

TAVR in Intermediate-Risk Patients

What the results from ongoing randomized trials may tell us about expanding TAVR to lower-risk patients.

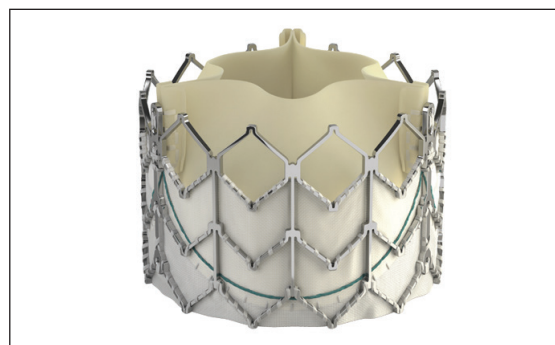
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Transcatheter aortic valve replacement (TAVR) has become an established treatment for calcific aortic stenosis (AS). Patients previously deemed at extreme or high risk for traditional open surgical aortic valve replacement (SAVR) now have a less-invasive alternative. Offering TAVR to patients at lower risk for surgical morbidity and mortality is intuitively attractive but remains controversial. Results from ongoing randomized trials may help guide the expansion of TAVR to lower-risk patients.

CURRENT INDICATIONS FOR TAVR

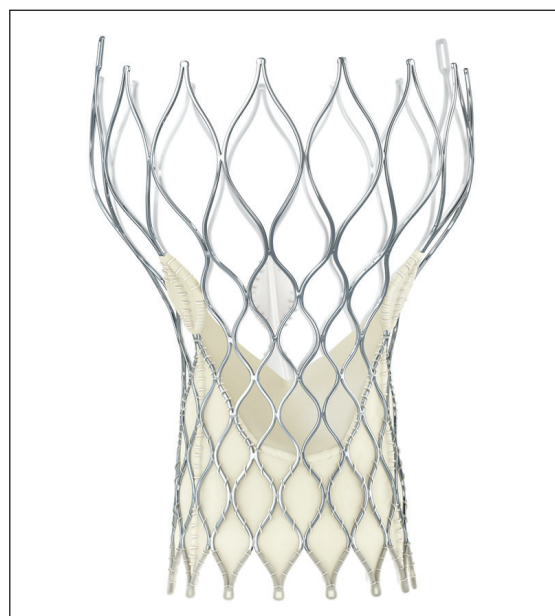
Evidence supporting the use of TAVR for the treatment of patients who are not considered candidates for SAVR based on comorbidities and anatomical considerations comes from the Placement of Aortic Transcatheter Valve (PARTNER) trial cohort B and the CoreValve United States Pivotal trial Extreme-Risk study. The investigators of the PARTNER trial randomized 358 patients with severe AS who were not candidates for surgery to either standard medical therapy including balloon aortic valvuloplasty or to TAVR using the Sapien (Edwards Lifesciences) balloon-expandable transcatheter valve (Figure 1) via a transfemoral approach. At 1 year, the mortality rate for TAVR was 30.7% versus 50.7% for standard therapy,¹ findings that have persisted at 3 years (54.1% vs 80.9%).² Given these results, a randomized trial comparing the self-expanding CoreValve (Medtronic; Figure 2) to medical therapy in inoperable patients with severe AS could not be performed. Instead, a prospective single-arm trial comparing the CoreValve to a prespecified goal was performed. The rate of all-cause mortality or major stroke in the trial arm was 26%, well below the performance goal of 43%.³

Randomized trials have shown the utility of TAVR for the treatment of patients who are candidates for SAVR but are at high risk for perioperative morbidity and mortality. The PARTNER trial cohort A randomized patients with severe AS with a high risk of operative mortality to treatment with SAVR or to TAVR with the Sapien transcatheter valve. *High risk* was defined as either a Society of Thoracic Surgeons (STS) predicted



Courtesy of Edwards Lifesciences.

Figure 1. The Sapien XT transcatheter heart valve is a balloon-expandable bovine pericardial valve mounted on a stainless steel frame.



Courtesy of Medtronic.

Figure 2. The CoreValve device is a porcine pericardial valve mounted on a self-expanding nitinol frame.

