TAVR Durability:
What We Know and When Will We Know What We Don't?

A discussion of what defines durability, an overview of the surgical and transcatheter experience to date, and future directions.

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Patients with severe aortic valve stenosis present with breathlessness, angina, and syncope and, if left untreated, are at an increased risk of death. Historically, the only effective treatment was open surgical aortic valve replacement (SAVR), typically with the choice of either a bioprosthetic or a mechanical valve to replace the function of the native aortic valve. Mechanical valves have excellent durability but are limited by valve thrombosis, which requires life-long anticoagulation, conferring a long-term risk of adverse bleeding. Bioprosthetic valves relieve the need for life-long anticoagulation but are less durable, and thus, the spectre of future redo surgery remains.

Transcatheter aortic valve replacement (TAVR) is a less invasive percutaneous method developed for replacing the aortic valve in patients with severe aortic stenosis and has unique benefits (Table 1). TAVR provides a treatment option for patients at extreme surgical risk, and randomized data support TAVR as an option for patients at high and intermediate surgical risk. The stage is now set to explore the possibility of TAVR expanding into lower-surgical-risk patients with a number of ongoing randomized trials, and so the question of TAVR durability

is brought clearly into the limelight. The first TAVR valve was implanted in 2002, CE Mark approval was granted in 2007, and FDA approval was not obtained until 2011. Initial experience was largely with inoperable and then high-surgical-risk patients, and owing to the limited life expectancy of these cohorts, robust longer-term durability data are not available from these early cohorts.

WHAT IS DURABILITY?

An ideal aortic replacement valve should replicate a healthy aortic valve going through 40 million cycles per year with unfaltering function. The biological tissue used in bioprosthetic valves are unfortunately prone to structural valve deterioration (SVD), which is a progressive process starting with morphologic changes and eventually culminating in hemodynamic deterioration with stenosis, regurgitation, or both. The development of SVD is thought to be related to both prosthesis characteristics such as anticalcification treatments, stent and leaflet design, and transvalvular gradients, as well as clinical factors such as infection, patient age (with younger patients experiencing more immune-related leaflet degeneration), subclinical valve thrombosis, or

TABLE 1. BENEFITS OF TRANSFEMORAL TAVR OVER SAVR: THE PATIENT'S PERSPECTIVE			
Procedure	**Risks**	**Early Outcomes**	**Long-Term Follow-Up**
· Less invasive · No cardiopulmonary bypass · No orotracheal intubation · No intensive care unit	· Lower risk of new-onset atrial fibrillation, bleeding events, and kidney injury · Major benefit in female patients	· Shorter hospitalization · Faster return to normal life · Faster regain of quality of life	· Assess the need for reintervention · Long-term anticoagulant therapy
Abbreviations: SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.			

abnormalities of metabolism or anticoagulation cascade (Figure 1). Bovine pericardial valves typically calcify, resulting in stiffening and subsequent restenosis, whereas porcine valves tend to tear, leading to aortic regurgitation (AR).[1]

One of the central issues regarding valve durability is the lack of a universal definition. Without an agreed-upon definition, durability is very hard to measure. This issue has plagued the surgical reporting of durability and makes comparisons between studies challenging. The literature on surgical valve durability is replete with observational studies using variable definitions of durability, often in a heterogeneous group of patients. Reintervention is often used as a surrogate for SVD, but this concept is flawed because some patients may be too frail to undergo reoperation despite a failing bioprosthesis or alternatively may undergo reoperation for reasons other than SVD.
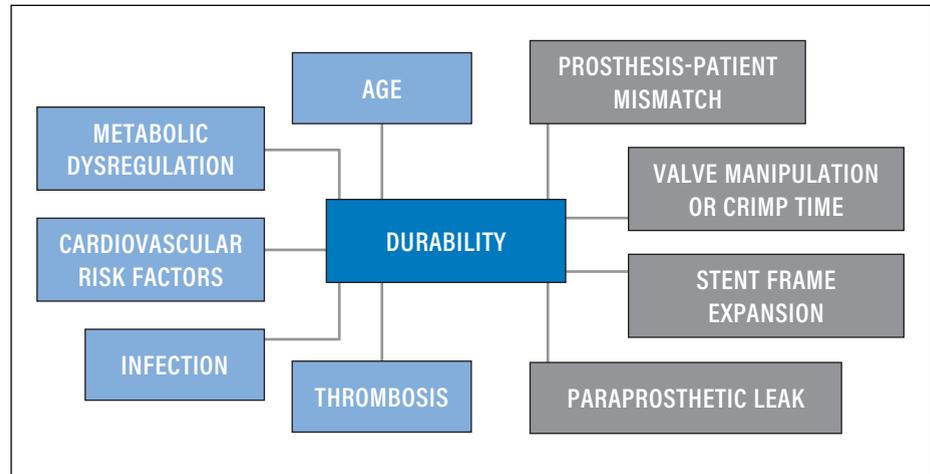

Figure 1. Possible factors implicated in TAVR durability.

