used f-EVAR techniques, not having specific comments about the follow-up in these patients. Another endovascular option for the treatment of paravisceral abdominal mycotic aneurysms is the Ch-EVAR. However, the rate of endoleaks with this technique in a review by Patel *et al*<sup>[4]</sup> was estimated at 5% to 37.5%.

In a recent review by Li *et al*<sup>[5]</sup> the rate of endoleaks type IA was 11.8% with a permeability of the branches of 96.6% at 6 mo. Because of these, in our case we this alternative was scorned in view of the high percentage of endoleaks (4 or 3 chimneys were necessary) and the consequent risk of rupture. In this location, the f-EVAR is a good choice to treat this

aneurysm. The only problem is the time of confection that limits the use in pseudoaneurysms that need an early resolution. In the last 2 years, it has been reported some cases of paravisceral aneurysms treated with Ch-EVAS technique that show promising result<sup>[6-8]</sup>. Torella *et al*<sup>[7]</sup> presented 2 cases of juxtarenal aortic aneurysms treated with Ch-EVAS with 2 chimneys in each case and without evidence of endoleaks type IA. Youssef *et al*<sup>[6]</sup> published recently a series of 7 patients treated with Ch-EVAS with four chimneys for patient in which they reported no early endoleaks with a permeability of 96% of the branches to 6 mo of follow-up.

The Ch-EVAS turns out to be a interesting concept since the polymer realizes a copy of the aortic anatomy occupying the space of the gutters that they originate with the conventional Ch-EVAR technique reducing the risk of endoleaks. The case that we presented it would be the first case treated with Ch-EVAS that has been reported since in the bibliographical review that we made we do not find cases of paravisceral abdominal mycotic aneurysms treated with this technology. While so far, the reports on Ch-EVAS are only clinical case reports, they represent encouraging results as a future alternative of first choice for the treatment of paravisceral aortic aneurysms.

## COMMENTS

### Case characteristics

A 72-year-old woman with a medical history of military tuberculosis with abdominal involment that was treated in two opportunities for a mycotic aortic aneurysm with compromise of the four visceral branches with endovascular technique was admitted at the emergency department with low back pain two months after the second treatment.

### Imaging diagnosis

Computed tomography angiogram showed an endoleak with mycotic aneurysm enlargement.

### Treatment

Endovascular treatment performed with Chimney endovascular aneurysm

sealing (Ch-EVAS) with good result with exclusion and absent of endoleaks in the final angiography control. In the follow up the patient continuous asymptomatic with no evidence of endoleaks or another complication.

### Experiences and lessons

A mycotic aneurysm of the aorta with involvement of the visceral arteries is a dreadful condition and repair it can be quite challenging. The endovascular treatment has become an important alternative. The Ch-EVAS turns out to be a interesting concept because it solves the endoleaks problems with the conventional chimney endovascular aneurysm repair). In the authors' bibliographical review, the authors did not find cases of paravisceral abdominal mycotic aneurysms treated with this technology.

### Peer-review

This is an interesting case report about the endovascular treatment of paravisceral mycotic aneurysm.

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## Percutaneous closure of congenital Gerbode defect using Nit-Occlud® Lê VSD coil

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### Abstract

We present a case report about percutaneous closure of a congenital Gerbode defect using Nit-Occlud® Lê VSD coil. The patient was referred to our hospital with a diagnosis of ventricular septal defect (VSD) and severe pulmonary arterial hypertension. But transthoracic echocardiography revealed a communication between the left ventricle (LV) and the right atrial (RA), called Gerbode defect. Catheterization confirmed the shunt from the LV to the RA. We successfully closed the defect with a VSD coil. After uneventful 6 mo follow-up, the patient was out of dyspnea, the symptom urged him to have medical attention. This case report is to discuss the diagnosis and percutaneous treatment approach for this rare congenital heart disease.

**Key words:** Congenital Gerbode defect; Nit-Occlud® Lê VSD coil; Congenital heart disease; Transcatheter device closure; Device embolization

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**Core tip:** Congenital Gerbode defect is rare, only accounts for about 0.08% among congenital heart diseases. The diagnosis is easily misinterpreted with others condition on clinical examination and echocardiography. The treatment of this disease is also lack of recommendation. There are several approaches can be applied for this kind of defect such as conservation, cardiac surgery, intravascular intervention or intra-operative device closure. There are several devices can be used for transcatheter closure such as ventricular septal occluder, atrial septal occluder, ADO I or ADO II. This is the first report using Nit-Occlud® Lê VSD coil to close Gerbode defect successfully.

