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Transcatheter Aortic Valve Replacement in Intermediate- and Low-Risk Patients

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Initially restricted to high-risk and inoperable patients with symptomatic severe aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) is increasingly being offered to younger and lower-risk patients with fewer comorbidities who are otherwise good operative candidates and until now would have undergone surgical aortic valve replacement (SAVR). This evolution in clinical practice is underpinned by robust evidence, but do the data support the universal use of TAVR in all patients with AS, or is there still a role for surgery? In this review, we will review the data of TAVR in operable patients, examine potential limitations of TAVR in younger patients, and highlight the areas in which more research is required.

Concepts of Risk Assessment

First, it is imperative to recognize that the widely used risk classification scheme for patients undergoing TAVR (extreme, high, intermediate, or low risk) is an artificial construct, important for the conduct of clinical trials, but not necessarily applicable to everyday clinical practice. The commonly used risk scores (Society of Thoracic Surgeons [STS], EuroSCORE, and EuroSCORE II) are designed to assess the risk of surgery and not TAVR. Although dedicated TAVR risk scores have been proposed, including the US STS/American College of Cardiology Transcatheter Valve Therapies,[1] these are not widely used in clinical practice. Surgical risk scores typically overestimate the risk of TAVR. Arbitrarily selected STS thresholds to define risk categories for the pivotal TAVR trials were modified over time and varied between trials. Furthermore, the SAVR patient population in the STS database has changed in recent years, with most high-risk patients now undergoing TAVR. As a result, individual patients' STS scores have fallen, meaning there is overlap between clinical trial risk-defined patient populations.[2] Second, "low-risk" does not necessarily mean "young." For example, it is theoretically possible for a 90-year-old man with severe AS and hypertension, but no other comorbidity, to have an STS score <3%, even though most Heart Teams would probably consider his surgical risk to be substantial. Although this example is extreme, it highlights that score-based risk assessment is just 1 factor to consider when weighing the relative advantages and disadvantages of TAVR or SAVR. In this review, we will focus on those patients who are deemed "operable" by the multidisciplinary Heart Team, analogous to the low- and intermediate-risk cohorts from the pivotal trials.

Clinical Trials in Operable Patients

Figure 1 illustrates the regulatory timeline of TAVR in the United States. TAVR has been proven to be an effective treatment for patients with symptomatic severe AS and high or extreme surgical risk.[3–5] Observational studies in Europe were the first to suggest that TAVR is safe in low- and intermediate-risk patients, with low rates of procedural complications and short-term mortality,[6–9] although a recent meta-analysis suggested increased intermediate-term mortality with TAVR compared with SAVR (relative risk 1.45, 95% confidence interval, 1.11–1.89, P=0.006) with median follow-up of 2 years.[10] More robust data were provided by the NOTION (Nordic Aortic Valve Intervention Trial), which randomized primarily low-risk patients to SAVR versus TAVR with the self-expanding CoreValve THV (Medtronic, Minneapolis, MN).[11] There were no differences between groups in 2-year mortality or composite outcome of all-cause mortality, stroke, or myocardial infarction (Tables 1 and 2). TAVR patients required a more permanent pacemaker (PPM), but had lower life-threatening bleeding, acute kidney injury, and new-onset atrial fibrillation.

Results from the first pivotal randomized clinical trial of TAVR in intermediate-risk patients using the balloon-expandable Sapien XT transcatheter heart valve (THV) (Edwards

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Lifesciences, Irvine, CA) were published in 2016.[12] TAVR was noninferior to surgery with regard to death and disabling stroke, but there was a higher rate of moderate/severe paravalvular leakage (PVL) with TAVR versus SAVR. Similar to NOTION, TAVR was associated with lower rates of severe kidney injury, severe bleeding, and new-onset atrial fibrillation. Use of the newer-generation Sapien 3 THV in intermediate-risk patients may be associated with even better results. Data from the registry arm of the PARTNER 2 (Placement of Aortic Transcatheter Valves) study comparing TAVR with the Sapien 3 THV with a propensity-matched surgical cohort demonstrated both noninferiority and superiority of TAVR versus SAVR for the composite outcome of death, stroke, and moderate/severe aortic regurgitation, with overall low complication rates using this newer THV (Table 1).[13] Comparable findings were revealed in the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial using the self-expanding CoreValve or Evolut R THV in intermediate-risk patients.[14] At 2 years, there was no difference in the composite outcome of all-cause death or disabling stroke. As with the balloon-expandable valves, the PPM implantation rate was higher with TAVR, but new-onset atrial fibrillation, significant bleeding, and acute kidney injury rates were lower (Table 1).