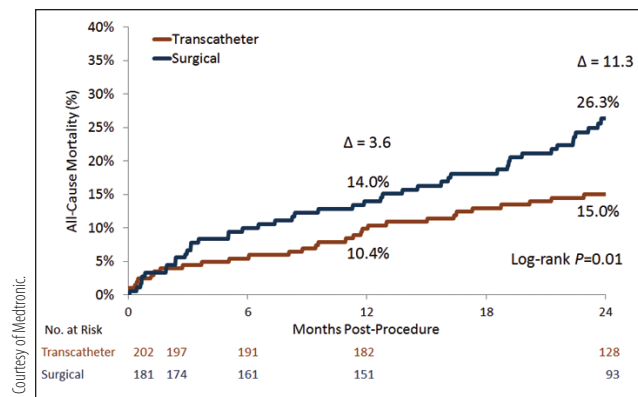


Figure 3. Two-year all-cause mortality from the CoreValve United States Pivotal trial High-Risk study for patients with an STS risk score ≤ 7 . Risk of death is lower among patients treated with TAVR than SAVR at 12 months, a difference that is more pronounced at 2 years.

risk of mortality of at least 10% or an expected risk of mortality of at least 15% as independently determined by two cardiac surgeons. The risk of death was similar between the two groups: 24.2% for TAVR and 26.8% for surgery at 1 year⁴ and 67.8% versus 62.4%, respectively, at 5 years.⁵ A trial randomizing patients at high risk for surgical mortality to CoreValve versus SAVR demonstrated improved 1-year survival with TAVR of 14.2% versus 19.1% for surgery, meeting prespecified criteria for superiority.⁶ High risk was defined as an expected risk of mortality of at least 15% as determined by two cardiac surgeons, using the STS risk score as one of several factors in determining risk. This difference increased at 2 years, with mortality 22.2% with TAVR versus 28.6% with SAVR.⁷ The mortality benefit was seen across all major subgroups and was more pronounced among patients with an STS risk score ≤ 7 (Figure 3).

As a result of the clinical trials, guidelines for the management of AS have been updated to include TAVR. The writers of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease have recommended TAVR for patients with severe AS who are at prohibitive risk for SAVR and with an expected survival > 12 months (class I, level of evidence B).⁸ They also recommend TAVR as a reasonable alternative to SAVR in patients with severe AS who are at high risk for surgery (class IIa, level of evidence B). In addition, the clinical trials' results have led to US Food and Drug Administration approval of the balloon-expandable Sapien valve and of the self-expanding CoreValve system for the treatment of severe calcific native aortic valve stenosis in patients at high or extreme risk of mortality from open SAVR.

The decision for using TAVR in lower-risk patients is complex. Current guidelines recommend SAVR in intermediate-

or low-risk patients.⁸ Even without randomized comparisons in lower-risk patients, guideline recommendations may not be followed due to patient or physician preference and bias. Marketing of TAVR centers and the TAVR procedure to patients and referring physicians may also play a role in the decision process. In general, whenever a percutaneous therapy is discussed with a patient, this option is considered preferable compared to a sternotomy incision and cardiopulmonary bypass. This is preferred even with a thorough discussion of proven risks and benefits and long-term outcomes of surgery compared to the paucity of data in lower-risk patients with TAVR.

DEFINING RISK

The ability to predict surgical outcomes is limited. Currently available and objective tools include the STS risk score and the EuroSCORE. Importantly, these databases only include patients who were deemed appropriate candidates to undergo surgery. Many elderly patients with aortic stenosis traditionally have not been offered surgery, with age and left ventricular dysfunction being the most notable factors associated with denial of surgical therapy.⁹ A comprehensive clinical evaluation may reveal additional factors not captured in the risk scores that may significantly affect a given patient's risk with surgery. Some of these factors may include frailty; potential for rehabilitation; cognitive impairment; and anatomic characteristics, such as a porcelain aorta, that may render surgery challenging and high risk. The authors of the AHA/ACC guideline for the management of patients with valvular heart disease recommend a comprehensive assessment of risk that uses the STS score, an objective evaluation of frailty, the number of major organ systems compromised and unlikely to improve after valve replacement, and any procedure-specific impediments.⁸ These added factors may help to identify patients at higher risk than relying on the STS score alone.

Importantly, although the CoreValve United States Pivotal trial High-Risk study included patients deemed to be at high risk for surgical mortality, the 30-day mortality rate among the surgical group was 4.5%, suggesting that perhaps the trial studied patients who had a lower risk than predicted by the STS risk score or that improvements in surgery have led to improved mortality. The STS risk score may not be adequately predictive of outcomes for AS patients.

