Surgical treatment of aortic valve disease is a well-established therapy, and nearly 60 years have passed since the first reported successful case. Long ago, issues of access and reproducibility were resolved, allowing surgeons to objectively focus on hemodynamics and long-term valve performance. Standard criteria to assess valve function have been established and the importance of using objective criteria to evaluate heart valve performance cannot be overstated.

STATEMENT OF THE PROBLEM
The more recent development of transcatheter aortic valve replacement (TAVR) therapy initially focused on safe delivery and reliable early performance. Now that these issues have largely been addressed, attention must be focused on the critical issue of longer-term valve performance and durability. These key issues are becoming increasingly important as TAVR therapy moves to a younger and healthier patient population with longer life expectancy.

THE IMPORTANCE OF DESIGN
Heart valve durability is heavily influenced by design. Materials including bovine pericardium, porcine valve tissue, and bovine venous valve tissue have been extensively studied and each displays characteristics contributing to in vivo durability in the aortic, mitral, and pulmonic positions. Beyond material application, the design of the supporting structure for the valve leaflets may also have important implications on durability. For example, bovine pericardium and porcine aortic leaflet tissue have excellent durability when the tissue is contained within the supporting architecture (ring and struts) of the valve, such as in the Magna (Edwards Lifesciences) and the Mosaic (Medtronic) valves. On the other hand, when the design puts pericardial leaflets external to the frame of the valve, such as in the Mitroflow device (Sorin Group) and Ionescu-Shiley valve (Shiley Inc., a Pfizer subsidiary), durability appears to suffer. These concepts underscore the need for careful study of the design characteristics of current transcatheter valves, as well as patient outcome data, in order to draw conclusions about TAVR durability and hemodynamic performance.

DURABILITY
Long-term durability data, traditionally considered to be 10 years or more, are currently unavailable in the TAVR treatment population. Unlike surgical aortic valve replacement (SAVR), where biologic valves have been used in all age groups for decades (although only recommended for those 60 years or older and, more recently, 50 years or older), TAVR has initially been applied in elderly inoperable patients with many comorbidities. Not surprisingly, 5-year all-cause mortality has been reported up to 71%, and therefore, most of these patients are not available for long-term follow-up. As treatment moves toward lower-risk patients with increasing life expectancy, careful monitoring of ongoing valve function will provide essential insight into the durability of TAVR. Establishing standard objective criteria for ongoing evaluation of bioprosthetic valve function, including the definition of structural valve deterioration, continues to be an active point of discussion. Among the many definitions proposed, the Valve Academic Research Consortium is in the process of finalizing an update to be considered in addition to a newly published European consensus statement. Once established, using objective uniform criteria, valve durability can be assessed as patients mature with their devices.

Although 10-year data are still lacking, important 6-year follow-up data have come from the NOTION trial, which was the first study to randomize lower-risk patients between SAVR and TAVR using early generation self-expanding valves. Six-year follow-up of hemodynamic performance with this early generation TAVR valve showed sustained low (single-digit) gradients, unchanged from year 1 through year 6. Importantly, valve gradient was significantly lower and the effective orifice area (EOA) was significantly greater than with surgical valves at every time point. This supports the concept that supra-annular design may allow improved hemodynamics versus the
intra-annular design in older-generation surgical valves and perhaps balloon-expandable valves. Moderate hemodynamic structural valve deterioration, defined as mean gradient of ≥20 mm Hg or increase in gradient of ≥10 mm Hg over baseline, was present in 3.6% of TAVR patients and 23.7% of surgical patients. Again, this suggests that a supra-annular TAVR design may be superior to the design of most surgical biologic valves. Valve thrombosis was not seen in either valve. Endocarditis rates were low (<6%) and not different between surgical and TAVR treatment groups.\(^\text{12}\)

Five-year data from the ADVANCE study show that among the 860 patients who had echocardiographic data after 30 days, 22 patients (2.6%) had aortic valve stenosis as defined by VARC-2 criteria.\(^\text{13}\) Longer-term follow-up from the POST-TAVI registry has been reported by the group at Heart Center in Bad Segeberg, Germany.\(^\text{14}\) Fifty-six patients with echocardiographic follow-up beyond 5 years (mean, 6.3 years; range, 5–8.9 years) had an EOA of 1.6 cm\(^2\) and mean gradient 6.7 mm Hg, signaling good durability beyond 5 years.

**DESIGN CONSIDERATIONS**

Human anatomic details also play a potential role in the long-term durability of aortic devices. The aortic annulus has measurable and somewhat fixed dimensions for each individual patient. As a result, there are limits to the amount of prosthetic material that can reside within the annulus without compromising the EOA. This becomes increasingly important in cases of small native annulus or a valve-in-valve case for a failed surgical prosthesis. Balloon-expandable devices are largely intra-annular, and therefore, by definition, the frame, leaflet, and skirt material are contained within the annulus. When the goal is to obtain the largest EOA, these valves are already challenged when compared to supra-annular self-expanding devices. The supra-annular self-expanding devices are positioned with only the low-profile nitinol frame and skirt within the annulus and the actual leaflets of the functional valve well above the annulus, providing a fundamental advantage when working in the fixed dimensions of the calcified native annulus. As annular size decreases, this advantage becomes increasingly important.