Phan QT, Kim SW, Nguyen HL. Percutaneous closure of congenital Gerbode defect using Nit-Occlud® Lê VSD coil. *World J Cardiol* 2017; 9(7): 634-639 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/634.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.634>

## INTRODUCTION

The left ventricular to right atrial (LV-RA) communication was first described by Frank Gerbode in 1958<sup>[1]</sup>. This defect can be either congenital or acquired. While congenital LV-RA shunt is very rare, acquired LV-RA shunt is reported more common, can be induced by endocarditis, trauma, valve replacement, myocardial infarction, *etc*<sup>[2]</sup>. There are several varieties of Gerbode defect<sup>[1]</sup>: Supravalvular (direct) type, subvalvular (indirect) type and a combination of these two lesions.

The diagnosis of congenital Gerbode defects is quite challenging: While the clinical symptoms may mimic ventricular septal defect (VSD), it can be misinterpreted on TTE with tricuspid regurgitation and pulmonary arterial hypertension. Further investigation by transesophageal echocardiography (TEE), magnetic resonance imaging (MRI), computed tomographic angiography (CTA), ... may help to determine the right diagnosis.

## CASE REPORT

A 31-year-old male who had dyspnea on exertion 3 mo before hospitalization, was referred to our hospital with a diagnosis of heart failure in patient with VSD and severe pulmonary hypertension. He had healthy active lifestyle, normal physical and mental development. The clinical examination showed a loud harsh holosystolic murmur (4/6 Levine scale) at 4<sup>th</sup> intercostal spaces along left sternal border, radiated downward and a systolic thrill could be palpated. His blood pressure was 125/85 mmHg. The ECG showed sinus rhythm. The BNP was slightly increased. Chest X-ray, ionogram, creatinine, glucose, blood count and clotting times were in normal range. The TTE revealed a shunt between the LV and the RA. The jet went into the RA looked similar to the tricuspid valve regurgitation flow with high velocity, about 4.8 m/s. The other findings included slight dilation of the right heart chambers, mild RV systolic dysfunction and Qp:Qs was 1.6.

Cardiac catheterization was performed. LV contrast injection illustrated quite large shunt from the LV to the RA. The defect was in long conical figuration with diameters of 9.5 mm at the biggest LV ampulla, 4.0 mm at the narrowest position and 8.5 mm length. It was quite far from the aortic valve and coronaries. The pulmonary arterial pressure was 56/22/35 mmHg.

After getting across the defect with a Terumo wire from LV and snaring the wire at the superior vena cava for making the arteriovenous loop, an 8F deli-

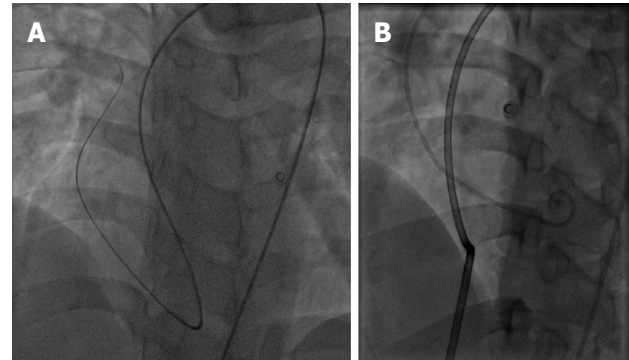


Figure 1 Through the defect, the Terumo wire was introduced to the right atrial and superior vena cava from left ventricle (A) and the 8F delivery catheter went from inferior vena cava and right atrium to the left atrium and aorta (B).



Figure 2 The Nit-Occlud® Lê VSD coil.

very catheter was introduced to LV and aorta from RA through the defect (Figure 1). Then, a 12 mm × 6 mm Nit-Occlud® Lê VSD coil (Figure 2) was deployed to close the defect with aortic approach (Figure 3). The procedure was quite similar to perimembranous VSD occlusion with likely satisfied result (Figure 4). There was only small residual shunt from LV to RA on LV contrast injections and echocardiography, no aortic regurgitation, no cardiac arrhythmia on ECG and the hemodynamic was stable.