The European Association of Percutaneous Cardiovascular Interventions consensus now standardizes the definition of SVD for all surgical and transcatheter valves, setting the scene for more robust reporting of durability going forward (Table 2).[2] However, one of the criticisms of this definition is the potential for inadvertently encompassing prosthesis-patient mismatch with measures of SVD, as valves that are too small for the intended annular anatomy will generate an increased gradient while mechanically functioning as intended.

TABLE 2. DEFINITION OF SVD
Moderate hemodynamic SVD (any of the following)
· Mean transprosthetic gradient ≥ 20 and < 40 mm Hg
· Mean transprosthetic gradient ≥ 10 and < 20 mm Hg change from baseline
· Moderate intraprosthetic aortic regurgitation, new or worsening (> 1+/4+) from baseline
Severe hemodynamic SVD (any of the following)
· Mean transprosthetic gradient ≥ 40 mm Hg
· Mean transprosthetic gradient ≥ 20 mm Hg change from baseline
· Severe intraprosthetic aortic regurgitation, new or worsening (> 2+/4+) from baseline
Morphologic SVD (any of the following)
· Leaflet integrity abnormality (ie, torn or flail causing intraframe regurgitation)
· Leaflet structure abnormality (ie, pathological thickening and/or calcification causing valvular stenosis or central regurgitation)
· Leaflet function abnormality (ie, impaired mobility resulting in stenosis and/or central regurgitation)
· Strut/frame abnormality (ie, fracture)
Hemodynamic and morphologic SVD
Abbreviations: SVD, structural valve deterioration.
Reprinted with permission from Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;38:3387.

These criticisms were incorporated in the proposed guidelines by Dvir et al, on behalf of the VIVID investigators, which stages SVD based on severity, excluding infective endocarditis, valve thrombosis, isolated prosthesis-patient mismatch without deterioration in valve function, isolated paravalvular regurgitation, and frame distortion without abnormal leaflet function.[3] Thus, there is still some ongoing debate preventing universal consensus on the definition of SVD.

SURGICAL EXPERIENCE

The durability of surgical bioprostheses at 10-year follow-up is reported to be > 85%.[4-6] Indeed, SVD is rare before 8 years but substantially increases after 10 years, with some studies showing freedom from reintervention or death at 50% to 80% at 15 years.[7-9] The recent publication of long-term outcomes after bioprosthetic SAVR in 672 consecutive patients (mean age, 72 ± 8 years) allows an insight into surgical valve durability as assessed by echocardiographic performance. SVD was defined as clinical when there was an increase in the mean transvalvular gradient > 20 mm Hg with a concomitant decrease in the effective orifice area (EOA) > 0.6 cm². Subclinical SVD includes an increase in the mean gradient of > 10 mm Hg and a concomitant decrease in EOA > 0.3 cm². Median follow-up was 10 years (interquartile range, 5–13 years). All-cause mortality was 64.3% and echocardiographic evaluation was available in 209 patients. The incidence of clinically relevant SVD was 6.6%, and subclinical SVD was substantial at 30.1%.[10] It is notable that no long-term data exist for recently introduced surgical bioprostheses, and despite some having a novel design, there are no age or risk restrictions for their implantation.

TAVR EXPERIENCE

The PARTNER trial collected early echocardiographic core lab data regarding 5-year medium-term durability in 424 surviving patients. These findings demonstrated low rates of SVD, with similar mean prosthetic gradients of approximately 10 mm Hg in both the TAVR and surgical arms, as well as reintervention rates of 0.8% and 0.3%, respectively. Moderate or severe transvalvular AR was present in 3.7% of this early balloon-expandable TAVR group.[11]

The randomized CoreValve pivotal high-risk trial included 391 patients who received self-expanding TAVR devices and 359 patients who underwent SAVR. Five-year data revealed severe SVD rates of 0.5% with TAVR and 0.6% with SAVR, along with an EOA of 1.9 ± 0.6 cm² for TAVR and 1.7 ± 0.6 cm² for SAVR. Transvalvular gradients were 7.1 ± 3.6 mm Hg for TAVR and 10.9 ± 5.7 mm Hg for SAVR. These data reaffirm that midterm severe structural deterioration is uncommon in surviving elderly high-risk patients treated with early generation self-expanding TAVR valves.[12]

