The Equivalence of SAVR and TAVR

Potential pitfalls as the use of TAVR is extended to low- and intermediate-risk patients.

BY ANDREW ROY, MD, FESC; DINESH NATARAJAN, MBBS, BMEDSCI; AND BERNARD PRENDERGAST, BMEDSCI, BM BS, MRCP, DM, FRCP, FESC

In just more than a decade since the first patients were enrolled in the PARTNER I trial, transcatheter aortic valve replacement (TAVR) has become the treatment of choice for elderly high-risk patients with severe aortic stenosis (AS) and those who are deemed unsuitable for conventional surgical aortic valve replacement (SAVR). As robust randomized data emerge from the PARTNER II, SURTAVI, and NOTION trials demonstrating the equivalence of TAVR and SAVR (and net superiority of TAVR when undertaken via femoral approach) in intermediate-risk patients, the stage is set for an expansion of TAVR indications to encompass more general low- and intermediate-risk patient cohorts.[1] However, a number of key factors and potential pitfalls should be considered as the indications and technology for the percutaneous treatment of AS rapidly evolves.

DEFINITIONS AND PATIENT SELECTION

The first and most difficult challenge lies in defining what constitutes low or intermediate risk for older populations with severe AS. The most commonly used mortality risk score is the Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM), which is derived from the STS surgical database, and is conveniently subdivided into tertiles of low- (STS score, < 4%; 80% of patients), intermediate- (STS score, 4%–8%; 14% of patients), and high-risk (STS score, > 8%; 6% of patients). For comparison, intermediate-risk patients in PARTNER IIA were defined as STS 4% to 8% (or < 4% with comorbidities not represented in STS-PROM).[1] Patients in the NOTION trial were younger (mean age, 79.1 ± 4.8 years; mean STS-PROM, 3% ± 1.7%).[2,3] Although these published randomized controlled trials (RCTs) enrolled intermediate-risk patients using STS-PROM as a key inclusion criteria, it remains an imperfect and poorly validated measure of risk for most TAVR populations.

Moving toward low-risk patients in ongoing clinical trials, the noninferiority PARTNER III study inclusion data defined low-risk patients as those aged > 19 years with an STS score < 4%, along with a number of anatomic exclusions (eg, congenital bicuspid aortic valves or severe accompanying mitral regurgitation). Similarly, in the noninferiority NOTION II trial, low-risk patients are defined as those aged < 75 years with an STS score < 4% and no severe peripheral vascular disease. However, although quantitative surgical risk scores (STS, EuroSCORE) have been the benchmark for defining RCT patient populations, numerous studies have shown that they lack true efficacy for predicting adverse events and mortality in TAVR-specific populations (principally driven by their failure to account for key patient-specific factors, such as frailty, gender, and aortic root anatomy). Paradoxically, very elderly patients with no comorbidities may be classified as low risk using STS-PROM. Clearly, although the scores used in current clinical trials may provide basic guidance for the extension of TAVR indications, there is a pressing need for the development of evidence-based, TAVR-specific risk scores. Meanwhile, management decisions for individual patients will rely on the judgment of the heart team, incorporating both clinical and specific anatomic criteria.

The heart team will also face challenges in identifying low-risk patients who will derive true benefits from TAVR rather than conventional surgery. Thus, although low-risk patients with less comorbidity will be easier to identify, procedural complications and associated phenomena may have a greater effect in this group. Examples include major vascular complications that may result in long-term morbidity, covered peripheral vascular stents that may develop restenosis, difficulties with coronary access during later revascularization procedures, the need for long-term anticoagulation for atrial fibrillation, and pacemakers or leads that may become infected or require later revision procedures.

EVIDENCE

The NOTION investigators randomized 280 patients with severe symptomatic AS to SAVR or TAVR using the first-generation CoreValve device (Medtronic), with planned follow-up at 5 years. Patients with significant coronary artery disease were excluded. One-year (7.5% vs 4.9%; *P* = .38) and 2-year (9.8% vs 8%; *P* = .54) mortality rates were similar between groups. Of note, almost 80% of patients were of low surgical risk (mean STS scores, 3% ± 1.9%), leading the investigators to conclude that the safety and effectiveness of TAVR and SAVR were comparable in low- and intermediate-risk patients. However, this was a small three-center study with low event rates and insufficiently powered for subgroup analysis.[2]

