

TAVR in Patients With Aortic Stenosis and Low Surgical Risk

Evaluating new clinical trial data to better understand the benefits and limitations of TAVR in patients at low surgical risk.

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Transcatheter aortic valve replacement (TAVR) was introduced as a treatment option for patients with severe aortic stenosis (AS) who were considered ineligible for surgical aortic valve replacement (SAVR). Subsequently, several randomized controlled trials (RCTs) have provided an evidence-based paradigm shift in the treatment of patients with symptomatic severe AS and increased surgical risk.¹⁻⁵ Thus, RCTs that examined patients at high, intermediate, and low surgical risk have shown that TAVR is at least noninferior to SAVR with regard to safety and efficacy profiles. At the American College of Cardiology's 2019 Annual Scientific Sessions in New Orleans, Louisiana, two additional landmark RCTs comparing TAVR and SAVR in patients at low surgical risk were presented with simultaneous publication in *The New England Journal of Medicine*.^{6,7}

THE NEW TRIALS

PARTNER 3 (sponsored by Edwards Lifesciences) randomized 1,000 patients with severe AS and low surgical risk at 71 centers in the United States, Canada, Australia, New Zealand, and Japan to undergo either transfemoral TAVR with the balloon-expandable Sapien 3 transcatheter heart valve (THV; Edwards Lifesciences) or SAVR. The primary composite endpoint (all-cause death, stroke, and rehospitalization at 1 year) was significantly lower in TAVR versus SAVR patients (8.5% vs 15.1%; $P < .001$ for noninferiority; hazard ratio, 0.54; 95% confidence interval, 0.37–0.79; $P = .001$ for superiority). At 1 year, TAVR also resulted in significantly lower rates of stroke, death or stroke, life-threatening or major bleeding, and new-onset

atrial fibrillation, whereas there were no differences in major vascular complications, new permanent pacemaker implantation, and moderate or severe paravalvular leak (PVL).

The EVOLUT Low-Risk trial (sponsored by Medtronic) compared TAVR using self-expanding supra-annular THVs (CoreValve, 3.6%; Evolut R, 74.0%; and Evolut PRO, 22.4%; Medtronic) to SAVR in 1,468 patients with severe AS and low surgical risk from 86 centers in the United States, Australia, Canada, France, Japan, the Netherlands, and New Zealand. The primary composite endpoint of death from any cause or disabling stroke at 24 months occurred in 5.3% of the patients in the TAVR group and 6.7% in the SAVR group (posterior probability of noninferiority $> .999$). SAVR was associated with higher early rates of disabling stroke, bleeding complications, acute kidney injury, and new-onset atrial fibrillation, whereas there was no difference in major vascular complications. Aortic valve hospitalization within 12 months was higher in the SAVR group (6.5%) than the TAVR group (3.2%).

CONTEXTUALIZING THESE TRIALS

One limitation of previous RCTs comparing TAVR and SAVR is that the mean age of the enrolled patients was approximately 80 years, despite embracing high, intermediate, and low surgical risk scores.¹⁻⁵ The 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease recommend TAVR in patients who are 75 years or older, particularly if it can be performed by a transfemoral approach.⁸

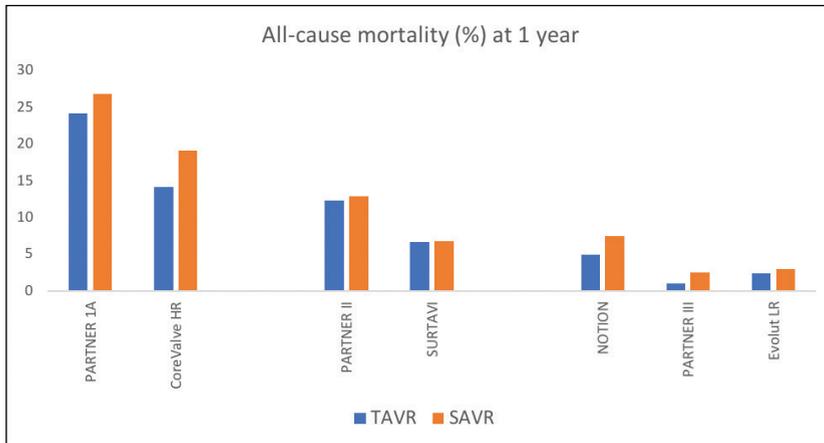


Figure 1. All-cause mortality at 1 year in RCTs involving patients at high surgical risk (PARTNER IA, CoreValve HR), intermediate surgical risk (PARTNER II, SURTAVI), and low surgical risk (NOTION, PARTNER 3, EVOLUT LR).