Early data presented from centers in Vancouver, Canada, and Rouen, France, studying patients who underwent balloon-expandable TAVR between 2002 and 2011 found that almost half of the patients had valve degeneration after up to 10 years of follow-up. However, these early retrospective data were based on a small sample size, and subsequent data have proven more reassuring.[13]

The NOTION trial was the first to prospectively randomize low-risk patients (> 70 years) to self-expandable TAVR (n = 139) and SAVR (n = 135). Moderate/severe SVD was defined as a mean gradient ≥ 20 mm Hg, an increase in mean gradient ≥ 10 mm Hg from 3 months postprocedure, or more than mild intraprosthetic AR, either new or worsening, from 3 months postprocedure. At 6 years, with 50 remaining patients in each arm, the rate of SVD was higher for SAVR than TAVR (24% vs 4.8%; P < .001), although the more clinically relevant rate of bioprosthetic failure (defined as valve-related death, aortic valve reintervention, or severe hemodynamic SVD) was low in both arms (6.7% vs 7.5%; P = .89).[14] This definition of SVD included prosthesis-patient mismatch, as the higher SVD in the surgical arm was mainly driven by the criterion of mean gradient > 20 mm Hg. Nevertheless, the results are promising for TAVR durability up to 6 years.

Five-year follow-up data from the FRANCE-2 registry revealed a cumulative incidence of severe SVD and moderate/severe SVD at 5 years of 2.5% and 13.3%, respectively, with echocardiographic follow-up available in 459 patients.[15] Reassuringly in this real-world registry data, there was little change in TAVR valve gradients over time, with mean gradients of 9 to 12 mm Hg at 5-year follow-up.

Paired postprocedural and late (median, 5.8 years; range, 5–10 years) echocardiographic data published from the UK TAVI registry, including 241 patients using a mix of self-expanding and balloon-expandable valves, showed a peak aortic valve gradient at follow-up that was lower than postprocedure (17.1 vs 19.1 mm Hg; P = .002).[16] There was only one case (0.4%) of severe SVD (5.3 years postimplantation presenting with new, severe AR) and 21 (8.7%) cases of moderate SVD (mean, 6.1 years postimplantation; range, 4.9–8.6 years); 91% of patients remained free of SVD between 5 and 10 years postimplantation.

Data from an Italian registry following 288 consecutive patients recently reported up to 8-year echocardiographic follow-up data, with bioprosthetic valve failure and severe SVD occurring in only 4.5% and 2.4% of patients, respectively.[17]

TABLE 3. FEATURES OF TAVR AND SAVR PROSTHESES

	Similarities	Differences
Implantation	—	Crimping/postdilation vs "no-touch" technique
Frame	Very low rates of frame fracture	Leaflets sutured to a rather rigid metallic stent with TAVR devices vs fixed on a slightly flexible stent in conventional xenograft
Leaflets	Material (glutaraldehyde-treated bovine or porcine pericardium)	Leaflet structure for transcatheter delivery
Anticalcification treatment	Present in SAVR and TAVR devices	—

Abbreviations: SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

FUTURE DIRECTIONS

Although the performance and durability of TAVR have been excellent to date, it may be reasonable to consider that these valves are more similar to traditional bioprostheses than different (Table 3). If this is the case, one might expect SVD to start to develop after 8 years and progressively increase thereafter. The recent discovery of often-transient subclinical leaflet thrombosis by four-dimensional CT imaging provides another avenue for investigation on the effects on longer-term durability and the potential effects of antithrombotic treatment regimens.[18] Perhaps novel biomarkers such as lipoprotein-associated phospholipase A2[19] or the apolipoprotein B/A-I ratio[20] will help detect SVD earlier and trigger a change in antithrombotic treatment in a bid to extend durability.

Several trials evaluating low-risk patients are currently recruiting (PARTNER 3 [NCT02675114], NOTION-2 [NCT02825134], EVOLUT Low Risk [NCT02701283]) and these younger cohorts will provide a longer runway to examine longer-term durability. We know from the surgical experience that SVD is accelerated in younger patients; however, this might be balanced by iterative improvements in TAVR design and more experienced implantation technique. The option for TAVR-in-TAVR procedures also leaves the door open for a solution to future valve failure, and perhaps our energy should be directed in optimizing transcatheter valves for this eventuality. We will always want to know more about the treatments we offer our patients, but in the meantime, we must inform them to the best of our ability with the data available and share the decision-making process to help serve them best. ∎

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