CONSIDERATIONS FOR EXPANDING TAVR TO INTERMEDIATE-RISK PATIENTS

Although TAVR has offered a less-invasive approach to the treatment of AS, some limitations have been noted. The primary issues relate to stroke, paravalvular regurgitation, access site vascular complications, and advanced atrioventricular block requiring permanent pacemaker implantation.

These issues, as well as lack of data on long-term durability of the percutaneous valves, are among the key concerns for expanding indications for TAVR to lower-risk patients.

In the PARTNER trial cohort A, the 1-year rate of major stroke was 5.1% after TAVR versus 2.4% after surgery.⁴ In contrast, in the CoreValve United States Pivotal trial High-Risk study, the major stroke risk was similar after TAVR and surgery: 5.8% versus 7%, respectively, as evaluated using neurologist assessment of stroke in all patients.⁶

Paravalvular regurgitation is common after both balloon-expandable and self-expanding TAVR and is due to inadequate sealing of the aortic annulus by the prosthetic valve. Causes may include inadequate inflation of a balloon-expandable prosthesis, undersizing of the valve, or the presence of a heavily calcified annulus. Moderate to severe paravalvular regurgitation is associated with increased mortality.¹⁰ In the PARTNER trial cohort A, the rate of moderate to severe paravalvular regurgitation was 12.2% for TAVR versus 0.9% for surgery at 30 days and 6.8% versus 1.9% at 1 year.⁴ The results were similar in the CoreValve United States Pivotal trial High-Risk study, with 30-day rates of 9% for TAVR versus 1% for surgery and 1-year rates of 6.1% versus 0.5%, respectively.⁶

Major vascular complication rates (3.8% in PARTNER⁴ and 5.9% in CoreValve⁶) have improved with lower-profile TAVR devices and greater operator experience. Pacemaker rates at 30 days (19.8% with CoreValve⁶ and 7.1% with Sapien⁴) may be different in a lower-risk patient population. Although data on long-term durability are lacking, outcomes at 5 years have been favorable, with low risk of significant prosthetic valve failure.^{5,11,12}

NONRANDOMIZED STUDIES OF TAVR IN INTERMEDIATE-RISK PATIENTS

A number of recent observational trials have suggested that some European centers have been performing TAVR in patients with a lower surgical risk than specified in the guidelines. An analysis from the German Heart Center Munich has evaluated the temporal changes and outcomes in TAVR. The authors demonstrate a decline in average STS score over time for patients undergoing TAVR from 7.1% to 4.8% from the first to the fourth quarter of the study, with an expected decrease in 6-month unadjusted mortality from 23.5% to 12.4%.¹³ A prospective study of contemporary practice from a single center in Switzerland that stratified 389 consecutive patients undergoing TAVR by STS score into low- (< 3%), intermediate- (3%–8%), and high-risk (> 8%) groups demonstrated favorable 30-day and 1-year outcomes in the low- and intermediate-risk groups when compared to the high-risk group.¹⁴ Ten and one-half percent of patients were low risk, 65.3% were intermediate, and only 24.2% were high risk, demonstrating a definite shift

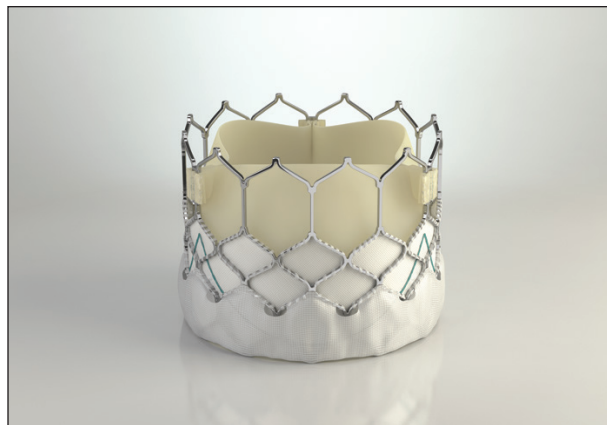


Figure 4. The Sapien 3 transcatheter heart valve has a lower-profile design to reduce vascular access complications. An outer skirt allows for better sealing of the native annulus and minimizes paravalvular regurgitation.