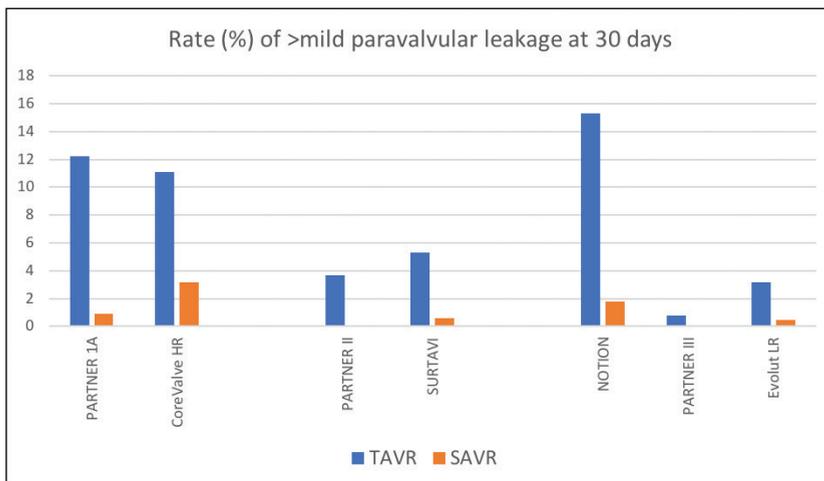


Figure 2. Rates of more-than-mild PVL at 30 days in RCTs involving patients at high surgical risk (PARTNER IA, CoreValve HR), intermediate surgical risk (PARTNER II, SURTAVI), and low surgical risk (NOTION, PARTNER 3, EVOLUT LR).

However, during the last few decades, the surgical community has used bioprosthetic aortic valves in increasingly younger patients. One reason for avoiding mechanical aortic valves is a patient preference to not be placed on anticoagulant therapy. Therefore, RCTs comparing TAVR and SAVR in patients with longer life expectancy are of utmost importance for the community.

Impact of Longer Life Expectancy

A simplified interpretation of postprocedural mortality is that the 30-day mortality reflects the safety of the procedure (which is high nowadays, even in older patients with high comorbidity burden due to

the combination of increasing implanter experience and improved devices), while 1-year mortality is mainly related to the characteristics of the treated patient cohort. Therefore, age, frailty, and comorbidity characteristics of the patients are the main drivers for mortality beyond the periprocedural period. Did the two recently presented low-risk RCTs include patients with longer life expectancy? PARTNER 3 included patients with a mean age of 73.5 years and Society of Thoracic Surgeons (STS) score of 1.9%, which is similar to patients in the EVOLUT Low-Risk trial with a mean age of 73.9 years and STS score of 1.9%. That these patients truly have longer life expectancy than in earlier trials is reflected by lower 1-year all-cause mortality rates of 1.0% and 2.4% in the TAVR groups (Figure 1).

Applying TAVR to patients with longer life expectancy also introduces TAVR-related issues that may not be relevant for patients treated to date. PVL and the need for new permanent pacemaker implantation have been the Achilles heel for TAVR. The use of CT to accurately determine the aortic annulus dimensions and correct sizing for bioprosthetic valves, as well as next-generation THVs,

has substantially reduced the rate of moderate and severe PVL. In PARTNER 3, more-than-mild PVL at 30 days was found in 0.8% and 0.0% in the TAVR and SAVR groups, respectively, whereas the corresponding numbers in the EVOLUT Low-Risk trial were 3.5% and 0.5% (Figure 2). Although the degree of moderate PVL after TAVR is now similar to what is seen with surgery, TAVR is still associated with a significantly higher rate of mild or greater PVL as compared to SAVR: 39.6% versus 5.5% in PARTNER 3 and 37.6% versus 3.1% in the EVOLUT Low-Risk trial, respectively. The long-term impact of mild PVL on left ventricular function, symptoms, and mortality in patients with longer life expectancy is still unknown.

