TAVI: Where Is the Evidence Taking Us?

A review of the current status.

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Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of symptomatic severe aortic valve stenosis. After well-designed randomized clinical trials, TAVI is considered the best option for treating patients with symptomatic severe aortic stenosis who are deemed inoperable and at high or intermediate operative risk of death.[1-7] As a result, international guidelines have recommended TAVI in inoperable and high-risk patients (class I) and, more recently, in intermediate-risk patients (class IIa).[8,9] Iterative device designs are being developed in an attempt to address the remaining drawbacks of the procedure, such as sealing fabric to prevent paravalvular leak (PVL), lower-profile devices to reduce vascular complications, and repositioning and/or recapturable features to avoid suboptimal deployment, which can result in conduction abnormalities and PVL. These different iterations, coupled with growing heart team experience and advanced imaging planning, have been associated with improved outcomes and fewer complications[10] and seem likely to lead to expanded indications in the low-risk population. The PARTNER 3 and EVOLUT Low-Risk trials published in 2019 confirmed noninferiority (and even superiority) of TAVI over surgical aortic valve replacement (SAVR) for some outcomes, such as early safety endpoints, faster discharge from the hospital, and fewer rehospitalizations.[11,12]

Do these trials of low-risk patients herald the end of isolated SAVR? Despite these very encouraging findings from these two trials, approximately one-third of patients in the PARTNER 3 trial and 15% of the patients in the EVOLUT Low-Risk trial failed the screening process. Therefore, the generalizability of these results may not be as obvious as we are led to believe. This article considers the limitations of transitioning TAVI to younger patients, discusses challenges to further expansion of TAVI indications, highlights ongoing trials, and identifies areas of unmet needs where continued refinements are required (Figure 1).

YOUNGER POPULATION

Although the mean age of patients enrolled in both low-risk trials was < 75 years, only 7% of patients randomized in PARTNER 3 were < 65 years, and only 1.3% of patients enrolled in the EVOLUT self-expandable low-risk trial were aged ≤ 60 years.[11,12] In both studies, reduced procedural risk was driven by less frequent comorbidities rather than reduced patient age. Therefore, further trials specifically targeting this younger cohort are mandatory before transitioning to TAVI in patients aged < 65 years.

Trials addressing the use of TAVI in younger lower-risk patients are underway in Europe. The Scandinavian randomized NOTION-2 trial (NCT02825134) is enrolling patients aged < 75 years with severe aortic stenosis and low surgical risk and will randomly assign them to either transfemoral TAVI or SAVR. The primary endpoint at 1 year is the composite of all-cause mortality, myocardial infarction, and stroke. The German DEDICATE trial (NCT03112980) is comparing TAVI versus SAVR in 1,600 patients with severe aortic stenosis and low-to-intermediate surgical risk using a noninferiority design with regard to short- and long-term mortality (1 and 5 years).

The expansion of TAVI indications to younger patients faces several challenges. Durability is a major concern in younger, low-risk patients with prolonged life expectancy, and robust data concerning the long-term durability of TAVI are scarce. In the PARTNER I trial, stable hemodynamic performance was reported at 5 years, as measured by mean gradient (10.6 ± 3.9 mm Hg) and aortic valve area (mean, 1.5 ± 0.3 cm^2); however, few patients lived long enough to study the lifespan of their valve.[13] Similar findings have been corroborated by Deeb et al at 3 years[14] and Gleason et al at 5 years[15] for the CoreValve device (Medtronic). In the CoreValve United States pivotal high-risk trial, severe structural valve deterioration (SVD) was observed in three (0.8%) patients in the TAVI group and six (1.7%) patients in the SAVR group ($P = .32$). Significantly fewer TAVI patients (9.2%) had moderate SVD compared with 26.6% of SAVR patients ($P < .001$).[15] In the NOTION trial,[16] there was significantly more moderate/severe SVD (according to the European Association