PARTNER IIA allocated 2,032 patients to aortic valve intervention with SAVR or the second-generation Sapien XT (Edwards Lifesciences) balloon-expandable device. Noninferiority was met at 2-year follow-up, with the primary endpoint (composite mortality or disabling stroke) occurring in 19.3% of TAVR versus 21.1% of SAVR patients (hazard ratio [HR], TAVR 0.89; 95% confidence interval [CI], 0.73–1.09; *P* = .25). Patients were considered intermediate risk (mean STS score, 5.8%), and 76.3% of TAVR recipients were treated via the femoral approach. In the femoral access cohort, TAVR resulted in lower mortality from any cause or disabling stroke compared with SAVR (HR intention-to-treat, 0.79; 95% CI, 0.62–1; *P* = .05; HR as-treated, 0.78; 95% CI, 0.61–0.99; *P* = .04).[1]

PARTNER II demonstrated the divergence of procedural risk between femoral and nonfemoral approaches as experience with the TAVR procedure continues to grow. This, in turn, questions the appropriateness of comparing two clearly different procedures in future trials. The expansion of indications for TAVR must also take account of the fact that limited national and multicenter registry data for a number of vascular approaches (direct aortic, carotid, or subclavian) demonstrated important differences in complication rates, length of hospital stay, and incidence of stroke.

Larger studies are required in the wake of the NOTION and PARTNER II trials to allow more meaningful comparisons between risk groups. Furthermore, direct comparisons between valve types are now required (in particular, for self-expanding and balloon-expandable devices) to address potential discrepancies in the rates of paravalvular leak, pacemaker requirement, and vascular complications. To this end, results from upcoming trials such as SURTAVI, UK TAVI, NOTION 2, and PARTNER III will provide invaluable data to address these issues.

ANATOMIC CONSIDERATIONS

There are a number of more challenging subgroups with aortic valve disease that need to be considered as we move toward treating low-risk patients. Data remain sparse for the optimal treatment of patients excluded from key trials: low-flow, low-gradient AS; AS with significant coronary artery or concomitant valve disease; AS with severe left ventricular outflow tract calcification; or previous valve surgery. Although recent registry data have shown that percutaneous treatment of most forms of bicuspid aortic valve disease and aortic regurgitation is safe and feasible, unique anatomic challenges remain related to differences in annular size, patterns of leaflet calcification, and orifice shape when compared to trileaflet valves.[4] It also remains to be seen whether all device types will produce similar results in these complex patient subgroups.

DURABILITY

Valve durability remains the cornerstone for discussion as TAVR evolves to low-risk patients whose life expectancy has the potential to supersede the lifespan of their TAVR device. Experience with failing surgical bioprosthetic valves points to an inverse relationship between age at implantation and subsequent structural valve degeneration, possibly related to differences in immune function and metabolic activity.[4] Mechanisms of valve failure include progressive calcification, pannus formation, infective endocarditis, and thrombus formation, whereas durability depends on a number of valve-specific design features.[5] Of concern are recent CT imaging studies identifying reduced leaflet motion in relation to possible subclinical leaflet thrombus affecting both TAVR and surgical bioprostheses, although the clinical relevance of these observations remains unclear.

Long-term echocardiographic evaluation of valve hemodynamic performance has confirmed that aortic valve area remains stable in TAVR recipients at 3 to 5 years and is superior to SAVR controls.[6] Similarly, the CoreValve ADVANCE study reported stable mean gradients and effective orifice areas of first-generation self-expanding systems at 3-year follow-up.[7] However, heeding the experience with surgical valve degeneration, more time is needed to understand the mechanisms of potential TAVR failure (and possible preventive strategies) and to ensure there is no precipitous drop in function or durability up to 10 years and beyond.

Reports of poor long-term functionality of some valves (albeit in small numbers) apply only to first-generation devices and were (for the most part) evaluated with transthoracic echocardiography alone. Reported rates of structural TAVR deterioration range from 0%

to 9.7%, depending on the definition and type of valve used. Toggweiler et al reported moderate failure of the first-generation Sapien valve in 3.4% of patients at 5 years, and rates of late prosthesis failure were only 1.4% in the Italian CoreValve Registry (with two patients undergoing successful redo valve procedures).[8] Systematic surveillance of TAVR recipients who underwent TAVR in the original pioneering centers more than 5 years ago, and further focused investigations using optimal imaging modalities (eg, multislice CT) are required to fully elucidate these questions as indications for TAVR expand.