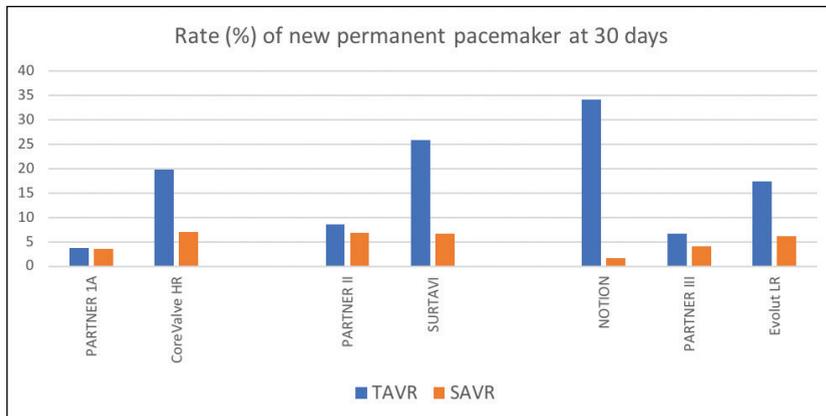


Figure 3. Rates of new permanent pacemaker at 30 days in RCTs involving patients at high surgical risk (PARTNER IA, CoreValve HR), intermediate surgical risk (PARTNER II, SURTAVI), and low surgical risk (NOTION, PARTNER III, EVOLUT LR).

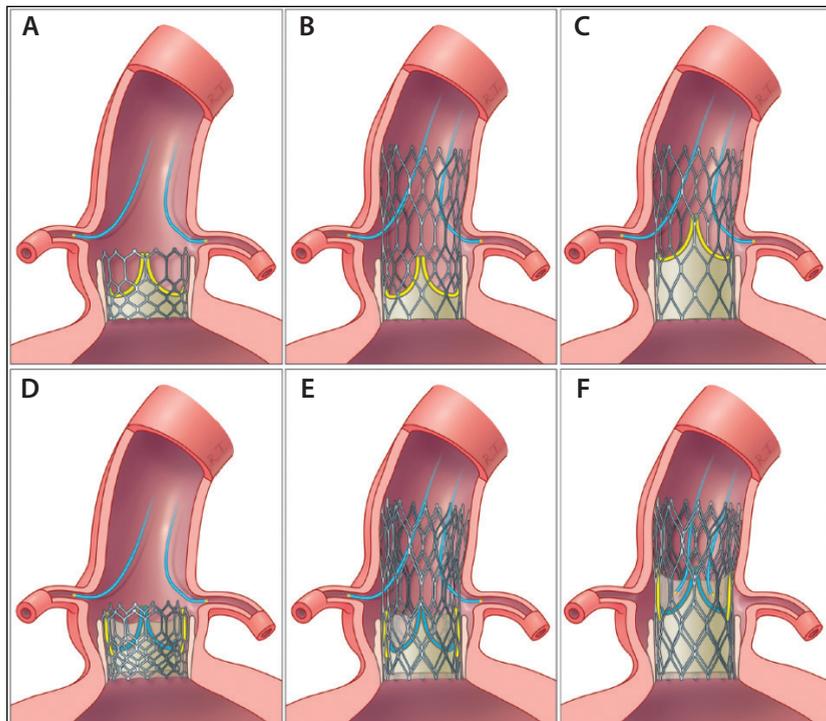


Figure 4. Access to the coronary arteries after first TAVR using a bioprosthetic valve with low-frame and intra-annular leaflet position (A), high-frame and intra-annular leaflet position (B), and high-frame and supra-annular leaflet position (C). After TAVR-in-TAVR, access to the coronary arteries may be possible in patients with low-frame and intra-annular leaflet position (D) and high-frame and intra-annular leaflet position (E), whereas access may be compromised in high-frame and supra-annular leaflet position (F). Yellow leaflets = leaflets in the first implanted THV; blue leaflets = leaflets in the second implanted THV; yellow/grey shading = tissue tunnel. Reprinted from *EuroIntervention*, 14/5, Søndergaard L and De Backer O, Transcatheter aortic valve implantation: don't forget the coronary arteries! 147–149, Copyright 2018, with permission from Europa Digital & Publishing.

