Transcatheter Aortic Valve Replacement in Low-Risk Patients Within the Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment Study

Observing the Unobserved

Michael N. Young, MD; Sammy Elmariah, MD, MPH

Transcatheter aortic valve replacement (TAVR) is a novel, disruptive technology that is revolutionizing the management of patients with aortic stenosis (AS). The landmark Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated that in patients with symptomatic severe AS who are not suitable for surgical aortic valve replacement (SAVR), TAVR significantly reduced the rates of death, with a number needed to treat only 5 patients to save 1 life at 5 years. In high-risk patients, the PARTNER trial demonstrated equivalent survival after TAVR using the Edwards Sapien balloon-expandable valve (Edwards Lifesciences, Corp, Irvine, CA) and SAVR although periprocedural risks differed with each procedure.1,2 Using the Medtronic self-expanding transcatheter heart valve (Medtronic, Inc, Minneapolis, MN), the CoreValve US Pivotal trial demonstrated the safety and efficacy of TAVR in extreme risk AS patients and superior survival with TAVR compared to SAVR in high-risk patients.3,4 These historic trials have generated unprecedented excitement and attention within the cardiology community. Cardiologists have eagerly pursued expanding indications, including, in large part, the expansion of this technology to healthier populations. Industry has also invested tremendously to rapidly address device pitfalls with novel transcatheter heart valve design iterations. Several valves are currently in development, and within a decade of the PARTNER trial, we are already commercially implanting third-generation devices.

Soon after the completion of the aforementioned landmark trials, attention shifted to the use of TAVR in intermediate-risk patients. Multiple observational studies—primarily based on European centers—have attempted to elucidate comparative outcomes for TAVR and SAVR in intermediate-risk patients and have shown comparable short and midterm mortality between groups using propensity-score methodology.5–7 Piazza et al7 conducted an observational study derived from a large database (n=3666) of patients undergoing percutaneous and surgical AVR at 3 European medical centers. Propensity-matched pairs with Society of Thoracic Surgeons scores between 3% and 8% comprised the intermediate-risk study population. Thirty-day and 1-year all-cause mortality did not significantly differ for TAVR versus SAVR (7.8% versus 7.1%; hazard ratio [HR], 1.12 [95% confidence interval (CI), 0.58–2.15]; 16.5% versus 16.9%; HR, 0.90 [95% CI, 0.57–1.42], respectively).7 In 2012, Latib et al8 published a case–control study comparing intermediate-risk pairs undergoing transfemoral TAVR or SAVR (logistic EUROSCORE, 23.2±15.1 versus 24.4±13.4; Society of Thoracic Surgeons score, 4.6±2.3 versus 4.6±2.6). Again, mortality rates at 30 days were identical between groups and not significantly different at 1 year.9

At the recent 2016 American College of Cardiology Scientific Sessions, results from the PARTNER 2 (Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients; NCT01314313) trial were presented. In this large multicenter randomized clinical trial (RCT) encompassing 2032 intermediate-risk patients, Leon et al10 compared rates of the primary end point, a composite of all-cause death or disabling stroke, with TAVR using the Sapien XT valve system (Edwards Lifesciences) and SAVR. Event rates were similar between groups at 2 years (19.3% versus 21.1% for TAVR and SAVR; HR, 0.89 [95% CI, 0.73–1.09]; Pnoninferiority<0.001; Psuperiority=0.25), although comparison of randomized patients in whom transfemoral access was feasible demonstrated superiority of TAVR over surgery (HR, 0.79 [95% CI, 0.62–1.00]; P<0.05). The third-generation Edwards Sapien 3 valve, which has demonstrated improved short-term clinical outcomes,9 was evaluated in intermediate-risk patients within a prespecified propensity-score matched analysis using the SAVR arm of the PARTNER 2 trial.10 The Sapien 3 was found to be noninferior (Pnoninferiority<0.001) and superior (pooled weighted proportion difference, −9.2%; 95% CI, −13 to −5.4; P<0.0001) to SAVR using a primary non-hierarchical composite end point of all-cause mortality, all stroke, or moderate or severe aortic regurgitation at 1 year. The study also demonstrated that rates of stroke (4.6%) and moderate or severe aortic regurgitation (1.5%) had improved with the Sapien 3 device relative to the Sapien XT. An additional RCT—the Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need...
Aortic Valve Replacement (SURTAVI; NCT01586910)—has completed enrollment and will hopefully shed further light on the performance of the second-generation self-expanding transcatheter valve in the intermediate-risk population.