In addition, it is important to appreciate that most subjects were elderly in the clinical trials of intermediate-risk patients, with mean age 79 to 82 years. Therefore, the results cannot necessarily be extrapolated to younger patients.

Potential Limitations of TAVR in Operable Patients

Because TAVR was initially reserved for extreme- and high-risk patients with advanced age and multiple comorbidities, very few patients lived long enough to test the lifespan of their bioprosthetic THV. So far, 5-year THV hemodynamic data appear comparable to surgical bioprostheses with no evidence of increased early structural valve deterioration.[15–17] Nonetheless, long-term THV durability remains unknown, which tempers widespread adoption of TAVR in younger patients. Mechanisms to explain the recent observation that THV appear more susceptible to subclinical leaflet thrombosis compared with surgical bioprostheses are still unclear.[18,19] The first comprehensive data on durability will likely come from long-term follow-up of patients from the intermediate-risk PARTNER 2 and SURTAVI trials. Additionally, the randomized US clinical trials in low-risk patients will follow subjects for 10 years with yearly echocardiography to assess for structural valve deterioration, and all include a subgroup of patients undergoing 4-dimensional contrast-enhanced cardiac computed tomography to assess for leaflet thrombosis and restricted leaflet motion. In the meantime, as more patients undergo TAVR, THV failure will become more common. TAVR-in-TAVR has been shown to be safe, with comparable short- and midterm clinical and hemodynamic outcomes to valve-in-valve TAVR for failed surgical bioprostheses.[20,21]

Over the past decade, the morbidity associated with the first-generation TAVR valves has dramatically improved. The increased risk of periprocedural stroke with TAVR compared with SAVR was a concern in high-risk patients. However, with device and procedural improvements, the rate of disabling stroke was consistently lower with TAVR versus SAVR in intermediate-risk patients (Table 2). Additionally, the rate of new-onset atrial fibrillation was significantly lower with TAVR versus SAVR in all of the clinical trials (Table 2). In the TAVR cohort of the NOTION study using the first-generation CoreValve self-expanding THV, the rate of clinically relevant

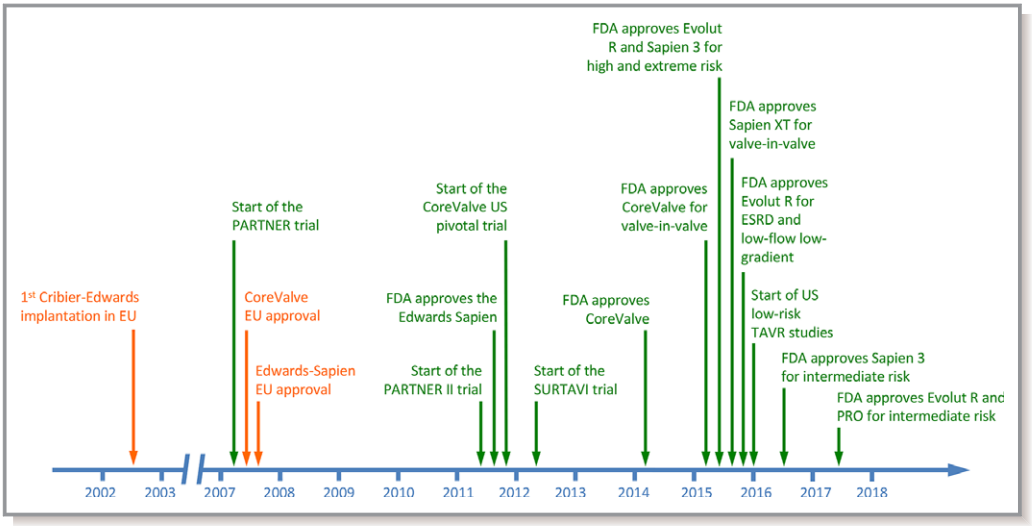

Figure 1. Regulatory timeline of TAVR in the US. ESRD indicates end-stage renal disease; EU, European Union; FDA, US Food and Drug Administration; TAVR, transcatheter aortic valve replacement.

