Editorial

Transcatheter Aortic Valve Replacement Failure
Déjà vu ou Jamais vu?

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The past half decade has seen transcatheter aortic valve replacement (TAVR) emerge as the standard of care for inoperable and high-risk patients with severe aortic stenosis: randomized data have demonstrated reduced mortality with TAVR compared with medical therapy or surgery in these respective situations. Accordingly, recent research efforts have reoriented from establishing the short-term safety and efficacy of TAVR to optimizing patient outcomes and assessment of transcatheter heart valve (THV) durability. Five distinct causes of THV failure have been identified: 3 are synonymous with surgical valve failure (structural valve dysfunction; prosthetic valve endocarditis [PVE]; and thrombosis) and 2 are unique to transcatheter valves (late migration; and compression). The limited information available on the incidence of these events and resultant uncertainty of THV durability are among the most significant impediments to widespread adoption of THV technology. Anecdotal experience and, more importantly, an ever-increasing quantity of published data suggest however that acute catastrophic failures are not characteristic of THVs. History has a tendency to repeat itself, and it is notable that a similar impasse relating to the adoption of surgical bioprosthetic valves played out almost 3 decades ago. On this subject, the British surgeon Dr Donald Ross provided the following commentary in 1982:

Undoubtedly valve durability emerges as the most persistent criticism of biological valves. However, we have come to recognize that failure or degeneration in a biologic valve is a slowly progressive process. This means that there is adequate warning and plenty of time for a safe, planned second operation. The message I am trying to deliver is that we should not be deflected by the mechanical valve proponents into believing that valve durability is the key factor keeping patients alive. The fact that the valve is fine and unmarked, after the patient is dead, is of little interest to anyone but the manufacturers. It is imperative that we remember that valve safety ranks more importantly than durability when related to the clinical scene.

Surgical bioprosthetic heart valve thrombosis is a well-recognized, but uncommon, prosthesis failure mode. The risk of surgical bioprosthetic thrombosis is greatest in the early postoperative period, and the reported incidence ranges from 0.5% to 2.3% per patient year. These rates are probably underestimated, as long-term systematic echocardiographic follow-up of surgical bioprostheses had not, somewhat surprisingly, been performed until the Placement of Aortic Transcatheter Valve Cohort 1A (PARTNER 1A) trial. The variety of clinical presentations of bioprosthetic thrombosis (valve failure, stroke, systemic embolization, and infective endocarditis) further complicates efforts to determine the true rate of bioprosthetic valve thrombosis. Although disparate thrombosis rates among various surgical bioprostheses have not been reported, several patient factors have been associated with increased valve thrombosis: atrial fibrillation, left ventricular dysfunction, prior thromboembolism, and hypercoagulable conditions.

To date, THV thrombosis has been rarely reported in the literature. A recent systematic review of TAVR failure identified 10 published reports, comprising only 15 individual cases. No cases were reported in the PARTNER trials, and only a single case (0.8%) was reported among the 130 TAVI recipients in the PARTNER EU trial. There remain, however, several theoretical reasons that TAVR thrombosis could be observed more frequently than in historical surgical series: (1) TAVR patients may be more likely to have coexisting prothrombotic conditions (eg, cancer), (2) a metallic THV frame could provide a nidus for thrombosis, (3) incomplete THV expansion creates leaflet folds and potential recesses for thrombus formation, (4) incomplete THV apposition to the aorta can delay endothelialization, and (5) native leaflet overhang and the tall sealing skirts can create areas of diminished blood flow and stagnation in either the bioprosthetic valve cusps or the native sinuses, respectively. Two important studies published in this issue of Circulation: Cardiovascular Interventions report on THV thrombosis and add important insight to our understanding of this key topic.

