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EDITORIAL COMMENT

The Long Quest for the Holy Grail in Transcatheter Aortic Bioprosthesis

Durability and Long-Term Performance*

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Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients with symptomatic severe aortic stenosis who are at intermediate to high/prohibitive surgical risk (1). TAVR is noninferior to surgical aortic valve replacement (SAVR) in terms of early and mid-term mortality and is likely to be superior if the transfemoral approach is used (2). In the real world, the countdown has already started for extending the use of TAVR to patients who are at low surgical risk. Several large randomized trials to examine the value of TAVR versus SAVR in younger patients without major comorbidities are ongoing. To date, the only published randomized trial in low-risk patients is NOTION (Nordic Aortic Valve Intervention Trial) (NCT01057173). In this study, 280 patients (82% of whom were low risk, Society of Thoracic Surgeons score <4%) were randomized 1:1 to TAVR (CoreValve self-expanding bioprosthesis, Medtronic, Minneapolis, Minnesota) or SAVR. There was no significant difference in the primary endpoint of all-cause mortality, stroke, or myocardial infarction at 2 years (15.8% vs. 18.8%) (3).

STRUCTURAL VALVE DETERIORATION

Valve durability remains the crux of discussion as the target population for TAVR evolves to include younger, low-risk patients (80% of patients with aortic stenosis undergoing surgery) who are likely to survive for a number of years after the procedure. The biological tissue from both surgical and transcatheter bioprostheses is prone to structural valve deterioration (SVD), which could lead to hemodynamic valve dysfunction (stenosis, regurgitation, or both) and development of symptoms (4). Durability is determined by numerous physical (e.g., tissue characteristics, anticalcification treatments, leaflet and valve design, and transvalvular gradients) and clinical factors (e.g., patient age and various metabolic abnormalities) (4). Reported rates of SVD are highly variable, depending on the definition and type of valve used. In most SAVR series, SVD was established on the basis of reoperation for bioprosthetic valve failure (BVF), referring to its clinical consequences rather than to new onset or worsening of morphological/functional abnormalities of the bioprosthesis (4). In fact, SVD is usually a progressive process, with gradual changes in hemodynamic valve performance and severity over time. Various stages of SVD can be highlighted, with morphological changes preceding the advent of hemodynamic deteriorations (5). These considerations have been differently expressed in recent consensus statements. Overall, 4 nosological entities characterize the term bioprosthetic valve dysfunction and may be responsible for BVF: SVD (leaflet fibrosis, calcification, tear, pannus formation), non-SVD (paravalvular leak, prosthesis malposition, late embolization), thrombosis, and endocarditis (**Figure 1**). As a point of criticism of the recent European consensus definition of bioprosthetic valve dysfunction, patient-prosthesis mismatch (PPM) is neither a deterioration nor a dysfunction, but describes the use of a prosthesis of a given type that is functioning normally but is too small for a patient of a given size (5). Therefore, it may warrant a separate

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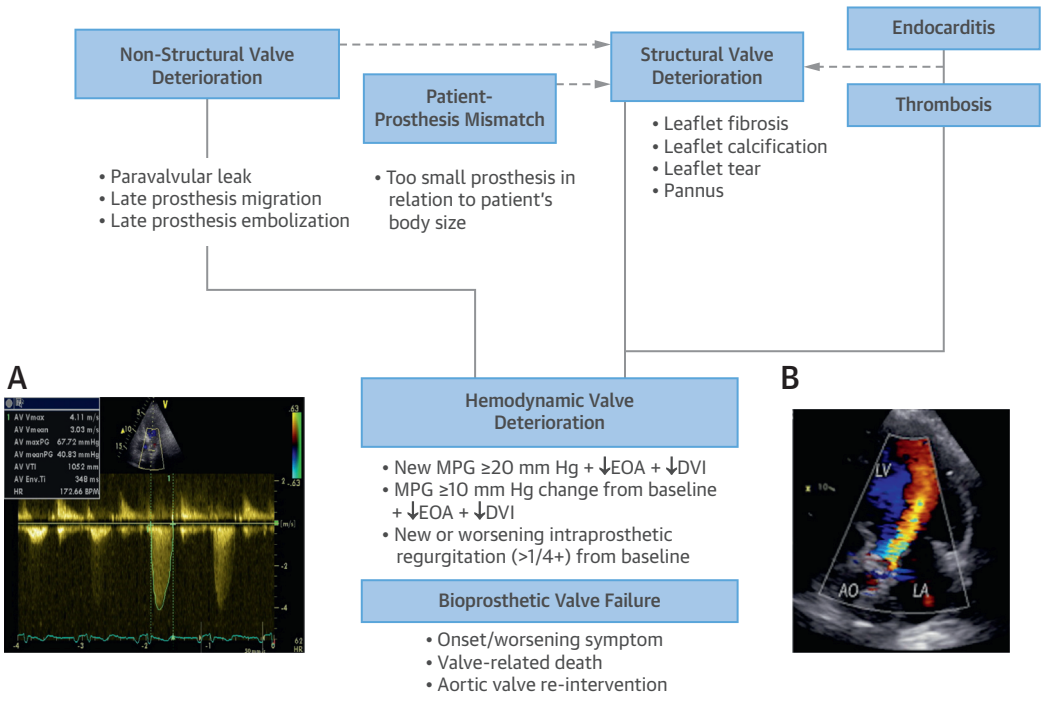
FIGURE 1 Schematic Representation of Transcatheter Valves With Bioprosthetic Valve Dysfunction