Table 1. Summary of Key Findings From TAVR Cohorts of Clinical Trials in Low- and Intermediate-Risk Patients

	PARTNER 2[12]	SURTAVI[14]	NOTION[11]	SAPIEN 3 IR[13]
Type of Transcatheter Heart Valve	Edwards Sapien XT	Medtronic CoreValve or Evolut R	Medtronic CoreValve	Edwards Sapien 3
Time to end point	30 d	30 d	30 d	30 d
All-cause mortality	3.9%	2.2%	2.1%	1.1%
Disabling stroke	3.2%	1.2%	1.4%	1.0%
Paravalvular leak (≥ moderate)	3.7%	3.5%*	15.3%†	3.8%
Major vascular complications	7.9%	6.0%	5.6%*	6.1%
Major and life-threatening bleeding	10.4%	12.2%	11.3%*	4.6%
Acute kidney injury (stage 2 or 3)	1.3%	1.7%	0.7%*	0.5%
New permanent pacemaker implantation	8.5%	25.9%	34.1%	10.2%
Time to end point	2 y	2 y	2 y	1 y
All-cause mortality	16.7%	11.4%	8.0%	7.4%
Disabling stroke	6.2%	2.6%	3.6%	2.3%
Paravalvular leak (≥ moderate)	5.5%	5.7%	15.7%	1.5%
New permanent pacemaker implantation	11.8%	25.6%	41.3%	12.4%

NOTION indicates Nordic Aortic Valve Intervention Trial; PARTNER 2, Placement of Aortic Transcatheter Valves; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVR, transcatheter aortic valve replacement.
*End point at hospital discharge.
†End point at 3 months.

PVL at 30 days, defined as moderate or severe by echocardiography, was 15.3%. The PARTNER 2 and SAPIEN 3 IR studies using balloon-expandable THV (Edwards Sapien XT or Sapien 3) demonstrated much lower rates of significant PVL under 4%, as did the SURTAVI trial using self-expanding THV (CoreValve or Evolut R) (Table 1). The Sapien 3 valve features a sealing skirt, and the latest-generation CoreValve Evolut PRO also incorporates a pericardial tissue wrap specifically designed to reduce PVL. However, the need for new PPM implantation remains the Achilles' heel of TAVR, with 30-day PPM rates of ≈10% for balloon-expandable THV[13] and ≈25% for self-expanding THV[14] (Table 1). In the SURTAVI trial, there was no difference in PPM rate between the CoreValve and Evolut R THV (25.5% versus 26.7%, respectively), although only 16% of patients in the study received the newer Evolut R THV. This compares with PPM implantation rates after SAVR of 1.6% to 7.3% in these same studies. Strategies for high implantation, accurate computed tomography–based sizing, and newer TAVR devices may reduce the rates of PPM implantation in the future. The long-term consequences of the need for a PPM following either TAVR or SAVR are unknown.

Do Clinical Trials of TAVR in Low-Risk Patients Herald the End of Isolated SAVR?

So long as TAVR was restricted for use only in high- and extreme-risk patients, there remained a clear role for surgery for the many more patients with symptomatic severe AS who were operable. However, data from PARTNER 2 and SURTAVI have convincingly demonstrated that TAVR is noninferior to

Table 2. Comparison of 30-Day Outcomes With TAVR Versus SAVR in Clinical Trials of Low- and Intermediate-Risk Patients

	PPM Implantation		Stroke		Moderate or Severe PVL		New Atrial Fibrillation	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
PARTNER 2[12]	8.5%	6.9%	3.2%	4.3%	3.7%*	0.6%*	9.1%*	26.4%*
SURTAVI[14]	25.9%*	6.6%*	1.2%	2.5%	3.5%*	0.7%*	12.9%*	43.4*
NOTION[11]	34.1%*	1.6%*	1.4%	3.0%	15.3%*	1.8%*	16.9%*	57.8%*
SAPIEN 3 IR[13]	10.2%	7.3%	1.0%*	4.4%*	3.8%*	0.6%*	3.2%*	28.5%*

NOTION indicates Nordic Aortic Valve Intervention Trial; PARTNER 2, Placement of Aortic Transcatheter Valves; PPM, permanent pacemaker; PVL, paravalvular leakage; SAVR, surgical aortic valve replacement; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVR, transcatheter aortic valve replacement.
*Statistically significant difference.