But while the patient was kept following on cathlab table for complications, mostly concerning bradycardia and heart block, we detected some free bizarre movement of device distal part (Video 1). The device was going to drift out of the defect at 15 minutes after coil release. We quickly retrieved the coil with multi-snare and 10F catheter from the RA through inferior vena cava (Figure 5). Another attempt to close the defect with a bigger 14 mm × 8 mm Nit-Occlud® Lê VSD coil was performed (Figure 6). The final result looked fine with mild residual LV-RA shunt, no aortic regurgitation, no arrhythmia. Six hours after the procedure, there was still a grade 2/6 murmur can be found on auscultation and mild shunt from LV to RA on echocardiography. After 24 h, both the murmur and residual shunt flow were gone. After 5 d of close



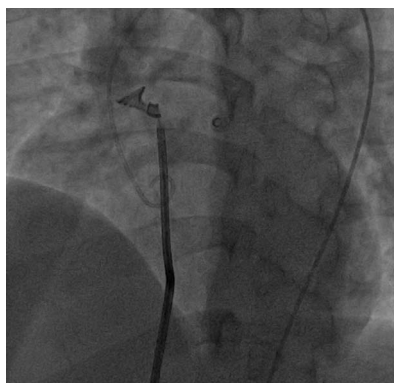


Figure 3 The 12 mm × 6 mm Nit-Occlud® Lê VSD coil was deployed with aortic approach.

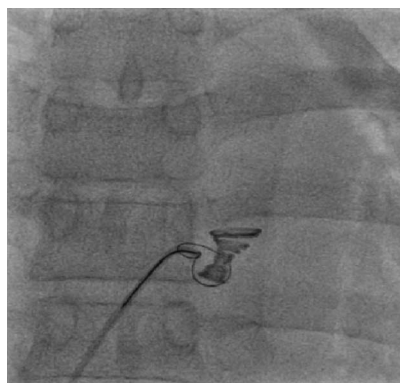


Figure 5 The drifting coil was retrieved with a multi-snare from the atrial side.



Figure 4 The 12 mm × 6 mm Nit-Occlud® Lê VSD coil immediately after release.

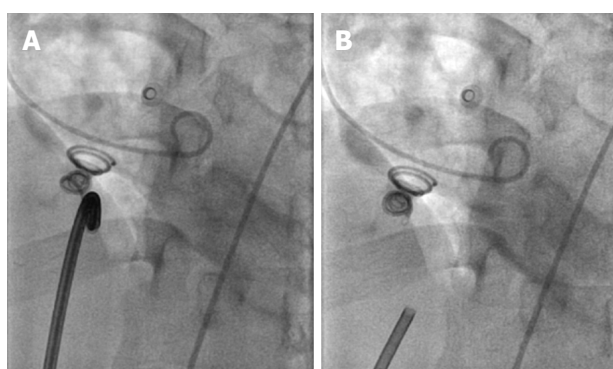


Figure 6 The bigger 14 mm × 8 mm Nit-Occlud® Lê VSD coil before (A) and immediately after release (B).

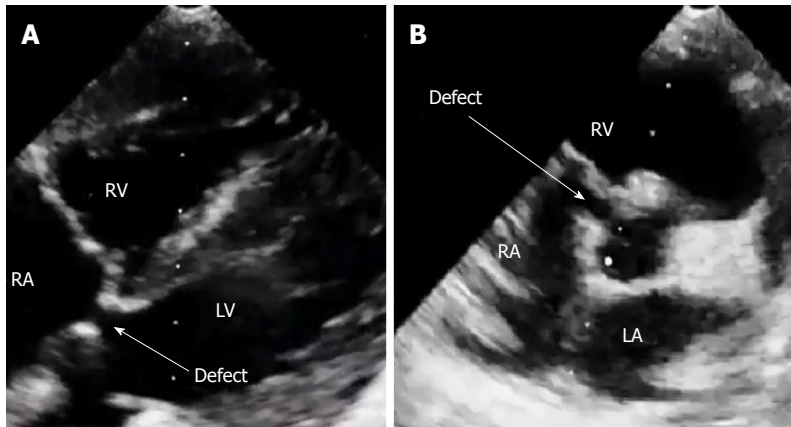
following up uneventful, the patient was discharged in good physical and mental condition. We have been checking the patient at 1 mo, 3 mo and 6 mo after the procedure. Till now, the patient has no symptom on exertion, the device is in good position without any shunt on echocardiography and there is no murmur on heart auscultation.

