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IMAGE

Large Bioprosthetic Aortic Valve Thrombi on DOACs

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Introduction

Aortic stenosis affects 3% of the over 75-year-old population [1]. When it becomes severe or clinically significant, replacement (via either a surgical or transcatheter approach) remains the treatment of choice [2]. Whilst mechanical valves are more durable, a bioprosthetic valve (BV) negates the need for long-term anti-coagulation [3].

Thrombus formation on aortic BV is an uncommon phenomenon with reported incidences of 0.03 to 5% (compared with 3.6 to 6% in mitral BV) [4–8].

Dabigatran has been shown to be less effective at preventing stroke in atrial fibrillation patients with mechanical heart valves [9]. However, the few studies on direct oral anti-coagulant (DOAC) use in BV patients have reported DOACs to be efficacious in both preventing and treating BV thrombi [10–13].

Currently, the American College of Cardiology guidelines (2017) recommend vitamin K antagonist use after bioprosthetic surgical aortic valve replacement (SAVR) for 3 to 6 months in low bleeding risk patients (class of recommendation IIa, level of evidence B) to protect against ischaemic stroke until valve endothelialisation has occurred [14]. After this, anticoagulant therapy is not recommended unless there are additional thrombotic risks (such as atrial fibrillation or hypercoagulability).

In this report, we describe two cases of large bioprosthetic SAVR thrombi occurring in patients taking DOACs. The thrombi were detected 6 and 7 years after surgery and as shown in the former case, warfarin effectively prevented valve deterioration.

Case 1

A 74-year-old Caucasian gentleman had an incidental finding of a bioprosthetic aortic valve lesion seen on routine transthoracic echocardiography at his outpatient cardiology clinic. His background was significant for a Carpentier-Edwards Perimount (Edwards Lifesciences, Irvine, CA, USA) bovine pericardial surgical aortic valve replacement 6 years earlier to replace a failed BV SAVR from 2003 for severe aortic regurgitation, as well as recurrent deep vein thromboses for which he was on life-long rivaroxaban 20 mg daily. He had had a renal transplant in 2010 for obstructive nephropathy and had stage II chronic kidney disease. He was partially blind after subcortical and cortical strokes leading to his wife dispensing his medications. A thrombophyllic screen in 2013 was unremarkable. His other medications of note included cyclosporin 75 mg twice daily, mycophenolic acid 720 mg twice daily, prednisolone 10 mg daily, sulfamethoxazole 400 mg daily, trimethoprim 80 mg daily. He had been feeling well with no recent symptoms of infection, thromboembolism or autoimmune pathology. At his previous outpatient clinic visit 5 months earlier, his transthoracic echocardiogram had revealed mildly increased gradients through the aortic valve.

A transthoracic echocardiogram showed severe stenosis with possible vegetation on the valve, so he was admitted to hospital for further evaluation. On admission, he was afebrile with an unremarkable examination. Initial investigations revealed: electrocardiograph (ECG) showed sinus rhythm at 76 bpm, with left ventricular hypertrophy; white cell count 6.7 × 10^9/L (WCC; normal range 4.0–11.0 × 10^9), prothrombin time 18.8 seconds (PT; normal range 11–15 seconds), activate partial thrombin time 41.7 seconds (APTT; normal range 24–36 seconds), C-reactive protein 8 mg/L (CRP; normal range <5 mg/L). Initial blood cultures grew *staphylococcus hominis* and he was started on intravenous vancomycin.

Transoesophageal echocardiography was performed which revealed two masses on the aortic valve and severe

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aortic stenosis. The non-coronary cusp mass measured 1.5 x 0.9 cm and involved the entire length of the leaflet with prolapse into the left ventricular outflow tract. A further left coronary cusp mass was measured at 1.0 x 0.5 cm (Figure 1). Transthoracic echocardiography revealed peak and mean gradients of 87 and 54 mmHg respectively.

Nine (9) subsequent blood cultures were negative and after 36 hours, antibiotic treatment was ceased as *S. Hominins* was a presumed contaminant.

Rivaroxaban was ceased, intravenous heparin, warfarin and low-dose aspirin were commenced. Heparin was ceased when warfarin levels were therapeutic (target international normalised ratio (INR) 2.5–3.5). Five (5) months later, repeat transthoracic echocardiography revealed improvement in aortic valve gradients with peak and mean gradients of 36 and 20 mmHg respectively.