SAVR in intermediate-risk patients and, if performed via transfemoral access, is associated with improved early health status improvements compared with SAVR.[22] Thus, in 2018, it is reasonable to favor TAVR in all operable patients with symptomatic severe AS and increased surgical risk.

Table 3 summarizes the study design of currently enrolling randomized clinical trials of TAVR in low-risk patients.[23–26] The first results from these studies are expected in 2018. Assuming these results demonstrate noninferiority of TAVR versus SAVR, in the future it will likely be reasonable to consider TAVR in all patients with symptomatic severe AS, regardless of operative risk (Figure 2). If this is the case, then we wholeheartedly support continued Heart Team collaboration between interventional cardiologists and cardiothoracic surgeons, although the requirement for 2 surgeons to evaluate each patient for operative risk before TAVR would become obsolete. Availability of TAVR for all, regardless of operative risk, would also allow more opportunity for patient preference to direct decision-making. Indeed, many low-risk patients may prefer TAVR over SAVR for personal reasons that current guidelines and indications cannot encompass.

However, risk assessment is but 1 element of the decision-making process. Special circumstances may still favor SAVR, namely, patient life expectancy, patients' preference for a mechanical valve, aortic valve and root anatomy, available vascular access, and comorbidities (Table 4).

Young Patients Requiring a Mechanical Valve

The 2017 American College of Cardiology/American Heart Association focused guideline update on the management of patients with valvular heart disease lowered the age cutoff above which a bioprosthetic valve is reasonable to 50 years with a Class IIa recommendation.[27] In patients under the age of 50 years, the guideline still recommends a mechanical valve unless the patient has a clear contraindication to anticoagulation. There is nonetheless a trend toward increased use of bioprosthetic surgical valves even in patients under the age of 50 years,[28] often driven by patient preference and desire to avoid long-term anticoagulation. Availability of newer mechanical valves that can safely be maintained with lower-dose warfarin (target INR 1.5–2.0) and low-dose aspirin[29] may convince more patients to select a mechanical prosthesis. Conversely, patients and physicians may feel more comfortable selecting a bioprosthesis because valve-in-valve TAVR is now an option if a surgical bioprosthesis fails in the future.[21] Irrespective of whether a mechanical valve or bioprosthesis is selected, aortic root enlargement surgery should be considered in patients with a small aortic annulus to prevent patient–prosthesis mismatch and facilitate TAVR valve-in-valve for the future.

Bicuspid Aortic Stenosis

The prevalence of a bicuspid aortic valve in the general population is 1% to 2%, with a 2:1 male-to-female ratio.[30,31] The specific genetic locus and protein abnormality in patients with a bicuspid aortic valve have not yet been identified; however, the tissue abnormality is not confined to the valve leaflets and these patients are at increased risk of aortic aneurysm and dissection. Although most cases of bicuspid aortic valve are sporadic, familial clusters have been

Table 3. Ongoing Clinical Trials in Low-Risk Patients

Name	Unique Identifier	Population	Study Design	Primary End Point	THV in TAVR Arm	Sample Size
LRT[23]	NCT02628899	No age restriction STS ≤3%	Feasibility study Prospective TAVR arm with historical SAVR controls	All-cause mortality at 30 d	Transfemoral SAPIEN 3 or Evolut R/PRO	200 TAVR in main arm Up to 100 TAVR in bicuspid arm
PARTNER 3[24]	NCT02675114	Age ≥65 y STS <4%	Noninferiority Randomized TAVR vs SAVR	All-cause mortality, all stroke, and rehospitalization at 1 y	Transfemoral SAPIEN 3	614 TAVR 614 SAVR
Medtronic TAVR in low risk patients[25]	NCT02701283	No age restriction STS <3%	Noninferiority Randomized TAVR vs SAVR	All-cause mortality or disabling stroke at 2 y	Transfemoral or subclavian Evolut R	625 TAVR 625 SAVR
NOTION 2[26]	NCT02825134	Age 18 to 75 y STS <4%	Noninferiority Randomized TAVR vs SAVR	Composite rate of all-cause mortality, myocardial infarction and stroke at 1 y	Transfemoral Any CE-approved THV	496 TAVR 496 SAVR

CE indicates Conformité Européene; NOTION, Nordic Aortic Valve Intervention Trial; PARTNER 2, Placement of Aortic Transcatheter Valves; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve.