in practice toward the use of TAVR in lower-risk patients. In a single-center retrospective study from Italy, the investigators compared 182 intermediate-surgical-risk patients with an average STS predicted risk of mortality of 4.5% who underwent TAVR to a propensity-matched surgical control group and found similarly low 1-year mortality rates of 6.4% for TAVR versus 8.1% for surgery.¹⁵ They noted lower periprocedural rates of acute kidney injury and strokes and higher rates of vascular complications with TAVR compared with surgical AVR. An observational trial from three European centers has demonstrated similar 1-year mortality rates for patients at intermediate surgical risk undergoing TAVR compared to a propensity-matched surgical group.¹⁶

The S3i registry, an intermediate-risk group of patients who received the Sapien 3 valve (Edwards Lifesciences) (Figure 4), evaluated 1,076 patients up to 30 days after the procedure.¹⁷ The average STS score was 5.3%. The all-cause mortality was 1.1%, and the all-stroke rate was 2.6%. The pacemaker rate was 10.1%, and the rate of no or mild aortic insufficiency was 96.3%. All of these results compared favorably to results seen in the PARTNER extreme- and high-risk groups.

RANDOMIZED TRIALS OF TAVR IN INTERMEDIATE-RISK PATIENTS

The growth of TAVR experience and number of TAVR centers making access to TAVR easier has created a trend toward treatment of lower-risk patients. Due to the promising real-world results in intermediate-risk patients, randomized trials have been designed to further guide treatment and patient selection. These trials hinge on the combined evaluation of cardiologists and surgeons (the heart team) to select appropriate patients for evaluation. Enrollment in

intermediate-risk trials has been challenging for a number of reasons, most prominently the identification of patients who are at intermediate risk, as well as the desire among patients and their referring physicians to avoid surgery when a percutaneous option may be available.

The PARTNER II cohort A trial is a randomized, controlled, multicenter trial comparing TAVR using the Sapien XT system (Edwards Lifesciences) to SAVR in patients at intermediate risk for surgical mortality (www.clinicaltrials.gov identifier NCT01314313). *Intermediate risk* for this study is defined as an STS score ≥ 4 and < 8 . The primary outcome is a composite of death and disabling stroke at 2 years. Trial enrollment has been completed, and data are forthcoming. Furthermore, data from the S3i registry will be compared to the surgical arm from the PARTNER II cohort A trial.

The investigators of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) study are randomizing approximately 2,500 patients with severe, symptomatic AS who are at intermediate surgical risk to TAVR using the CoreValve system or to SAVR (www.clinicaltrials.gov identifier NCT01586910). *Intermediate risk* is defined as a heart team unanimous agreement on intermediate risk categorization, with an STS score between 4 and 10 as a guide. The primary outcome is all-cause mortality or disabling stroke at 2 years using a dynamic noninferiority analysis. As of the publication of this article, approximately 1,200 patients have been enrolled in SURTAVI, with an interim analysis planned after the enrollment of 1,500 patients.

The Nordic Aortic Valve Intervention (NOTION) trial is the first randomized trial of 280 patients (145 TAVR, 135 SAVR) for low- and intermediate-risk patients (mean TAVR STS, 2.9; mean SAVR STS, 3.1).¹⁸ The primary outcome of stroke, myocardial infarction, and all-cause mortality at 1 year was 13.1% for TAVR and 16.3% for SAVR ($P = 0.43$). Statistically significant clinical secondary endpoints for TAVR versus SAVR included less bleeding (11.3% vs 20.9%), acute kidney injury (0.7% vs 6.7%), and atrial fibrillation (16.9% vs 57.8%). Patients who underwent SAVR had less pacemaker utilization (1.6% vs 34.1%). Valve performance was excellent with large effective orifice area (aortic valve area, 1.7 cm² for TAVR and 1.3 cm² for SAVR) and low mean gradients (8.6 mm Hg for TAVR vs 12.5 mm Hg for SAVR). There was no or mild aortic insufficiency in 84.3% of TAVR patients versus 99% of the SAVR group at 1 year.

CONCLUSIONS

Clinical trials in intermediate-risk patients may help to answer numerous clinical questions. Further validation of the utility of STS risk score, EuroSCORE, and frailty and disability assessment will be possible. Some issues will remain unanswered, such as treatment of low-gradient AS or direct outcome comparisons of various TAVR devices. Although

cardiovascular mortality and stroke event rates will be essential, improvement in outcomes regarding reduction in paravalvular leak, vascular complications, need for pacemaker rates, and proven long-term durability of TAVR in younger patients will become necessary to expand TAVR to a new group of lower-risk patients. ■

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