Permanent Pacemaker Implantation in TAVR Patients

Similarly, the higher rate of conduction abnormalities and need for a permanent pacemaker after TAVR as compared to SAVR may also impact outcomes for these patients. Although a pacemaker may be beneficial for patients in the immediate postprocedural period after TAVR due to the risk of late atrioventricular block and sudden cardiac death, the long-term effects of ventricular pacing may be harmful for the patient.⁹ It is well known that the rate of conduction abnormalities is related to the type of THV prosthesis, which is also reflected in the two low-risk trials. Thus, the rate of new permanent pacemaker implantation at 30 days for the balloon-expandable THV in PARTNER 3 was 6.6% and not statistically different from the 4.1% in the surgical group. On the other hand, the pacemaker rate in the EVOLUT Low-Risk trial of 17.4% for the self-expanding THV was significantly higher than 6.1% with SAVR (Figure 3). These considerations may be relevant when choosing a THV prosthesis for patients with longer life expectancy.

Valve Durability

Another important aspect is the durability of bioprosthetic aortic valves. Currently, with mainly elderly patients treated with TAVR, the longevity of a THV is likely to exceed patient life expectancy. However, patients with longer life expectancy may survive one or even more bioprosthetic aortic valves. Little is known about the long-term durability of THV prostheses, but 6-year data from the NOTION trial showed that the rate of structural valve deterioration was lower and the rate of valve failure was similar for the CoreValve self-expanding

device compared to surgical bioprosthetic valves.¹⁰ One factor that may contribute to the lower rate of structural deterioration may be the larger aortic valve area of self-expanding THV devices. Importantly, the aortic valve area was a mean of 2.2 cm² after TAVR compared with 2.0 cm² after SAVR in the EVOLUT Low-Risk trial, whereas the corresponding values were 1.7 cm² and 1.8 cm² in PARTNER 3. The balloon-expandable THV thus provided a smaller aortic valve area compared to the self-expanding THV, as well as compared to surgical bioprostheses. Whether this will impact long-term durability is unknown.

Although TAVR-in-TAVR is feasible in case of valve failure, it may reduce the effective orifice area of the valve with risk of prosthesis-patient mismatch and—importantly—make it difficult or even impossible to access the coronary arteries, particularly for THVs with supra-annular leaflets (Figure 4).¹¹ This may become a major issue if a TAVR patient is admitted with acute coronary syndrome at a later time point.

In younger patients, AS is often related to bicuspid aortic valves. Although TAVR in bicuspid AS has been associated with less favorable outcomes than in tricuspid aortic valves, a better understanding of valve sizing, optimized implantation techniques, and next-generation THV prostheses has led to improved results. However, TAVR is currently only used for patients with bicuspid aortic valves at increased surgical risk. Because patients with bicuspid aortic valves were excluded from the two low-risk trials, there is still no evidence to support TAVR in patients with bicuspid aortic valves and low surgical risk.

CONCLUSION

The PARTNER 3 and EVOLUT Low-Risk RCTs provide important evidence for expanding TAVR as an alternative to SAVR in patients at low surgical risk. Compared to SAVR at 1 year, TAVR is associated with a lower rate of stroke, acute kidney injury, new-onset atrial fibrillation, major bleeding, and rehospitalization, whereas mortality and major vascular complications are similar. Furthermore, the rates of moderate PVL as well as new permanent pacemaker implantation are the same for TAVR with Sapien 3 and SAVR but are more frequent with Medtronic's self-expanding THVs (CoreValve, Evolut R, and Evolut PRO) than after SAVR.

The next logical step should be to explore TAVR versus SAVR in younger patients. In the two low-risk

trials, the mean age was approximately 74 years. However, surgical bioprosthetic aortic valves are offered to patients who are 60 years or younger at many sites. Furthermore, the outcomes with TAVR in younger patients who have bicuspid aortic valves also needs to be evaluated against SAVR. Currently, NOTION-2 (NCT02825134) is the only RCT addressing these issues. ■

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Disclosures: Received consultant fees and institutional research grants from Abbott, Boston Scientific Corporation, Edwards Lifesciences, Medtronic, and Symetis.

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Disclosures: Consultant to Medtronic, HighLife, and Microport.