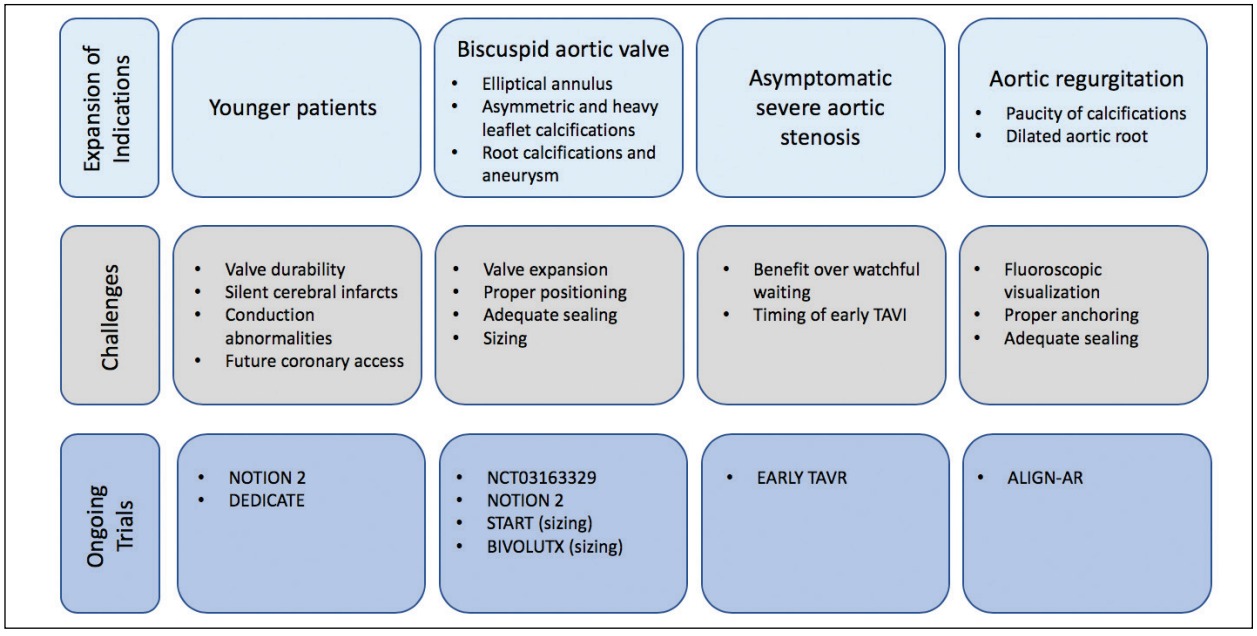

Figure 1. Challenges for TAVI indications expansion.

of Percutaneous Cardiovascular Interventions/European Society of Cardiology/European Association for Cardio-Thoracic Surgery definition[17]) for SAVR than for TAVI at 6 years (24% vs 4.8%; $P < .001$), which was primarily driven by differences in measures of moderate hemodynamic SVD. In the FRANCE-2 registry at 5 years, severe and moderate/severe SVD were reported in 2.5% and 13.3% of patients, respectively, independent of the implanted device type.[18] On the other hand, aortic valve reintervention was more frequent among patients in the TAVI group at 5 years in PARTNER IIA compared with those in the SAVR group (3.2% vs 0.8%; hazard ratio [HR], 3.28; 95% confidence interval [CI], 1.32–8.13); reinterventions after TAVI were due to progressive stenosis in half of the cases.[19] Despite these overall reassuring findings, we await 10- and 15-year data that will allow more reliable comparisons of durability between TAVI and SAVR bioprostheses. Ten-year echocardiographic follow-up data of randomized trials in low-risk cohorts, including younger patients with a longer life expectancy, are required to respond to the controversy on valve durability.