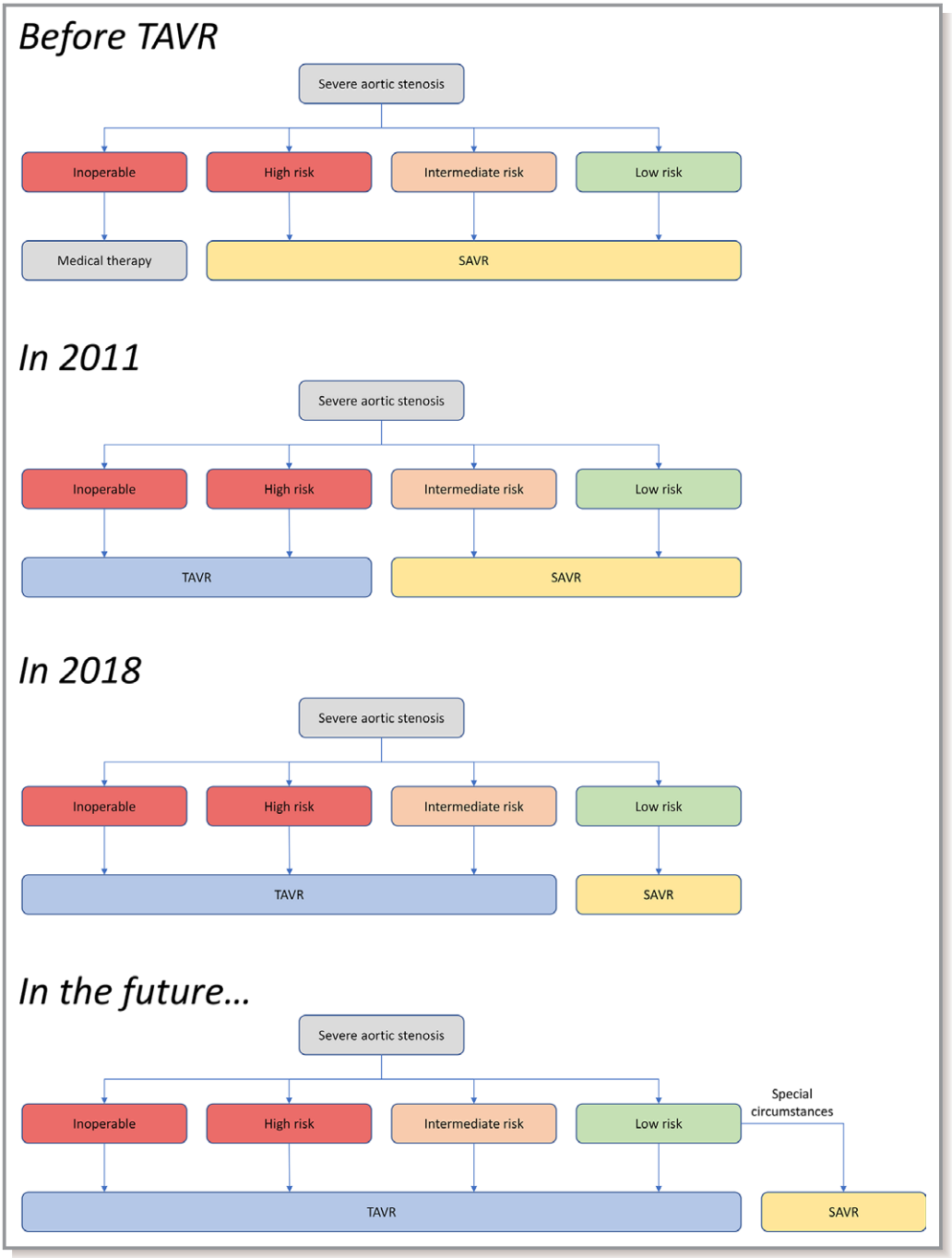

Figure 2. Evolution of the treatment algorithm for patients with aortic stenosis in the United States. SAVR indicates surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

identified. The high incidence of familial clustering is suggestive of autosomal-dominant inheritance with reduced penetrance.[32]