(A) Severe increase in mean pressure gradient; **(B)** severe intraprosthetic regurgitation. DVI = Doppler velocity index; EOA = effective orifice area; MPG = mean pressure gradient.

entity, just like thrombosis and endocarditis, although it is not considered reversible.

SAVR AND LONG-TERM PERFORMANCE

Previously, in the absence of a standardized definition of SVD, there were several barriers to comparing the durability of specific bioprosthetic valves. Most comparative studies were observational rather than randomized, with wide variability in patient management and follow-up. Meta-analyses including porcine and pericardial aortic bioprostheses showed that SVD commonly begins 8 years after implantation, with a much higher SVD rate after 10 years (6,7). Pibarot et al. (8) reported overall freedom from reintervention or death in surgical valves of 95% of patients at 5 years, 70% to 90% at 10 years, and 50% to 80% at 15 years. Other studies also confirmed excellent long-term results, with BVF fluctuating between 10% and 20% in a 10-year period (4). Nevertheless, when both morphological and hemodynamic valve deterioration using Doppler echocardiography are considered, the rates of bioprosthetic valve dysfunction are substantially higher (10% to 30% at 5 to 10 years post-SAVR) (9).

TAVR DURABILITY: WHEN THE DEFINITION OF SVD MATTERS!

In the field of TAVR, data on durability are currently very limited. Toggweiler et al. (10) reported favorable 5-year outcomes with excellent hemodynamics and signs of moderate prosthetic valve failure observed in only 3.4% of the 88 patients receiving a first-generation Sapien valve (Edwards Lifesciences, Irvine, California). No patient developed severe valvular regurgitation or stenosis. Subsequently, Dvir (11) reported a worrying incidence of degeneration in 378 patients receiving Cribier-Edwards, Edwards Sapien, or Sapien XT valves (Edwards Lifesciences), with up to 50% SVD within 8 years after implantation, generating concern among the structural heart community regarding the durability of TAVR prostheses. The investigators also noted gradually increasing calcification in the TAVR valve that progressed to valve degeneration within the first 5 years, with a

steep increase in valve degeneration after 5 years. Degeneration was defined in this analysis as moderate regurgitation (intravalvular and paravalvular) and/or a mean gradient ≥20 mm Hg not present at 30 days post-procedure that has clearly contributed to the overestimation of SVD incidence. In the definition of SVD proposed in the European position statement (5), paravalvular regurgitation belongs to non-SVD, whereas moderate SVD is defined as a mean gradient ≥20 mm Hg and/or an increase in mean gradient ≥10 mm Hg during follow-up and/or new onset or worsening of transprosthetic regurgitation with a final moderate regurgitation grade. Severe SVD is defined as mean gradient ≥40 mm Hg and/or an increase in mean gradient ≥20 mm Hg during follow-up and/or new onset or worsening of transprosthetic regurgitation and final severe regurgitation grade. Using this new European definition, Eltchaninoff et al. (12) reported a 3.2% incidence of SVD and a 0.58% incidence of BVF at 8 years in 378 patients. Holy et al. (13) also reported excellent valve performance, with no severe SVD at 8 years of follow-up. All this is in line with recent data from TAVR pivotal randomized control trials and large-scale registries demonstrating reassuring durability data, with low rates of SVD at 6 to 8 years of follow-up, regardless of the valve type (2,14,15).

TAVR AND LONG-TERM DURABILITY: NEW EVIDENCE

In this issue of the *Journal*, 2 studies have brought out new evidence about TAVR and long-term durability. First, Blackman et al. (16) reported excellent valve performance with low incidence of hemodynamic SVD 5 to 10 years post-procedure in the UK TAVI Registry. Moderate SVD was noted in 8.7% of the study population (regurgitation in 57%, stenosis in 43%), whereas severe SVD (1 with CoreValve, 0 with Edwards) was observed in 0.4% of the study population. No patients developed non-SVD during follow-up. Therefore, it would not be unjustified to conclude that TAVR appears durable in these elderly patients who were at increased risk for surgery. Morphological SVD and clinically overt forms of BVF were, however, not reported, and only a small portion (241 patients were alive at follow-up, with CoreValve in 150 and Edwards valve in 80) of the entire registry population (N >1,500), for which echocardiographic data were available both at baseline and >5 years, was analyzed. Median follow-up was only 5.8 years, with <15% having follow-up beyond 8 years. Numbers of patients at risk beyond 5 years were, however, relatively reasonable (68 at 6 years) when compared with previous registries. Intriguingly, there was a progressive decrease in peak gradient and in the degree of regurgitation from mild to none/trivial from baseline to follow-up in the CoreValve group. Although of interest, these data should be interpreted with caution and considered hypothesis-generating only.

