Management of bioprosthetic cardiac valve thrombosis

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ABSTRACT

Valvular thrombosis is a known complication of bioprosthetic valve replacement that usually occurs within a year of implantation. Four-dimensional computed tomography is quickly becoming the gold standard to directly visualize thrombus. Current guidelines for prophylaxis include aspirin for all bioprosthetic valve replacements, dual antiplatelet therapy for aortic valves, and anticoagulation for mitral valves. However, new trials have suggested single-agent antiplatelet therapy or anticoagulation for treatment of bioprosthetic valve thrombosis. Three cases are presented that illustrate the use of anticoagulants and new techniques for detecting thrombosis on imaging.

KEYWORDS Anticoagulation; bioprosthetic valve replacement; thrombosis

Bioprosthetic valve thrombosis was previously thought to be relatively rare, but recent evidence suggests it is much more common.¹ Thrombus can be difficult to directly visualize on echocardiography; often only elevated transvalvular gradients, a finding that lacks optimal specificity, may suggest the diagnosis. However, with the advent of four-dimensional computed tomography (4D-CT) scanning, reduced leaflet mobility and the presence of thrombus on the valve leaflets can be directly confirmed.^{1,2} Treatment options for valvular thrombosis remain controversial. This case series illustrates the usage of anticoagulants and new techniques for detecting thrombosis on imaging.

CASE DESCRIPTIONS

Three patients underwent bioprosthetic valve replacement through either a surgical or transcatheter approach and later experienced valve thrombosis. The first, a 74-year-old woman with a history of coronary artery disease, hypertension, hyperlipidemia, and stage 3 chronic kidney disease, presented with progressively worsening fatigue and exertional dyspnea associated with chest pain. The second was a 61-year-old man with hypertension who presented to the hospital with chest pain associated with dyspnea, lower leg swelling, and palpitations. The third case, an 82-year-old woman with hypertension, hyperlipidemia, diabetes mellitus,

and combined systolic and diastolic heart failure, presented with nausea, vomiting, fatigue, and chest pain. Two patients experienced atrial fibrillation postoperatively, which was treated with amiodarone. All three underwent routine echocardiogram, with the time to thrombosis ranging from 4 to 78 months. They were treated with anticoagulation, with clinical resolution of their symptoms and improvement of their valve gradient. *Table 1* summarizes the findings in each case.

DISCUSSION

The reported incidence of valvular thrombosis after replacement with a bioprosthesis has been reported to be as low as 0.01% to 1.26%, with most cases occurring within 6 to 12 months. However, some cases can occur >24 months after implantation.^{1–5} The thrombosis prophylaxis differs depending on the valve being replaced and the surgical procedure elected. Guidelines recommend aspirin in all bioprosthetic aortic or mitral valve replacement and dual antiplatelet therapy for 6 months in the case of transcatheter aortic valve replacement (TAVR), while it appears reasonable to start anticoagulation on patients undergoing bioprosthetic mitral valve replacement (MVR).^{1,2,5–7}

Recently, it has been suggested that subclinical valve thrombosis may occur more often than expected.¹ For those presenting symptomatically, the most common symptom is worsening dyspnea.^{2,3} It is theorized that the mechanism of

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Table 1. Findings for each case of bioprosthetic cardiac valve thrombosis.

Variable	Case 1	Case 2	Case 3
Age (years)	74	61	82
Sex	Female	Male	Female
Cardiac valve replaced	Mitral	Aortic	Aortic
Approach	Minimally invasive	Surgical	Transcatheter
Bioprosthetic type (mm)	St. Jude Epic (29)	Medtronic Mosaic (25)	Edwards Sapien 3 (23)
Pre-valve replacement reason	Mitral regurgitation	Aortic stenosis	Aortic stenosis
Postoperative atrial fibrillation	Yes	Yes	No
Mean valvular area after valve replacement (cm ²)	1.9	2	1.4
Transvalvular mean gradient after valve replacement (mm Hg)	3.6	20	14
Transvalvular mean gradient after thrombosis (mm Hg)	8.4	39	26
Treatment option after valve thrombosis	Warfarin	Apixaban	Warfarin
Mean valvular area after treatment (cm ²)	1.5	1.9	1.4
Transvalvular mean gradient after treatment (mm Hg)	3.6	27	18

thrombosis involves flow disturbance at the site of implantation, incomplete expansion, apposition, or comorbid prothrombotic conditions, which cause a steady rise in the mean gradient across the valve.⁴