Case 2

A 79-year-old Caucasian woman was admitted from an outpatient cardiology clinic after she had complained of mild angina and exertional dyspnoea. She had a Sorin Mitroflow Pericardial (Sorin Group Inc, Vancouver, Canada) aortic valve replacement performed 7 years previously. In addition, she had chronic atrial fibrillation for which she took apixaban 5 mg twice daily, sleep apnoea and chronic obstructive pulmonary disease. Examination revealed crepitations in her left lung base and dual heart sounds without murmur. She was afebrile with normal observations. Inflammatory markers including blood cultures were normal (WCC 10.3×10^9/L, CRP 3.1 mg/L), APTT was 31.8 seconds and PT was 16 seconds. Transthoracic echocardiography detected a large mass on her aortic valve. Subsequent transoesophageal echocardiography confirmed a 2.8 cm mobile mass on the non-coronary cusp with trivial aortic regurgitation (Figure 2).

Apixaban was ceased with intravenous heparin and broad spectrum antibiotics initiated. The working diagnosis was a vegetation, thus given its size, surgical replacement of the valve was performed. Subsequent histopathology revealed thrombus with no microbial growth. She was discharged after 14 days on warfarin (target INR 2.0–3.0).

Discussion

Bioprosthetic valve can fail for a number of reasons including fibrotic pannus ingrowth, endocarditis, degeneration and thrombosis [15,16]. Risk factors for BV thrombosis can be divided into patient-related (such as pro-thrombotic states), procedural-related (tissue injury or sub-optimal positioning) or valve-related (mismatched valve size) [8,17,18]. Thrombosis is often suspected when patients present with dyspnoea or systemic embolisation. It can be confirmed on imaging with reduced leaflet motion and/or increased transvalvular gradients or regurgitation [18,19].

The consequences of thrombosis, if left untreated, include valve dysfunction, heart failure and thromboembolism [20]. Compared with mechanical valve thrombosis, BV thrombosis has a more indolent course where immediate treatment is not always mandatory [5]. Thrombosis has been described as occurring as early as 2 days to as late as 54 months [21–23]. The heterogeneity seen in presentations, as well as the increased incidence of subclinical thrombosis, raises concern that thrombosis and stroke risk are higher than previously believed [24].

Early thrombosis can often be assumed to be prosthesis related, whereas late BV thrombosis (after one year) might arise for other reasons such as atrial fibrillation, left atrial thrombus or bacterial leaflet vegetation [18]. Establishing BV dysfunction aetiology is necessary as treatment options vary significantly depending on cause and symptomology. In haemodynamically stable patients, the 2017 ACC/AHA guidelines recommend BV thrombi should be treated with a vitamin K antagonist (IIa recommendation). If the patient is haemodynamically unstable or has advanced heart failure, surgery or thrombolysis should be considered [14].

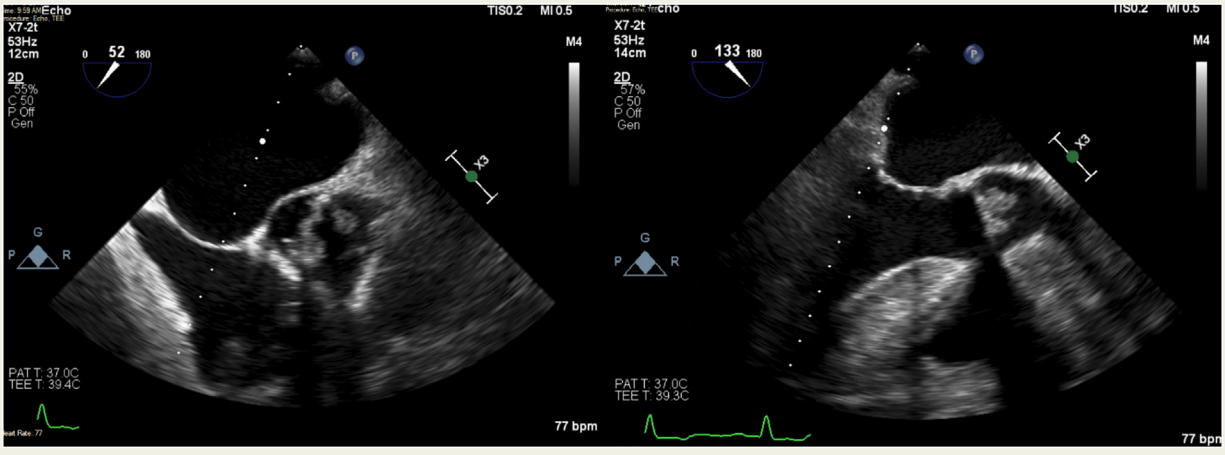

Figure 1 Transoesophageal echocardiography displaying the non-coronary cusp and left coronary cusp lesions at mid-oesophageal level long short-axis and long-axis views.

