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EDITORIAL COMMENT

Bioprosthetic Heart Valves, Thrombosis, Anticoagulation, and Imaging Surveillance*

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It is estimated that valvular heart disease affects >100 million patients worldwide, which will increase further with the aging population and a subsequent increase in degenerative valve disease (mitral regurgitation, aortic stenosis). By the year 2050, expectations are that annually 850,000 valves will be implanted. Currently, worldwide, more than 200,000 aortic valve replacements are performed annually, and analysis of the Society of Thoracic Surgeons National Database indicated a massive shift from mechanical to bioprosthetic valve replacements between 1997 and 2006: the use of mechanical valves decreased to 20.5%, whereas the use of bioprosthetic valves increased to 78.4% (1). This shift was associated with a reduced annual mortality from 3.4% to 2.6% and a reduction in stroke rate from 1.7% to 1.3%. The change to bioprosthetic valves was partially ascribed to younger individuals refusing long-term anticoagulation and elderly patients being at higher bleeding risk.

Recently however, the topic of surgical bioprosthetic valve thrombosis (BVT) has attracted significant attention (2). Similarly, early transcatheter aortic valve replacement (TAVR) thrombosis has been recognized. The discussion on thrombosis is characterized by the following issues:

1. Increased recognition and prevalence of thrombosis
2. How to detect thrombosis
3. Confusion around valve thrombosis versus deterioration
4. Implications for surveillance and treatment

In this issue of *JACC: Cardiovascular Interventions*, Egbe et al. (3) report on BVT of surgically implanted valves, and the outcome after warfarin therapy. The same group reported in 2015 about prevalence and detection of surgical valve thrombosis (4). We will address these 4 topics in view of the currently available published reports and the 2 studies by Egbe et al. (3,4).

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INCREASED RECOGNITION AND PREVALENCE OF THROMBOSIS

The long-term follow-up of patients receiving surgical bioprosthetic valves has mostly focused on assessment of potential structural failure, whereas the risk of early BVT was considered irrelevant (5), and for bioprostheses in the aortic position, the incidence was estimated at 0.03% events per patient year (derived from a meta-analysis based on microsimulation, but the estimate was based only on 3 events in 9,925 patient-years of follow-up) (6). In 2012, Brown et al. (7) reported on 8 reoperations for BVT of porcine valves (incidence ranging from 0.19% to 0.7%). In 2015, Egbe et al. (4) reported on histologically proven BVT in 46 of 397 (prevalence 11.6%) patients, which related to an estimated incidence of 0.74% (4); and in this issue of *JACC: Cardiovascular Interventions* (3), these authors report more specifically on their patient registry (obtained during 2013 to 2016) with a tentative diagnosis of BVT.

Various authors reported on retrospective analyses of transthoracic or transesophageal echocardiograms of patients with bioprosthetic valves and reported a prevalence of 6% (8,9). This higher prevalence of BVT may relate to an increased awareness among physicians and improved definition of diagnostic echocardiographic criteria (5).

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Similarly, the initial large studies on TAVR did not report on BVT. Recently, various studies used (more sensitive) computed tomographic (CT) imaging and reported on suspected or proven thrombosis ranging from 4% to almost 15% of patients with TAVR (10–13).

HOW TO DETECT?

The first-choice technique to detect BVT is echocardiography. The earlier study by Egbe et al. (4) evaluated 46 patients with explanted valves and proven thrombosis. On the basis of review of the echocardiograms, 3 independent echocardiographic predictors of surgical BTV were identified. These included >50% increase in mean transvalvular gradient within 5 years from baseline, increased cusp thickness, and abnormal cusp mobility. Application of these criteria yielded a sensitivity of 76% with specificity of 93%. In 2016, recommendations for assessment of prosthetic heart valves were published (14). Echocardiographic criteria defining BVT included morphological leaflet characteristics (thickened and restricted motion), restriction of the color flow at the bioprosthesis orifice and hemodynamic impairment. In aortic bioprostheses, the proposed hemodynamic parameters suggesting thrombosis are an increase in mean gradient during follow-up ≥10 mm Hg and an effective orifice area <0.8 cm^2 whereas in mitral bioprostheses, the increase in mean gradient during follow-up should be >5 mm Hg and the effective orifice area <1.0 cm^2.