Latib et al report a multicenter experience of 26 cases of THV thrombosis among 4266 patients treated in 12 centers over almost 7 years. The overall incidence of THV thrombosis was 0.61%: 0.71% for the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA) and 0.41 for the Medtronic CoreValve (Medtronic Inc, Minneapolis, MN). The median time to diagnosis was 181 days (interquartile range [IQR], 105 to 288 days) and time to treatment was 61 days (IQR, 35 to 94 days). The authors conclude that the incidence of THV thrombosis remains low, although the event rate was increased in patients with atrial fibrillation. The study also serves to emphasize the need for early and aggressive management in both surgical and transcatheter valve prosthesis thrombosis, as well as the importance of sufficient follow-up to ensure proper valve function.

See Article by Latib et al
See Article by Leetmaa et al
See Article by Olsen et al
45–313; range, 3–735), and most patients presented with progressive dyspnea and increasing echocardiographic transvalvular gradients. Gratifyingly, oral anticoagulation resulted in resolution of symptoms and adverse echocardiographic findings in all treated patients, whereas the few patients treated surgically also had favorable outcomes. This is the largest study to date to estimate an incident rate of THV thrombosis and provide a description of the clinical course of this condition. The risk of THV thrombosis is, however, an ongoing or continuous hazard, and thus a linearized event rate would have provided a useful comparator for surgical valve thrombosis and the development of TAVR-specific objective performance criteria. It is also important to consider the design limitations of such a voluntary registry, and it is anticipated that the risk of THV thrombosis is significantly underestimated in this population. Moreover, the small number of incident cases precludes detailed analysis on the impact of antplatelet or anticoagulant therapy, prosthesis type, and patient/procedural factors on the incidence of THV thrombosis.

In this same issue, Leetmaa et al\(^\text{13}\) report a 4% incidence of THV thrombosis at 3 months among 140 consecutive Edwards Sapien valve implants at their center. Crucially, these diagnoses were established by planned computed tomography, and 4 of 5 patients had no clinical or echocardiographic evidence of THV dysfunction. The computed tomographic appearance was similar to that previously reported with echocardiography: leaflet thickening and restriction. These data make for uncomfortable reading and lend further credence to the belief that bioprosthetic thrombosis is underdiagnosed. Indeed, the findings of Leetmaa et al raise important questions relating to the definition, classification, and diagnosis of bioprosthetic thrombosis: (1) Is echocardiography insensitive to early THV thrombosis? (2) In what circumstances should computed tomography be considered? (3) What is the clinical course of asymptomatic nonobstructive THV thrombosis? (4) What is the real contribution of THV thrombosis to post-TAVR stroke? (5) What time points should patients undergo routine valve imaging follow-up? Given the low rates of clinically apparent THV thrombosis, routine postimplantation computed tomography is hardly justifiable in the asymptomatic patient, but should probably be considered in patients with echocardiographic evidence of THV dysfunction or where cardiac embolism is suspected, irrespective of the echocardiographic findings.

The optimal antithrombotic and antiplatelet strategies after TAVR have not yet been defined. Current extreme- and high-operative risk TAVR recipients are at increased risk of both bleeding and stroke, although the magnitude of this hazard will diminish in lower risk patient populations. The dearth of published trials and hence clear evidence-based practice guidelines on the subject of antithrombotic therapy in TAVR have led to the adoption of heterogeneous antplatelet and anticoagulant regimens.\(^\text{14,15}\) A Dutch TAVR survey reported the use of dual antplatelet therapy (DAPT) for 3 months in 69%, 6 months in 23%, and 1 month in 8% of centers.\(^\text{16}\) Where oral anticoagulation was indicated (eg, atrial fibrillation), concomitant clopidogrel was prescribed in 64%, aspirin in 29%, and no antiplatelet therapy in 7%. A recent meta-analysis suggested clinical equipoise in the incidence of stroke or myocardial infarction at 30 days between aspirin monotherapy and DAPT after TAVR.\(^\text{17}\) Although the studies included were small with limited follow-up, it was not surprising to note that DAPT was associated with more bleeding. It is axiomatic that larger studies with longer follow-up are required to better understand the impact of various post-TAVR antithrombotic regimens on clinical outcomes. Thankfully, 3 such comparative outcome trials are already recruiting: (1) the Aspirin Versus Aspirin+Clopidogrel Following Transcatheter Aortic Valve Implantation (ARTE) trial (NCT01559298) will compare aspirin monotherapy with 3 months of DAPT; (2) the Dual Antiplatelet Therapy Versus Oral Antiocoagulation for a Short Time to Prevent Cerebral Embolism After TAVI (AUREA) trial (NCT01642134) will compare the efficacy of 3 months of DAPT with oral antiocoagulation on cerebral thromboembolism, as assessed using magnetic resonance imaging; (3) finally, the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial (NCT02247128) will compare 3 treatment strategies: (1) aspirin monotherapy; (2) DAPT for 3 months; and (3) clopidogrel with oral anticoagulation.