## DISCUSSION

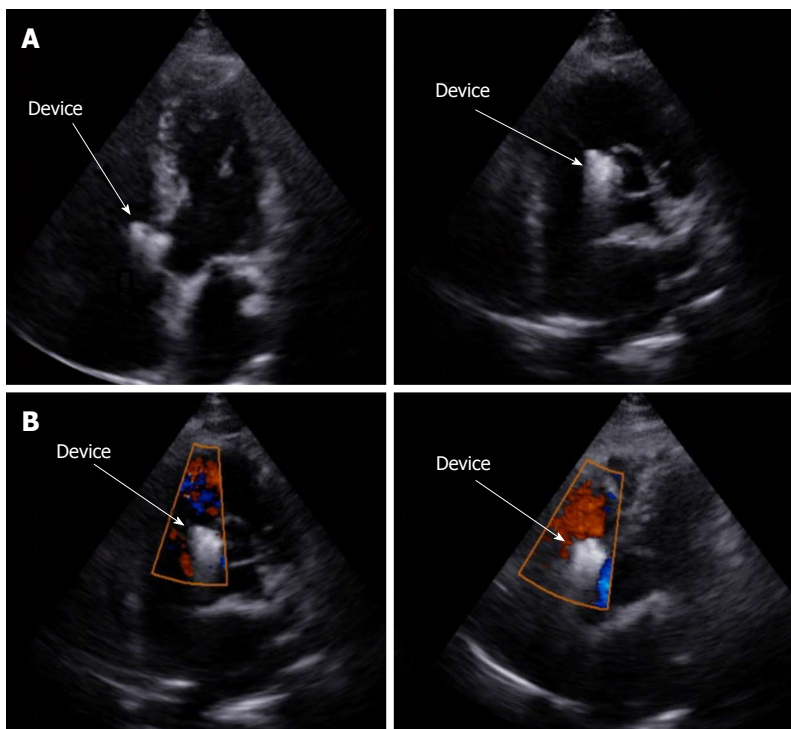
Congenital Gerbode defect is rare, only accounts for about 0.08% among congenital heart diseases<sup>[1]</sup>. Patients may have symptoms or not depends on the defect size and the shunt from LV to RA. Heart auscultation can detect a systolic murmur with position and intensity similar to the VSD but slightly lower and radiating downward.

TTE is useful for diagnosis of Gerbode defect. In 2D mode, the LV-RA shunt may be detected in some views, such as parasternal short axis, four and five chambers or subcostal views (Figure 7). The image quality was better in subcostal view as there was no bone or lung tissue to obstruct the view. Pulsed wave Doppler was helpful in detecting the shunt by the high turbulent audio signal. Continuous wave Doppler helped detect and measure peak systolic velocities across the shunt. Color flow imaging was useful in

localizing defect position and shunt flow. However, in Gerbode defect, the shunt flow, affected by the septal leaflet of the tricuspid valve, may change direction unexpectedly. So, it can mimic the direction of tricuspid regurgitation flow and made sonographers misrecognize as tricuspid regurgitation in the setting of severe pulmonary artery hypertension<sup>[3]</sup>. In this case, at first, the clinical physician thought about VSD and sent the patient to the sonographer for more detail. The conclusion they received was VSD with very high systolic pulmonary arterial pressure, about 115 mmHg. Both the clinical physician and sonographer were cheated by the shunt flow. So quick clinical examination and echocardiography in this kind of defect may easily lead to a misdiagnosis. The sonographer should meticulously look for Gerbode defect if physical examination suspects VSD but echocardiography can not detect any high velocity flow or aliasing in the right ventricle. The presence of normal diastolic pulmonary arterial pressure using pulmonic regurgitation jet is also very useful to distinguish the true pulmonary arterial hypertension from high velocity jet in the RA caused by Gerbode defect<sup>[4,5]</sup>. Actually, only about 2/3 of the LV-RA shunts of either congenital or acquired origin can be well diagnosed with TTE<sup>[6]</sup>. The 1/3 of others have to rely on other means like contrast echo, TEE, MRI, CTA or catheterization for accurate diagnosis.



**Figure 7** The Gerbode defect were best seen on echocardiography at subcostal five chamber view (A) or parasternal short axis view (B).



**Figure 8** Six months following up showed steady result with good device position and no shunt on echocardiography. A: Transthoracic echocardiography performed 6 mo after the procedure showed good device position at apical five chamber view (left) and parasternal short axis view (right); B: Colour doppler showed no residual shunt at apical five chamber view (left) and parasternal short axis view (right) 6 mo after device deployment.

Till now, there has been no clear official guidance for optimal treatment of Gerbode defect. Physicians may personally choose suitable therapy among conservation, cardiac surgery, intravascular intervention or intraoperative device closure. Patients without symptom and right ventricular volume overload, due to a small LV-RA shunt, may not need the treatment<sup>[7]</sup>. But if left untreated, the significant LV-RA shunt may lead to progressive congestive heart failure<sup>[8]</sup> and up to 8.7% of patients with LV-RA shunt developed infectious endocarditis in long-term follow-up<sup>[9]</sup>. So, some authors<sup>[10-14]</sup> suggested that correction of this type of defect with significant LV-RA shunt is necessary.