Leaflet shape is also thought to contribute to long-term durability. Much like the long cables of a suspension bridge (eg, the Golden Gate Bridge) that distribute forces over a large area to gain stability, the taller leaflets of the self-expanding design are thought to distribute stress over a larger area, thereby reducing risk of failure at any given point (data on file at Medtronic). Additional evidence of the importance of proper leaflet shape and orientation has been obtained in vivo. Overexpansion, underexpansion, or irregular expansion of the balloon-expandable valve have been shown to result in either improper leaflet contact (pinwheel effect) or incomplete leaflet coaptation, both of which are thought to contribute to early valve failure.\(^\text{15}\) This effect is not seen in the supra-annular self-expanding devices, in which the leaflets are unconstrained by the annulus and can reliably take the shape of the frame in the larger area of the sinuses of Valsalva.

At the current time, failure of TAVR valves is relatively uncommon. In general, valve failure occurs by either restenosis of the leaflets or leaflet tear. Both of these mechanisms will have profound effects on the hemodynamics. In the more common failure mode, restenosis, there is usually a slow progression of increasingly rigid leaflets, resulting in an increasing transvalvar gradient. For this reason, trends in gradient development provide a signal on durability and deserve consideration.

Strategies to enhance the performance of the leaflet tissue itself may also play an important role in durability. Recently, a four-dimensional CT radiographic finding described as hypoaattenuated leaflet thickening (HALT) has gained attention. This finding, when extensive, is believed to diminish leaflet mobility and lead to subacute valve failure. Midha et al recently described how balloon-expandable valves with HALT were noted to be those that were expanded to a greater degree than those without HALT.\(^\text{15}\) It is unclear how, if at all, this information could be used to guide procedural details, but it is notable that this relationship was not present in the self-expanding cohort. In vitro studies also suggested that supra-annular valves have significantly less stagnation of flow but may be at risk with increasing depth of implantation. If true, potential mitigation strategies might include accurate and precise deployment enabled by the recapture and repositioning features of self-expanding technology. The topic and impact of HALT continue to be widely discussed and there is debate about the clinical implications. Anticoagulation as a strategy to mitigate this finding must be cautiously approached due to heterogeneity of comorbidities among patients treated with TAVR. Patient-independent strategies to reduce leaflet degradation may offer a solution. One such strategy involves processing the leaflet tissue with alpha-omega oleic acid, a naturally occurring long-chain fatty acid shown to reduce calcification in vitro.\(^\text{16},\text{17}\) This strategy is currently in use in the Evolut valve (Medtronic).

Certain patient-specific factors can also pose challenges to long-term valve durability. The presence of a small previously placed bioprosthetic valve, prosthesis-patient mismatch (PPM), and altered calcium metabolism are examples of patient-specific conditions that affect durability. Patients who have previously been treated with a small (19 mm) surgical valve and have developed restenosis also represent a particular challenge. These patients are typically elderly, frail, and poor surgical candidates. Relief of gradient is an important feature because residual gradient portends a poor outcome. A supra-annular TAVR design (eg, Evolut R, Medtronic) is critical in these cases to maximize the resultant EOA. In our experience, high deployment (1–2-mm depth) has shown good results. At our institution, five patients with...
stenois of a 19-mm prosthetic aortic valve underwent treatment with a 23-mm Evolut R or CoreValve (Medtronic), which resulted in low gradient (mean gradient, 12; EOA, 1.3) and excellent symptom relief (unpublished data). Reports from the Global Valve in Valve Registry18 (Valve-in-Valve International Data [VIVID]19) show that treatment of small bioprosthetic valves with CoreValve did not increase the occurrence of high gradient after TAVR, whereas the use of a Sapien valve (Edwards Lifesciences) resulted in a substantial increase in the frequency of high residual gradient.

Treatment of small prosthetic valves with the Sapien device was an independent predictor of leaflet distortion and valve failure.20

When patients are found to have an unexpectedly high gradient across a prosthetic valve, such that the effective orifice is inadequate for the patient’s size, this condition is known as PPM. The transvalvular gradient (TVG) is calculated by dividing the square of the flow (Q) by the square of the EOA multiplied by a constant:

\[
TVG = \frac{Q^2}{k \times EOA^2}
\]

Because the gradient is directly related to the square of the flow and inversely related the square of the EOA, relatively small changes in either the flow or the EOA have a large impact on increasing or decreasing the gradient. Due to the fact that TAVR has been shown to have a lower gradient than SAVR,22 TAVR should be viewed as a protective strategy in those patients at risk for PPM and as therapeutic strategy for treating prosthetic valve degeneration or PPM. The less material placed within a degenerative prosthetic valve (especially in sizes ≤21 mm), the lower the expected gradient. Supra-annular valves appear to have an advantage in this situation. The strategy of TAVR, in place of surgical root or annular enlargement in patients with very small native anatomy, is gaining popularity. This is particularly effective when using a supra-annular valve that has a lower gradient and larger EOA than surgical valves.22

Finally, the issue of accelerated calcium metabolism and secondary hyperparathyroidism is most common in patients with end-stage renal disease (ESRD). This challenging population has a high prevalence of cardiovascular disease and typically shows extensive vascular calcification. TAVR with CoreValve or Evolut can be performed with low procedural mortality (5%) despite a Society of Thoracic Surgeons Predicted Risk for Operative Mortality score of 16 ± 7. In the national trial, gradients remained low (<10 mm Hg) throughout the 1-year follow-up period.23 In many centers, TAVR has become the standard of care for ESRD patients because of an unexpectedly low procedural mortality and good early functional results under the most challenging metabolic conditions.

CONCLUSION

The continued application of TAVR to lower-risk patients demands careful attention to valve performance and long-term durability. Early and midterm performance look very promising but ongoing consideration of hemodynamics, structural design, and precise placement will allow us to provide effective solutions for patients with aortic valve disease.


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