Nearly all patients with a bicuspid aortic valve will require valve surgery during their lifetime. A study of excised aortic valves revealed bicuspid morphology in 62% of patients aged 50 to 70 years undergoing isolated SAVR before the advent of TAVR.[33] Bicuspid aortic valves are more prone to calcific degeneration leading to stenosis at a young age, and therefore, patients with bicuspid AS are likely to fall into low- and intermediate-risk categories. Computed tomography analysis of aortic annulus and valve morphology demonstrates more eccentric annular calcification in bicuspid versus tricuspid valves (68% versus 32%).[34] Consequently, TAVR could theoretically be associated with increased risk in patients with bicuspid versus tricuspid valves. First, the rate of moderate or severe PVL could be higher. Observational studies have reported PVL rates in bicuspid valves to range

Table 4. Indications for SAVR in Operable Patients

Indications
1. Young patient requiring a mechanical valve
2. Bicuspid aortic stenosis with dilation of the ascending aorta
3. Very large aortic annulus
4. Patients ineligible for transfemoral access
5. Aortic stenosis with multivessel coronary artery disease

SAVR indicates surgical aortic valve replacement.

from 9.6% to 28.4%.[35,36] However, careful valve sizing using cardiac computed tomography angiography can reduce the incidence of PVL substantially.[36] Use of newer-generation valves that incorporate features to reduce PVL may be particularly advantageous in the setting of bicuspid AS. Second, the rate of valve embolization could be higher, although the same observational studies suggest that embolization with conversion to open chest surgery occurs rarely in bicuspid AS (2.2–4.0%).[36,37] Third, the rate of prosthesis–patient mismatch could be higher because the abnormal aortic valve morphology could prevent full expansion of the transcatheter valve.[38] Fourth, the rate of PPM implantation could be higher, although a German TAVR registry analysis actually reported lower rates in patients with bicuspid versus tricuspid valves (17% versus 35%).[39]

All of the pivotal randomized clinical trials comparing TAVR and SAVR excluded patients with bicuspid aortic valves. However, observational studies suggest that TAVR may be safe and effective in this setting. A multicenter registry of 108 patients reported 30-day and 1-year mortality rates of 8.3% and 16.9%, respectively.[35] An analysis of 139 low- and intermediate-risk patients (mean STS score 4.9±3.4%) in 12 European centers corroborated these findings with 1-year mortality of 17.5%.[36] Another multicenter observational study comparing TAVR in patients with bicuspid versus tricuspid aortic valves did not demonstrate any difference in 30-day mortality.[40] A comparison of outcomes in high-risk patients with bicuspid versus tricuspid aortic valves from the German national TAVR registry also demonstrated no difference in 1-year mortality.[39] A recent multicenter observational study of 51 patients in Canada and Europe with bicuspid aortic valve undergoing TAVR with the latest-generation Edwards Sapien 3 valve reported promising results with low 30-day mortality (3.9%) and no clinically significant PVL. These results suggest that the latest-generation balloon-expandable THV may achieve superior hemodynamic results compared with earlier-generation devices. However, the rate of new PPM implantation was high at 23.5%.[41] Further data on the safety and feasibility of TAVR in low-risk patients with bicuspid AS will be provided by the LRT (Low Risk TAVR) study, which includes a separate bicuspid registry arm.[23]

Regardless of these promising results, up to 80% of adult patients with bicuspid AS have concomitant dilation of the ascending aorta, and half of these patients meet criteria for surgical repair.[42,43] According to current guidelines, patients with ascending aorta diameter ≥4.5 cm should undergo surgical repair at the time of aortic valve replacement for bicuspid aortic valve pathology,[44] and therefore TAVR is probably inappropriate. However, in patients with ascending aorta <4.5 cm in diameter, the best strategy is to review historical imaging of the aorta to assess the rate of dilation. Rapid progression may push toward SAVR and ascending aortic repair, whereas slowing or absence of progression over preceding years may reassure that TAVR is a reasonable strategy.

Very Large Aortic Annulus

Commercially available THV are indicated for aortic annuli measuring up to ≈30 mm in diameter (maximum area 683 mm^2 for the 29-mm Sapien 3; maximum perimeter 94.2 mm for the 34 mm Evolut R). Case reports and a small series support the safety and feasibility of overexpansion of the 29-mm Sapien 3 THV up to a maximum annulus area of 800 mm^2, which roughly corresponds to an annulus diameter of 32 mm.[45,46] However, the effect of overexpansion on THV leaflet function and long-term durability is not known. The data for CoreValve THV in large annuli are less favorable with high rates of implantation of a second valve.[47] Therefore, at present, SAVR should still be considered in patients with a very large annulus.