Even though the surgical closure is accepted as a treatment of choice<sup>[12]</sup>, some successful transcatheter closures for Gerbode defect have been reported. There is a paucity of information in the existing literature on transcatheter therapy for this type of defect. Indications of intervention may be same as those in the left to

right shunt lesion<sup>[14]</sup>. The devices used for occlusion this kind of defect varies from centers to centers. The first device reported used to close of an acquired Gerbode defect following VSD surgical correction was Amplatzer ventricular septal occluder<sup>[11]</sup>. Another device, amplatzer septal occluder (ASO) commonly used for atrial septal defect closure, also being used to close Gerbode defect complicated from mitral valve surgery with marked improvement in exercise tolerance<sup>[13]</sup>. The smallest patient reported, a 3-mo old baby with an acquired Gerbode shunt after VSD patch closure, was treated using an amplatzer duct occluder (ADO) with complete closure achieved 2 wk after device deployment and good long term follow-up<sup>[12]</sup>. Recently, a report of 12 Gerbode defect patients that were transcatheterly closed with ADO II showed satisfactory outcomes<sup>[14]</sup>. Until now, there is no specific device purposely manufactured for Gerbode defects closure. The devices used to occlude this kind of defects are borrowed from

products created for other defect types such as atrial septal defect, VSD, patent ductus arteriosus, etc. In this case, giving the size and shape of the defect, a suitable device could be chosen for transcatheter occlusion among ADO, ADO II, membranous or muscular VSD occluder, VSD Coil or ASO. With a quite big and long defect like that, heart block and injuring adjacent structures could likely happen when using ADO, VSD occluder or ASO. A good device might be ADO II, but it was not available in our center at that time. So, we finally decided to use the Nit-Occlud® Lê VSD coil (PFM Medical, Germany), which are commonly used for VSD closure. This device is made of Nitinol coils with securely attached polyester fibers and a cone-in-cone configuration (Figure 2). The bigger proximal cone is more flexible and will be partially deployed on the left ventricular side of the defect. The smaller distal cone will be deployed on the other side of the defect and its diameter should be at least twice the defect smallest diameter. The first device chosen might be undersized purposely, for minimizing surrounding structures injury. That could explain for device embolization after deployment. The second bigger device was appropriate for the defect with firmly sitting in the correct position. So, choosing a suitable device with correct size is very important to prevent device embolization in transcatheter Gerbode defect closure.

After device successfully released, there was rising concern of hemolysis and hematuria because the contrast ejection and echocardiography showed small residual shunt. But after 24 h, the murmur on heart auscultation and residual shunt on echocardiography was completely gone. Six months following up also showed steady result with no heart murmur, good device position, no shunt on echocardiography (Figure 8) and the patient achieved almost normal life.

In conclusion, the diagnosis of congenital Gerbode defect is quite challenging, can be easily misinterpreted. Percutaneous device occlusion offers a feasible, safe and effective therapy for this type of defect. Among devices used for transcatheter closure of Gerbode defects, the Nit-Occlud® Lê VSD coil may be a good candidate.

## COMMENTS

### Case characteristics

A 31-year-old male who had normal physical and mental development presented with dyspnea on exertion and a loud harsh holosystolic murmur at 4<sup>th</sup> intercostal spaces along the left sternal border with a systolic thrill could be palpated.

### Clinical diagnosis

Ventricular septal defect.

### Differential diagnosis

Tricuspid regurgitation, mitral regurgitation, pulmonic stenosis, patent ductus arteriosus.

### Laboratory diagnosis

The BNP was slightly increased. Other labs were within normal limits.

### Imaging diagnosis

Echocardiography showed a shunt from left ventricle to the right atrium.

### Pathological diagnosis

Communication between the left ventricle and right atrium (congenital Gerbode defect).

### Treatment

The defect was transcatheterly closed using a Nit-Occlud® Lê VSD coil with no residual shunt at 6 mo follow-up.

### Related reports

Congenital Gerbode defect is a rare congenital heart disease and can be easily misinterpreted. Percutaneous device occlusion offers a feasible, safe and effective therapy for this disease.

### Experiences and lessons

In congenital Gerbode defect, careful review of echocardiography is an important key to avoid misdiagnosis and the transcatheter closure with an appropriate device is a crucial factor to ensure the procedural success.

### Peer-review

The reported case is well described and interesting.

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