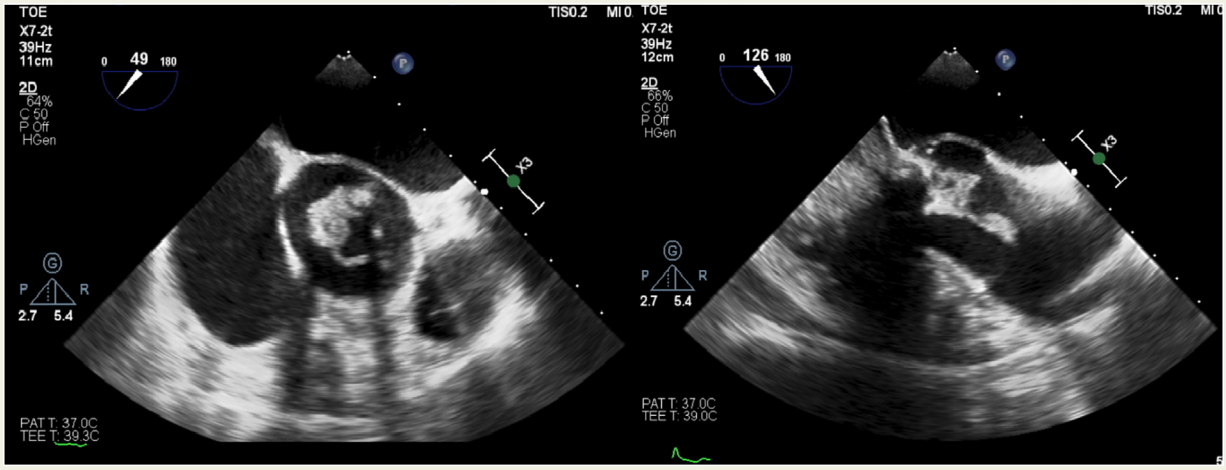

Figure 2 Transoesophageal echocardiography revealing the 2.8 cm non-coronary cusp lesion at mid-oesophageal level short-axis and long-axis views.

With the advent of transcatheter aortic valve implantation (TAVI), it has been observed that subclinical leaflet thrombosis is less common in SAVR compared with TAVI [12]. Chakravarty et al. [12] found that subclinical thrombosis (as defined by hypo-attenuating lesions seen on computed tomography with at least moderate restriction of leaflet motion) occurred in 13% of TAVI patients versus 4% of SAVR patients. Out of 106 patients who had evidence of subclicinical BV leaflet thrombosis three patients had been taking DOACs. It is unclear whether these were TAVI or SAVR patients.

In one of the largest multi-centre studies looking at TAVI thrombosis, Latib et al. [8] reported a thrombosis rate of 0.61% with a median time of 181 days post valve implantation. Whilst BV thromboses have been reported in patients taking warfarin [25], of the 26 cases that Latib et al. reported, only one was reported to have been taking dabigatran (for atrial fibrillation) at the time of thrombus formation. Subclinical BV leaflet thrombosis on DOACs post-TAVI has also been reported by Yanagisawa et al., who found that two patients who reliably took dabigatran and rivaroxaban showed signs of reduced leaflet motion [26].

Whilst studies suggest that certain valves have higher thrombotic risks: mechanical compared to bioprosthetic; porcine compared to bovine; stented compared to stentless [27–30], there have been no trials comparing different pericardial BVs. Both the Mitroflow (Sorin Group Inc, Vancouver, Canada) and the Carpentier-Edwards Perimount (Edwards Lifesciences, Irvine, CA, USA) pericardial valves, used in the aforementioned cases, have been available for over 30 years. Though there have been concerns raised of early valve deterioration in the former due to its structural design [31], Bourguignon et al. [32] found that of 2,659 patients implanted with the latter, valve lifespan approaches 20 years.

As demonstrated by these cases, whilst both patients had strong risk factors for thrombus formation, accurate DOAC therapy (as demonstrated by raised APTT and PT) does not always prevent against bioprosthetic aortic valve thrombi. Both of these cases are unusual in that the thrombi developed so late after surgery, with both valves previously functioning without issue. As a result, the presumptive diagnosis for each had been infective endocarditis. With hindsight, recognition that thrombi can occur on DOACs could have spared both patients courses of antibiotics, and our second case from repeat valve surgery. These cases demonstrate the importance of routine transthoracic echocardiography in detecting bioprosthetic valve thrombi. Finally, with the recent early termination of a phase III clinical trial evaluating rivaroxaban use for thromboprophylaxis in TAVI patients due to increased thrombo-embolism, death and bleeding, we suspect that this phenomenon will become more widely reported in future [33].

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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