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Second, Søndergaard et al. (17) have also significantly contributed to further enriching our knowledge about TAVR durability. Using data from the NOTION randomized study cohort to compare rates of SVD and BVF (valve durability defined according to current European standardized definitions), the investigators reported sustained clinical outcomes 6 years after self-expandable CoreValve implantation. All-cause mortality at 6-year follow-up was similar in both groups (TAVR 42.5% vs. SAVR 37.7%), but rates of moderate to severe SVD were significantly higher after surgery (24.0% vs. 4.8%), whereas rates of non-SVD, endocarditis (5.9% vs. 5.8%), and BVF (6.7% vs. 7.5%) did not differ according to the mode of intervention. Notably, the effective orifice area was significantly greater for TAVR than for SAVR at all timepoints post-procedure, with an area of 1.53 cm^2 versus 1.16 cm^2 for surgical valves at 6 years. No cases of clinical thrombosis were noted in either group, but computed tomography scans were not used to detect subclinical thrombosis. Although the overall results of the NOTION trial are promising, the trial is likely underpowered because there were only 50 TAVR and 50 SAVR patients with 6 years of data available. The echocardiographic measurements were not adjudicated by an echocardiography core lab, and TAVR was performed exclusively using the self-expanding first-generation CoreValve device. Whether similar results could be obtained with other devices (notably, balloon-expandable systems and more recent second- and third-generation self-expanding devices) needs to be addressed.

Significantly, both the NOTION trial and the TAVI UK registry defined SVD as a combination of genuine SVD and PPM (mean gradient ≥20 mm Hg at baseline), which overestimates the true incidence of SVD, especially in the subset of patients with a higher prevalence of PPM (e.g., SAVR, valve-in-valve). Indeed, with the European definition, a patient harboring a mean gradient ≥20 mm Hg due to PPM would be considered as having SVD even if there were no significant valve hemodynamic deterioration during follow-up (e.g., mean gradient of 22 mm Hg at 1 month and 21 mm Hg at 7 years, or 18 mm Hg at 1 month and 21 mm Hg at 5 years). Given that the

prevalence of PPM is higher in SAVR than in TAVR, the use of this definition may bias the comparison of SVD incidence in favor of TAVR. As a matter of fact, in the NOTION trial, the higher rate of SVD was mainly driven by the mean gradient ≥20 mm Hg criterion: 22.2% versus 2.9%. With the increase in mean gradient ≥10 mm Hg criterion from the 3-month echocardiogram, a more robust criterion for SVD, the SVD rates were 11.1% versus 1.4%. Hence, the true incidence of SVD in the NOTION trial as well as in UK TAVI was likely much (~2-fold) lower than reported. Nevertheless, even with the more restrictive and robust criteria for SVD based on valve hemodynamic deterioration during follow-up, the rates of SVD remained significantly higher in SAVR versus TAVR (moderate: 11% vs. 1.4%; and severe: 3% vs. 0.7%), which is an interesting and encouraging testimony to TAVR durability. This also indirectly raises the issue of the link between PPM and early SVD. PPM is facilitated through increased hemodynamic stress on the deteriorating leaflet valve, as demonstrated in a large SAVR cohort (18). Lower incidence of PPM in TAVR may delay SVD compared with SAVR, as the present data imply. The rate of SVD using the hemodynamic deterioration criterion (i.e., an increase in gradient ≥10 mm Hg) but excluding the criterion of a mean gradient ≥20 mm Hg (at any follow-up echocardiogram) was actually similar in the NOTION trial for SAVR (11%) versus that (13.4% at 5 years) reported recently by Salaun et al. (19) in a single-center study including 1,387 patients who underwent SAVR. Therefore, there is a need to further refine the standardized definitions of SVD recently proposed in the published data (5). Finally, in the NOTION trial, the similar incidence of BVF, despite a much higher incidence of SVD in SAVR versus TAVR, may be explained by the fact that the vast majority of SVD were moderate, with likely no or minimal clinical impact, at least in the short term.

Although data from the NOTION trial and the UK TAVI registry are very reassuring, further long-term studies are warranted, particularly with respect to the desire to extend the indications of TAVR to young, low-risk patients. In fact, heeding the experience with surgical SVD (usually not seen until 5 to 10 years post-procedure) and the inverse relationship between age at SAVR and subsequent SVD, more time would be needed to accurately assess long-term valve durability and to understand the mechanism of potential BVF, which, in turn, will enable us to devise preventive strategies.

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