Prior to the advent of 4D-CT, echocardiography was used to assess thrombus; however, direct visualization was difficult.¹⁻³ Due to the increasing availability of 4D-CT, it is fast becoming the gold standard for detecting thrombosis after valve replacement.¹⁻³ It should be noted that no formal diagnostic criteria have been established for valve thrombosis.³ However, a subset of findings are typical for thrombus, including increased transvalvular gradient, thickened valvular leaflets, and progressive dyspnea.^{2-5,8} These signs and symptoms strongly suggest valve thrombosis.^{2-5,8} A recent study conducted by the Mayo Clinic used three criteria for prosthetic valve thrombosis: (1) >50% increase in prosthetic gradient within 5 years of valve implantation; (2) increased cusp thickness; and (3) abnormal cusp motion.⁹ An emerging imaging technique used for evaluating valve thrombosis uses 4D-CT to assess for reduced leaflet motion, which seems to be more accurate than echocardiography.^{1,2}

Treatment of valvular thrombosis has been an evolving process, which has included valve explantation and reimplantation, dual antiplatelet therapy, and oral anticoagulation.^{2,3,9} The American Heart Association/American College of Cardiology 2014 valve guidelines recommend aspirin for all bioprosthetic aortic and mitral valve replacements, and aspirin and clopidogrel for 3 to 6 months after TAVR; after MVR, those with additional risk factors for thrombosis may benefit from initiation of anticoagulation.^{6,10-12} Of note, the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) was a small

randomized clinical trial that showed that single-agent antiplatelet therapy reduced the risk for major or life-threatening events while not increasing the risk for myocardial infarction or stroke and not compromising valve hemodynamics.¹³ Dual antiplatelet therapy was associated with a higher risk of major or life-threatening bleeding events.¹³ However, recent studies have shown that dual antiplatelet therapy does not prevent all thrombotic events from occurring, but prompt initiation of oral anticoagulation can return baseline gradient and function in select patients.^{2-4,9,14} Typically the transvalvular gradient returns to baseline values within 1 to 10 months of oral anticoagulation, with most gradients returning to baseline within 2 months.^{3,10} Despite these good outcomes seen with initiating oral anticoagulation for valvular thrombosis, this remains a controversial topic because approximately 17% of those initiated on anticoagulation will not restore baseline valvular gradient despite additional weeks of anticoagulation.^{9,10,14} Additionally, with increased surveillance imaging being performed, it is unclear if all partial thromboses require treatment and what exactly is the natural history of this condition. Finally, it is unknown if the predilection to thrombosis is an early phenomenon or if the risk persists; therefore, the required duration of therapy is unknown. In this case series, it is noted that the change in gradient was not dramatic (Case 1, 8.4 to 3.6; Case 2, 39 to 27; Case 3, 26 to 18), but the patients experienced complete resolution of their symptoms and echocardiographic evidence of thrombus resolution.

A new study involving the RESOLVE and SAVORY registries analyzed patients undergoing transcatheter or surgical aortic valve replacement and evaluated “subclinical leaflet thrombosis and usage of novel oral anticoagulants.”^{1,7} Both novel oral anticoagulants and traditional warfarin were

effective in treatment of thrombosis, but dual antiplatelet therapy was not.^{1,7,11} We also await results from the large, multinational GALILEO trial that studied rivaroxaban versus dual antiplatelet therapy after TAVR for prevention of valvular thrombus. More research is needed to determine the optimal antiplatelet or anticoagulant strategy after prosthetic valve replacement in various scenarios in different populations.

It is important to mention the role of atrial fibrillation after valve replacement. New-onset atrial fibrillation is a common complication noted in TAVR and surgical aortic valve replacement procedures; it is a known cause of thromboembolic stroke after valve replacement and likely a contributing factor to subclinical and clinical valvular thrombosis.¹⁵ Antithrombotic management remains controversial, with emerging evidence of the role of anticoagulation and the role of single-agent antiplatelet versus dual antiplatelet therapy in the post-replacement period for prevention and treatment of thromboembolic stroke and valvular thrombosis.¹⁵

In this case series of both surgical and transcatheter-based procedures involving both aortic and mitral valves, each procedure was complicated by a thrombotic event despite the fact that the patient was on dual antiplatelet therapy. Oral anticoagulation including vitamin K antagonists and novel oral anticoagulants all resulted in reduction or complete resolution of thrombosis. This case series also illustrates the importance of early recognition of bioprosthetic valve thrombosis by general internists and cardiologists to avoid adverse events. It is important for practitioners to maintain a high index of suspicion when valve replacement recipients present with signs and symptoms of thrombus.

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