Patients Ineligible for Transfemoral Access

In the PARTNER 1 study in high-risk patients, transthoracic access was an independent predictor of 2-year all-cause mortality with hazard ratio 1.52 (95% confidence interval, 1.12–2.07), P=0.008.[48] Similar findings were observed in the PARTNER 2 study in intermediate-risk patients, with hazard ratio 1.55 (95% confidence interval, 1.23–1.96), P<0.001.[12] A much smaller prospective randomized trial of transapical TAVR versus SAVR in operable patients (the STACCATO trial) was stopped early because of a higher complication rate in the transapical TAVR arm, specifically death and stroke.[49] Furthermore, health status improvements using the Kansas City Cardiomyopathy Questionnaire at 30 days in the PARTNER 2 study were greater with TAVR compared with SAVR, but only in patients who underwent transfemoral TAVR.[22] Those who underwent transthoracic TAVR (transapical or transaortic) did not show any early health status improvement benefit over surgery. Transfemoral TAVR has been shown to be more cost effective than transthoracic TAVR in high-risk patients[50] and was recently demonstrated

to be more cost effective than SAVR in intermediate-risk patients (Cohen DJ, Meeting Presentation, Transcatheter Cardiovascular Therapeutics, 2017). Combined, these data suggest that there is likely to be little benefit of TAVR over SAVR in operable patients who are ineligible for transfemoral access because of small or diseased iliofemoral arteries. However, newer options for percutaneous or surgical minimally invasive alternate access, such as transcaval,[51] subclavian,[52] transaxillary,[53] or carotid,[54] have been shown to be safe and appear to avoid the morbidity of transthoracic access, although none have been compared with transthoracic access in a randomized trial. Some can be performed with patients under conscious sedation, allowing rapid ambulation after TAVR and shorter hospital length of stay. Further studies are needed to determine whether TAVR via these newer alternate access approaches confers benefit over SAVR in operable patients. Indeed, all of the ongoing clinical trials in low-risk patients (Table 3) mandate transfemoral access exclusively and therefore will not provide any new information on alternate access in low-risk patients.

Multivessel Coronary Artery Disease

Patients with unrevascularized multivessel coronary artery disease were excluded from all of the pivotal TAVR trials, including from ongoing trials in low-risk patients. The Interventional Section Leadership Council of the American College of Cardiology recommends that patients undergo limited percutaneous coronary intervention (PCI) to proximal coronary stenoses before TAVR[55] even though this indication is not consistent with current PCI guidelines. It is important to recognize that this recommendation is based on expert consensus in the absence of randomized clinical trial data. However, a number of studies are under way to address this paucity of data. The ACTIVATION (percutaneous coronary intervention prior to transcatheter aortic valve implantation) study is a randomized trial of PCI versus no PCI before TAVR.[56] The FAITAVI (Functional assessment in TAVI) study, a randomized trial of fractional flow reserve versus angiography-guided PCI before TAVR, aims to explore the role of invasive physiological assessment of coronary stenoses to guide revascularization in patients with AS.[57]

Conclusions

In summary, the use of TAVR in intermediate-risk patients with both balloon-expandable and self-expanding THV is supported by robust data from multiple randomized clinical trials. Comparable data in low-risk patients are not yet available because the pivotal trials are ongoing. Nonetheless, the balance of evidence in operable patients is certainly leaning toward the use of TAVR as the preferred strategy for most patients with symptomatic severe AS. Choice of strategy should continue to be personalized based on individual patient demographics, aortic valve and root anatomy, available vascular access, and relevant comorbidities.

Disclosures

Rogers reports consulting for Medtronic. Thourani reports consulting for Abbott Vascular, Boston Scientific, Claret Medical, Edwards Lifesciences, JenaValve, and Gore Medical. Waksman reports consulting for Abbott Vascular, Biosensors International, Biotronik, Boston Scientific, Medtronic Vascular, Symetis, Lifetech; Speakers Bureau: AstraZeneca, Boston Scientific, Biotronik, Abbott Vascular; grant support from Biosensors International, Biotronik, Boston Scientific, Edwards Lifesciences, and Abbott Vascular.

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