Echocardiography is superior for hemodynamic valvular assessment (functional assessment), but is not perfect for distinguishing BVT. Recently, CT has been used and the definition of aortic BVT was the presence of hypoattenuated leaflet thickening with or without rigidity of the leaflets (12). CT imaging has been applied mostly in patients with TAVR (and some patients with surgical aortic bioprosthesis), but the same criteria could be applied to mitral bioprostheses.

Interestingly, when echocardiography and CT were compared in patients undergoing TAVR, it became evident that CT identified BVT significantly more often than echocardiography. Hansson et al. (10) reported possible BVT on CT in 7% of 405 patients undergoing TAVR, whereas the mean gradient and the effective orifice area were in the normal range (10 ± 7 mm Hg and 1.5 ± 0.5 cm^2, respectively). This may relate to definitions of valve thrombosis versus deterioration.

CONFUSION AROUND VALVE THROMBOSIS VERSUS VALVE DETERIORATION: DEFINITIONS

With the increasing discussion around BVT, it becomes clear that precise differentiation between thrombosis and degeneration is difficult. In 2015, Egbe et al. (4) compared echocardiographic findings of patients with proven surgical BVT (n = 46) or structural failure (n = 92) ("proven diagnoses" because the valves were explanted during follow-up) (4). Patients with thrombosis often showed increased leaflet thickness, reduced motion, and increased gradients, whereas structural failure often revealed calcified leaflets, reduced mobility, and significant regurgitation. Thrombosis occurred mostly within 2 years after surgery, whereas degeneration occurred later. It has been proposed by Stewart (5) that "thrombosis and degeneration represent the same disease at different points in time." Based on this hypothesis, it can be that CT detects "subclinical thrombosis" at an early stage, and that echocardiography detects thrombosis (or degeneration) at a later stage, when hemodynamic (or functional) changes occur. This may also explain why CT detects more valve thrombosis than echocardiography, because thrombosis likely precedes the hemodynamic abnormalities. Dangas et al. (2) recently stated that prosthetic heart valve dysfunction can be seen as "a continuum of the same pathological process with early thrombus formation; later fibrotic pannus formation followed the end-stage of degeneration and dysfunction."

POTENTIAL IMPLICATIONS FOR TREATMENT AND SURVEILLANCE

Recent studies demonstrated that suboptimal antithrombotic treatment was an important predictor of BVT or valve degeneration, and that warfarin treatment resolved symptoms and imaging findings (12,15). In this issue of *JACC: Cardiovascular Interventions*, Egbe et al. (3) report a prospective study including 52 patients with suspected surgical BVT (mostly in aortic and mitral positions) on echocardiography, who underwent a trial of anticoagulation (warfarin). The trial was effective in 83% of patients, with the majority responding within 3 months. Only 2 minor bleedings were reported. The current results are in line with previous reports showing that warfarin treatment resulted in thrombus resolution in patients with BVT (8,9). Current guidelines recommend warfarin only for 3 months after surgery (16), whereas Egbe et al. showed that thrombosis occurs mostly within 2 years postsurgery, but at varying times, and may even occur after 2 years (3). Timely treatment may prevent stroke, but also subsequent degeneration. It is currently unclear how long anticoagulation should be continued after bioprosthetic valve surgery. In addition, warfarin is not recommended after TAVR, whereas thrombosis and degeneration appear to occur not infrequently

(10–12). Currently, various studies with novel oral anticoagulant agents after TAVR are underway; at the same time, bleeding risk will be important in this elderly population.

Another area concerns imaging surveillance; current guidelines do not recommend echocardiography early and regularly after bioprosthetic valve implantation or TAVR (16). Egbe et al. (4) reported that BVT can be detected with a systematic echocardiographic approach, where a >50% increase in baseline transvalvular gradient was an important predictor. This however, requires a baseline "fingerprint" echocardiogram early after surgery, and systematic echocardiographic surveillance at regular intervals. This approach permits early thrombosis detection, followed by a trial of anticoagulation, which may prevent development of valve degeneration (and subsequent need for reoperation). Randomized controlled trials regarding imaging will be difficult to perform, and future guideline recommendations may depend on expert opinions. Another question is should CT be used for early detection of thrombosis (given the higher sensitivity)? But sequential CT imaging is not preferred given the associated radiation.

In conclusion, Egbe et al. (3) have provided novel information regarding BVT, imaging, and anticoagulation use. Further studies are needed to optimize anticoagulation therapy and imaging surveillance.

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