Subclinical stroke is also an important consideration in the younger population. Although stroke rates have dramatically decreased with device iterations, silent cerebral ischemia remains common after TAVI.[20] Even if not studied specifically in patients undergoing TAVI,[21] silent cerebral infarcts have been associated with decline in cognitive function.[22] Criteria for the use of embolic device protection need to be better defined, especially in this category of patient. Younger patients may also develop coronary disease later in life, and many will require subsequent coronary interventions after TAVI. The metal frame of the valve can prevent selective coronary engagement, and device selection should ensure optimal future coronary access. Moreover, future valve designs should take into account subsequent coronary access. TAVI, particularly with self-expandable devices, has also been associated with higher rates of conduction abnormalities.[23] Despite long-standing debate, the impact of new bundle branch block or permanent pacemaker requirement after TAVI on long-term survival, rehospitalization, and left ventricular function are increasingly reported.[24] These considerations are particularly true and pertinent in younger patients with a long life expectancy.

BICUSPID AORTIC VALVE

Bicuspid aortic valve (BAV) is the most common congenital valve abnormality, with a prevalence of 0.5% to 2% in the general population.[25] Calcific degeneration occurs more rapidly in bicuspid valves, leading to aortic valve stenosis in younger patients who usually have a low-intermediate risk profile. The aortic annulus may also be more eccentric and heavily calcified in the setting of BAV,[26] leading to (1) suboptimal device expansion and consequent PVL (ranging from 2.7%–28.4% after TAVI[27,28]) that may be mitigated with new-generation devices; (2) higher frequency of conduction abnormalities (17.9% pacemaker implantation rate in a recent meta-analysis of observational studies[29]); (3) device migration, which may be less frequent using a device with repositioning and/or recapturable features; and (4) increased risk of aortic root injury, owing to heavy root calcification and aneurysm formation.[30]

BAV patients have been excluded from all randomized trials of TAVI except NOTION-2, and data on TAVI in BAV

disease are scarce. A Chinese randomized noninferiority trial (NCT03163329) comparing long-term results of TAVI and SAVR in the setting of BAV is ongoing, and results are expected by the middle of 2024. Meanwhile, device iterations and better preprocedural planning using CT measurement have improved outcomes of TAVI in BAV. Yoon et al compared early and new-generation devices in the setting of BAV, demonstrating that use of new-generation devices improved device success (80.9% vs 92.2%) and reduced significant PVL (8.5% vs 0%), the need for a second valve (6.5% vs 1%), and conversion to SAVR (4% vs 1%).[28] Perlman et al also reported superior hemodynamic results in the setting of BAV using Sapien 3 valves (Edwards Lifesciences) compared with earlier-generation devices.[31]

Device sizing can be difficult, and a variety of approaches have been proposed. A recent retrospective study comparing annular and supra-annular sizing approaches showed that supra-annular sizing resulted in a divergent size selection in 38.7%, with potential improvement in a few cases with annular sizing errors but potential worsening due to improper size selection in a much larger proportion of patients.[32] An approach using balloon sizing reported device downsizing in 92% and procedural success in all patients.[33] The randomized START (NCT02541877) and BIVOLUTX (NCT03495050) trials will study different sizing approaches and algorithms to address this controversy in the future.

PROHIBITIVE TRANSFEMORAL ACCESS

In the PARTNER II trial, transthoracic access was an independent predictor of all-cause mortality at 2 years (HR, 1.55; 95% CI, 1.23–1.96).[3] In addition, quality-of-life measures at 30 days were significantly better after transfemoral TAVI compared with SAVR, suggesting that open surgery may be a better option in some patients who are unsuitable for transfemoral access. Nonetheless, alternative access routes have emerged with results comparable to the transfemoral approach in high-volume centers,[34,35] with an overall trend toward minimalistic, less invasive procedures.[36] More recently, in a propensity-matched study, the FRANCE TAVI group reported that alternative access TAVI was associated with outcomes similar to transfemoral TAVI regardless of center volume, except for a twofold lower rate of major vascular complications and unplanned repairs.[37]