To date, robust clinical trial data in support of percutaneous therapies for severe AS in low-risk patients are limited. The Nordic Aortic Valve Intervention Trial (NOTION) was an all-comers trial that randomized 280 patients above the age of 70 years with severe degenerative aortic valve stenosis to TAVR (self-expanding prosthetic only) or SAVR from December 2009 to April 2013. Of enrolled patients, 81.8% were considered low-risk based on mean Society of Thoracic Surgeons, EuroSCORE I, and EuroSCORE II estimates (3.0±1.7, 8.6, and 2.0, respectively). The primary composite outcome consisted of death from any cause, stroke, or myocardial infarction at 1 year. The NOTION investigators found no statistically significant difference in the primary outcome between treatment arms. At 30 days, SAVR patients more frequently experienced major bleeding events, cardiogenic shock, acute kidney injury, and new-onset or worsening atrial fibrillation. There were significantly higher rates of permanent pacemaker implantation post TAVR. Neurological events, including stroke and transient ischemic attacks, did not differ between groups.

In this issue of Circulation: Cardiovascular Interventions, Rosato et al report a subgroup analysis of the Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment (OBSERVANT) registry comparing TAVR versus SAVR in low-risk patients as defined by a EuroSCORE II of <4%. The OBSERVANT study is a large prospective observational cohort that enrolled patients undergoing transcatheter and surgical AVR at 93 Italian centers for an 18-month time period and coordinated by the Italian National Institute of Health. The original aim of OBSERVANT was to characterize the comparative effectiveness between these treatment modalities in a real-world setting. The authors should be congratulated on attempting to address a key question within the realm of transcatheter valve intervention, namely, the comparative efficacy of TAVR and SAVR in the low-risk AS population.

In the OBSERVANT substudy, the investigators identified 355 propensity-matched pairs of low-risk TAVR and SAVR subjects for comparison. Despite using the Sapien XT and early generation CoreValve prostheses, 30-day survival did not differ between groups (97.1% and 97.4% for SAVR and TAVR, respectively) although the distribution of early complications differed with each therapy. TAVR was more frequently complicated by cardiac tamponade, pacemaker implantation, vascular injury, and moderate-to-severe paravalvular aortic regurgitation but less likely to result in acute kidney injury or blood transfusion, whereas SAVR patients were more likely to experience cardiogenic shock, major bleeding, and higher AV gradients postoperatively. The primary outcome of 3-year survival was significantly higher in the SAVR group compared with TAVR (83.4% versus 72.2%; \( P=0.0015 \)). One-, 2-, and 3-year freedom from major adverse cardiovascular and cerebral events favored SAVR as well (89.6%, 84.6%, and 80.9% for SAVR and 84.6%, 75.9%, and 67.3% for TAVR; stratified Log-rank test, \( P<0.001 \)). The authors, therefore, conclude that the expansion of TAVR to low-risk populations is not justified.

The results of the OBSERVANT substudy must be interpreted in the context of the aforementioned NOTION trial and the growing weight of evidence from well-conducted, large RCTs, supporting the safety and efficacy of TAVR. In OBSERVANT, 1-year mortality rates were 7.8% and 11.4% (stratified Log-rank rest, \( P<0.001 \)) for SAVR and TAVR, respectively. By contrast, NOTION demonstrated 1-year mortality rates of 7.5% and 4.9% for SAVR and TAVR (\( P=0.38 \)). Although the rates of mortality after SAVR and complications after TAVR are comparable in both studies, rates of mortality after TAVR were twice as high within OBSERVANT when compared with NOTION. The reasons for this discrepancy are elusive and highlight the challenges of interpreting these results derived from disparate study designs. The question then arises, why did these 2 studies produce contradictory results? Foremost, NOTION was an RCT in which low-risk patients consented to inclusion and randomization to either TAVR or SAVR. The study excluded a large number of patients, possessed several unblinded outcomes, and was underpowered. In comparison, OBSERVANT was a nonrandomized registry with relaxed exclusion criteria that captured patients receiving TAVR despite being low-risk. It would be informative to elucidate the patient-level factors in OBSERVANT that were used to justify the performance of TAVR in low-risk patients. The fact that 15.6% of patients in OBSERVANT were being treated with TAVR despite being low-surgical risk candidates suggests a tremendous amount of indication creep, especially at this early time period (2010–2012) in the evolution of transcatheter valve interventions. Although EuroSCORE II measures were low in these patients, there are likely unknown or unobserved factors that may have influenced provider judgment, thus swaying physicians to choose TAVR in these patients. Presumably, a majority of the salient clinical variables were controlled for through the use of propensity-score matching, but inherent bias remains a possibility. Without further granularity of patient detail, it remains conjecture whether the driving rationale for the practice of performing TAVR in this low-risk cohort was because of indication drift, patient discretion, perceived high surgical risk, or other. Ultimately, these points simply emphasize the value of the randomized trial design, in that unobserved variables are balanced between comparator groups.