Prosthetic valve endocarditis is another important cause of bioprosthetic valve failure. Surgical series report incidences of PVE between 0.3 and 1.2% per patient year, with associated mortality rates of up to 38% for early-PVE and 25% for late-PVE.\(^\text{18–20}\) Transcatheter pulmonary valve implantation has been associated with a relatively high annualized incidence rate (2.1%) of PVE.\(^\text{21}\) Thus, it is plausible that a higher incidence of PVE may occur with TAVR than with historical surgical series. There are several potential reasons for this:\(^\text{1}\): (1) the advanced age and constellation of comorbid illnesses in TAVR cohorts; (2) comparatively less sterility in many catheterization laboratories compared with operating theatres; (3) higher incidence of paravalvular leak and associated paravalvular turbulent blood flow; (4) the requirement to remove, resheathe, and reimplant a malpositioned THV; (5) and low implantation of a THV resulting in interaction with the anterior mitral valve leaflet. To date, reported rates of PVE-related PVE range from 0.6% to 3.4%.\(^\text{22,25}\)

Also in this issue of *Circulation: Cardiovascular Interventions*, Olsen et al\(^\text{26}\) report 18 cases of PVE after CoreValve implantation, among their large single-center experience of 509 CoreValve procedures, with a median follow-up of 1.4 years (IQR, 0.5–2.5 years). PVE occurred most commonly in the first year after TAVR (3.1% [confidence interval, 1.4%–4.8%]). All but 1 patient was treated with intravenous antibiotics, and PVE-associated mortality was 22%. Predictors of PVE identified on multivariable analysis included low implant position, (hazard ratio, 2.8 [1.1–7.2]), zgrade 2 paravalvular regurgitation (hazard ratio, 4.0[1.5–11]), THV-in-THV implantation (hazard ratio, 5.2 [1.5–18]), and vascular complications (hazard ratio, 3.8 [1.5–9.8]). These data add significantly to our knowledge of TAVR-related PVE and indeed suggest that technical factors relating to TAVR implantation may be associated with a higher incidence of PVE. This underscores the need for surgical-level sterility, the importance of achieving an optimal implantation,
and adherence to antibiotic prophylaxis protocols during the index procedure and during follow-up. These results may not be applicable to other TAVR devices, although they do suggest that newer generation TAVR systems with sealing skirts to reduce paravalvular leak and/or are repositionable have the potential to reduce the incidence of TAVR-related PVE.

TAVR research is approaching an important crossroads. The short-term safety and efficacy of THV technology have been established, but the long-term durability and factors threaten that longevity now requires detailed exploration. Optimizing patient outcomes for the decades that follow a THV implantation is now required, particularly as we move to treat younger and lower risk patients. This road has been travelled before, by the early champions of surgical bioprosthetic heart valves, although the level of rigor and scrutiny that will accompany this journey will be unprecedented. The important studies of Latib, Leemter, and Olsen represent small steps in the right direction.

Disclosures
Dr Piazza is a consultant for Medtronic. Dr Mylotte reports no conflicts.

References


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