ASYMPTOMATIC SEVERE AORTIC VALVE STENOSIS

More than half of patients with severe aortic stenosis are asymptomatic,[38] with an annual risk of sudden death of approximately 1.5%.[39] Both European and United States guidelines recommend SAVR for asymptomatic severe aortic valve stenosis in certain circumstances.[8,9] A recent South Korean randomized trial compared early SAVR to a watchful waiting strategy in patients with asymptomatic severe aortic valve stenosis.[40] The primary endpoint was a composite of death during or within 30 days after surgery or death from cardiovascular causes during the entire follow-up period. A primary endpoint event occurred in one patient in the early surgery group (1%) and in 11 of 72 patients in the conservative care group (15%) (HR, 0.09; 95% CI, 0.01–0.67; P = .003). Several other studies have suggested the benefit of early SAVR for patients with asymptomatic severe aortic valve stenosis, and a meta-analysis reported a 3.5-fold higher rate of all-cause mortality at 4 years in patients treated conservatively.[41] Similarly, a propensity-matched analysis showed significantly lower all-cause mortality and hospitalizations for heart failure in patients treated with early SAVR.[39] The randomized controlled EARLY TAVR trial (NCT03042104) is currently enrolling patients with asymptomatic severe aortic valve stenosis (confirmed by treadmill testing) to either early TAVI or a conservative approach. The primary outcome is a composite of all-cause death, stroke, and unplanned cardiovascular hospitalization. Results are expected by the end of 2021.

PURE AORTIC VALVE REGURGITATION

SAVR remains the gold standard interventional treatment for severe pure aortic regurgitation (AR). However, although patients with severe AR who are not offered SAVR have an annual mortality of approximately 10%,[42] recent data from the Euro Heart Survey demonstrate symptomatic undertreatment—with only 21.8% of patients with left ventricular ejection fraction (LVEF) between 30% and 50% and 2.7% of patients with LVEF < 30% referred to SAVR.[43] Severe pure AR is usually associated with larger aortic annular dimensions and paucity of annular calcification, which may preclude proper anchoring and sealing of transcatheter devices and increase the risk of PVL and valve migration/embolization. A systematic review and meta-analysis pooled data from different series describing off-label use of TAVI in the setting of severe pure AR.[44] Self-expandable devices were used in approximately 80% of cases. Device success ranged from 74% to 100%, with implantation of a second valve required in 7% of patients and conversion to surgery in 2.5% of patients. The estimated rates of 30-day all-cause mortality and moderate-to-severe postprocedural AR were 7% (95% CI, 3%–13%; I2 = 37%) and 9% (95% CI, 0%–28%; I2 = 90%), respectively. The JenaValve (JenaValve Technology, Inc.) is the only CE Mark–approved device for AR and relies on a clipping mechanism for fixation to the native valve leaflets via a transapical approach. In a series of 30 patients, the procedural success rate was 97%, with no residual moderate-to-severe AR at discharge, and 30-day

and 1-year mortality of 10% and 20%, respectively.[45] The ALIGN-AR trial (NCT02732704) will study the safety and effectiveness/performance of the transfemoral JenaValve pericardial TAVI system in the treatment of patients with severe symptomatic AR. The primary endpoint is all-cause mortality at 30 days, and results are expected by the middle of 2020. Some first-in-human uses of devices using a nitinol anchor ring or a self-expandable nitinol stent, such as the J-Valve system (JC Medical) or the Helio transcatheter aortic dock (Edwards Lifesciences), have also been reported.[46,47]

CONCLUSION

TAVI is an accepted treatment option for elderly patients with severe symptomatic degenerative tricuspid aortic valve stenosis across the entire spectrum of operative risk. Indications for TAVI will certainly expand as devices evolve with features that ensure optimal deployment, anchoring, and sealing and as operator experience grows. Well-designed randomized trials with robust data remain mandatory to cross the remaining boundaries. ■

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Disclosures: Consultant to Boston Scientific Corporation, Medtronic, Edwards Lifesciences, Cephea, Microport, GE, Abbott; received research support grant from Edwards Lifesciences.