Furthermore, NOTION used the self-expanding CoreValve transcatheter heart valve, whereas OBSERVANT included both the self-expanding CoreValve and the balloon-expandable SAPIEN XT valves. As a consequence, none of the enrolled patients in NOTION underwent transapical TAVR, which is known to be associated with increased mortality. It would, therefore, be useful to know rates of transapical TAVR within OBSERVANT and associated mortality rates, as well as the rates of cardiac versus noncardiac death.

Beyond the confines of study design, the more specific limitations of the OBSERVANT study should also not be overlooked as the authors have clearly delineated in their discussion. First, EuroSCORE II represents one of the several instruments available to help stratify operative risk. A sensitivity analysis using low Society of Thoracic Surgeons score as a cutoff may have been helpful to ensure external consistency. Also, the use of nonstandardized definitions for postprocedure complications outside of the Valve Academic...
Research Consortium-2 (VARC) is certainly an issue that must be carefully considered. Although the authors allude to the theoretical overestimation of risk when applying VARC classifications to SAVR, the paradox then is whether the outcomes—as defined in OBSERVANT—inadvertently biased the primary or composite secondary end points toward the surgical comparator group. It is also unclear how the lack of discharge data for postprocedure antithrombotic therapy may have confounded the long-term outcomes.

At the end of the day, the central question remains whether TAVR should be offered as an option for low-risk patients who do not have a contraindication to surgery. As Rosato et al. intimate in their conclusions, there are currently insufficient data to justify an expansion of TAVR to low-risk subgroups. Although their findings would suggest that such patients fare worse with TAVR than SAVR in terms of both mid- and long-term outcomes (ie, survival and major adverse cardiovascular and cerebral events), their mortality rates after TAVR seem disproportionately high compared with other recent studies, especially in light of the low-risk study population. In addition, TAVR technology has evolved rapidly with incremental improvements in clinical outcomes and reductions in TAVR-related complications (paravalvular aortic regurgitation, conduction disturbance, etc), and several additional devices are under development that promise to further mitigate the curative complications (paravalvular aortic regurgitation, conduction disturbance, etc), and several additional devices are under development that promise to further mitigate the current limitations of TAVR. Results of the PARTNER 2 trial, using both Sapien XT and Sapien 3 valves, have been promising in intermediate-risk in patients and have supported the recent United States Food and Drug Administration investigational device exemptions for clinical trials of TAVR in low-risk AS patients using the Edwards Sapien 3 (NCT02675114) and Medtronic CoreValve Evolut R (NCT02701283) transcatheter valve platforms. Until definitive data emerge from these trials, clarifying the comparative effectiveness of transcatheter and surgical aortic valve replacement in low-risk patients, SAVR remains the standard of care for low-risk patients with symptomatic severe AS.

In summary, the study by Rosato et al adds to the burgeoning observational literature, informing us of the current practice patterns and outcomes for lower risk patients undergoing TAVR. Despite the continued evolution of percutaneous valves, delivery equipment, and techniques, conventional surgery remains the standard of care for low-surgical risk subgroups. Although TAVR is an exciting technology that has already saved countless lives, we must not lose sight of the tremendous merit and favorable clinical outcomes provided by SAVR. We eagerly await results of RCTs, assessing the safety and efficacy of TAVR in low-risk patients. Until then, careful and meticulous expansion of TAVR that is observant of the clinical guidelines and device indications is warranted, especially in low-risk patients.

Sources of Funding

We are appreciative of support from the American Heart Association (14FTF20440012 to S.E.) and the MGH Heart Center Hassenfeld Cardiovascular Research Scholar program (to S.E.).

Disclosures

None.

References


Key Words: Editorials • aortic valve stenosis • heart valve prosthesis • transcatheter aortic valve replacement
Transcatheter Aortic Valve Replacement in Low-Risk Patients Within the Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment

Study: Observing the Unobserved

Michael N. Young and Sammy Elmariah

doi: 10.1161/CIRCINTERVENTIONS.116.003830

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/9/5/e003830