Adjunctive antithrombotic therapy also remains a key component of any discussion concerning valve durability. Currently, there are no clear recommendations regarding the optimal combination and duration of antiplatelet agents, or whether anticoagulation with conventional vitamin K antagonists or novel oral anticoagulants (NOACs) may reduce the long-term incidence of ischemic events, stroke, or structural valve degeneration. Maintaining the balance between valve efficacy and the risks of bleeding remains a key challenge. Oral anticoagulation has been associated with lower rates of structural valve degeneration after TAVR, whereas new atrial fibrillation after TAVR increases all-cause mortality at 1 year, partly as a result of anticoagulant-induced bleeding.[9,10] A number of RCTs focusing on single versus dual antiplatelet therapy and NOAC use compared to warfarin or aspirin are currently underway. The potential role of concomitant left atrial appendage occlusion in TAVR patients who are in atrial fibrillation and at high bleeding risk also requires clarification.

MAJOR VASCULAR COMPLICATIONS

Technologic innovations continue the drive toward lower-profile delivery systems, and rates of major vascular complications have diminished considerably. In two recent high-risk registry studies examining outcomes after CoreValve Evolut R implantation using a 14-F delivery system, major vascular complication rates were 5.3% and 7.5%, respectively.[11,12] Nevertheless, there are large variations in sheath requirements for currently available TAVR systems (14–22 F), and vascular complications remain an important source of immediate- and long-term comorbidity.

PARAVALVULAR LEAK

Clinically meaningful paravalvular leak after TAVR remains an important concern with a prevalence of 23.6% in the CoreValve registry and an associated increase in late mortality (63% vs 51%; $P = .034$).[8] Newer-generation devices that are fully retrievable or incorporate skirts or modified frame designs have significantly reduced rates of paravalvular leak, ranging from 5.3% to 7.7% for the CoreValve Evolut R device to 3.8% for the Sapien 3 device.[13] Although preprocedural planning and accurate annular sizing using multislice CT have improved assessment of the aortic valve complex and reduced valve undersizing, further improvements and reduction in the rates of paravalvular leak will be required for lower-risk cohorts with longer life expectancy.

PACEMAKER IMPLANTATION

The potential negative effect of pacemaker implantation requires major attention as we move into low-risk populations. Implantation rates observed in current trials range between 11.7% (CoreValve Evolut R), 13% (PARTNER II S3), and 17.4% (Italian CoreValve Registry 5-year follow-up) and may be even higher with the Lotus valve (Boston Scientific Corporation), which was recently voluntarily recalled (for unrelated reasons concerning the device locking mechanism). Despite improved understanding of the importance of valve implantation depth, these rates remain uncomfortably high, contributing to an increased cost of the procedure as well as longer-term morbidity associated with device, lead infection, or need for replacement. Perhaps acceptable in elderly high-risk patients, further device improvements will be necessary to reduce pacemaker implantation rates in younger, lower-risk cohorts.

STROKE

Reported rates of stroke after TAVR vary widely (0.4%–5%), partly as a result of operator and center proficiency but also due to underreporting and the lack of standardized definitions for periprocedural cerebrovascular events.[14] For younger or low-risk patients, questions still remain as to the true cognitive effect of MRI-detected lesions, despite their frequent transient nature. The move toward the use of periprocedural cerebral protection devices is in its infancy, and trials using current devices have only confirmed safety and feasibility with no affect on stroke prevention. Ongoing attempts to further minimize stroke rates will be a key challenge in these populations.

CONCLUSION

There are many challenges and pitfalls ahead, but once these are overcome, it seems likely that TAVR will become the gold standard interventional treatment of AS for virtually all patients. The days of conventional SAVR seem numbered, and exponential rates of TAVR growth are already being observed worldwide.

Nevertheless, these developments must be supported by robust evidence, and further studies on newer device iterations will be necessary as indications for TAVR move progressively toward low-risk cohorts. As Vince Lombardi once said, "Perfection is not attainable, but if we chase perfection, we can catch excellence." ■

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Andrew Roy, MD, FESC
St Thomas' Hospital
London, United Kingdom
Disclosures: None.

Dinesh Natarajan, MBBS, BMedSci
St Thomas' Hospital
London, United Kingdom
Disclosures: None.

Bernard Prendergast, BMedSci, BM BS, MRCP, DM, FRCP, FESC
Department of Cardiology
St Thomas' Hospital
London, United Kingdom
bernard.prendergast@gstt.nhs.uk
Disclosures: Speaker fees from Edwards Lifesciences, Boston Scientific Corporation, and Symetis.