Keynote Lecture Series

What did the transcatheter aortic valve replacement-surgical aortic valve replacement (TAVR-SAVR) trials tell us?

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Two families of randomized trials comparing transcatheter aortic valve replacement (TAVR) to surgery for both the Balloon Expandable Valve and the Supra Annular Self-Expanding Valve have been completed to include all surgical risk levels. The result of these trials has led to the approval of TAVR for symptomatic severe aortic stenosis without using risk level as the sole criterion. We have seen an explosion of TAVR in the US to over 98,000 commercial cases in 2022. We have also seen a rapid increase in the use of TAVR in patients less than 65 years of age. With these increases, it is important to ask if they are being driven largely by the data or just the desire for TAVR by both patients and their physicians. Heart team input is a class I indication when deciding between TAVR and surgery. For surgical members of the heart team to appropriately counsel patients, a full understanding of what the TAVR surgery trials tell us as well as what they do not is essential. In this article we will explore those questions.

Keywords: Surgical aortic valve replacement (SAVR); transcatheter aortic valve replacement (TAVR); lifetime management of aortic stenosis (lifetime management of AS)

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A number of trials continue to shape the field of cardiac surgery but none more so than the randomized trials comparing surgical aortic valve replacement (SAVR) to transcatheter aortic valve replacement (TAVR). These large, multicenter randomized trials have been widely discussed and resulted in a substantial impact on the treatment of aortic stenosis (AS). These trials are designed as non-inferiority trials. At all treatment levels, they show non-inferior or superior primary endpoints for TAVR as a treatment option. The outcomes of these trials led to the current 2021 American Heart Association/American College of Cardiology (AHA/ACC) guideline recommendations for the treatment of AS (1). For patients <65 years of age or likely to live 20 years or longer, SAVR is recommended. For patients >80 years of age or likely to live less than 10 years and are anatomically suitable for transfemoral (TF) TAVR, TAVR is recommended. For those 65–80 without an anatomical contraindication for TAVR then a shared decision with the patient is recommended. Risk as a solitary criterion is no longer mentioned. Many in the cardiology and even the surgical field seem to consider TAVR appropriate for almost all patients. In 2022, the STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) registry recorded 98,504 commercial TAVR cases in the US. A recent review of the Vizient national database which included 279,066 patients revealed an increase from 2015 to 2021 in TAVR cases in patients under 65 years of age, such that in 2022 47% of isolated AVR were TAVR (2). In our valve clinic, we routinely see patients in their early 60s and even their 50s referred in after being told they will receive a TAVR. Counselling these patients on the appropriate treatment decision requires the surgeon to understand that although these are excellent randomized trials, they apply only to populations like the ones tested. In this manuscript, we explore who was and was not tested in the randomized trials

and the impact this should have on our decision making for the lifetime management of AS.

The two families of randomized trials were the Edwards Balloon Expandable Valve (BEV) and the Medtronic Self-Expanding Valve (SEV) trials. Each tested extreme, high, intermediate, and low-risk patient groups (3-10). Extreme risk contained patients unsuitable for surgery and will not form part of this discussion. Both high-risk trials had a mean age of 84 years and a primary endpoint of all-cause mortality. The BEV trial (5) was non-inferior for TAVR and the SEV trial (6) was superior for TAVR at the 1-year endpoint, and TAVR was approved for high-risk patients. At 5 years, the mortality in the BEV trial for SAVR and TAVR were 62.4% and 67.8% (P=0.76) respectively (11). The SEV high-risk trial showed mortality at 5 years for SAVR and TAVR as 39.5% and 39.7% (P=0.80) respectively (12). Both were non-inferior at 5 years. Because the BEV high-risk trial had a significantly higher stroke rate for TAVR, the primary endpoint for both intermediate-risk trials was changed to all-cause mortality or disabling stroke. Both BEV and SEV trials had a mean age of 81 years and were found to be non-inferior for TAVR at their initial endpoints (7,8). TAVR was subsequently approved for intermediate-risk patients. The 5-year endpoint of all-cause mortality or disabling stroke for the BEV trial for SAVR and TAVR was 43.4% and 47.9% (P=0.21) respectively with the lines crossing at 3 years (13). The SEV SURTAVI intermediate-risk trial had a 5-year all-cause mortality or disabling stroke rate for SAVR and TAVR of 30.8% and 31.2% (P=0.85) respectively (14). Both intermediate-risk trials will have a 10-year follow-up. The low-risk trials had a mean age of about 74 years but different primary end points. In the low-risk population, we would expect less events. To achieve statistical significance, one must add patients, time or events. The BEV low-risk trial added events with a composite endpoint of all-cause mortality, all stroke or rehospitalization, and was superior for TAVR (9). The SEV trial stayed with a primary endpoint of all-cause mortality or disabling stroke and used a Bayesian 2-year endpoint, and was non-inferior for TAVR (10). Outcomes at 2 years for the BEV trial (15) and at 3 years for the SEV trial (16) have been reported. This led to all risk levels being approved but does this translate into all patients?

Both low-risk trials showed early advantages in mortality, stroke, length of stay and quality of life. Mortality was 0.4% at 30 days in both trials and 1.1% and 1.2% at 1 year for the BEV and SEV trials respectively. The BEV trial has shown a decrease in the TAVR advantage in both the primary endpoint and mortality at 2 years (15). The SEV trial shows an increasing advantage of TAVR over 3 years (16). The 5-year results for the low-risk BEV trial and the 4-year results for the SEV low-risk trial will both be presented in the fourth quarter of 2023. Although encouraging for TAVR in this population, these are very early results and both trials will be followed for 10 years.

Randomized trials provide us with some of our best data. Randomized trials however only apply to populations similar to the ones tested. Now let us consider who was not tested in these randomized trials and where knowledge gaps exist in recommending TAVR. By protocol, bicuspid aortic valves, significant coronary artery disease (CAD), unfavorable anatomy for TAVR, associated procedures [other than coronary artery bypass (CAB)] and those appropriate for mechanical valves were all excluded. These protocol restrictions remove many of the patients referred to our valve clinics for treatment of AS.

Bicuspid aortic valves were excluded from the randomized trials but have been tested in low-risk patients with acceptable results (16). Bicuspid anatomies that yield both acceptable and poor results have been defined (17). Heavy calcification of the raphe and the opposite leaflet has been associated with less optimal outcomes. It is clear that we can treat some bicuspid valves with TAVR but surgeons should learn the anatomies that are acceptable and be able to delineate these with both patients and referring physicians who may be unaware of the differences. Ideally, a randomized trial would help us provide better data in this area (18).

By protocol, the BEV trial excluded patients with a Syntax >32 and the SEV trial a Syntax >22. The SEV trial had a separate arm for patients requiring revascularization; defined as patients in whom the surgeon would revascularize if the patient randomized to SAVR. The mean Syntax in the revascularization arm was 7. Neither trial treated patient with significant CAD. Despite this, we often see patients with significant 3 vessel CAD, low-risk and AS referred for TAVR "since the low-risk trials were positive". Further trials of TAVR with significant CAD are ongoing but this currently remains a knowledge gap where outcomes are known for surgery but not TAVR.

Unfavorable anatomy for TAVR includes an aortic annulus that is either too big or too small for the available TAVR valves which is easy to understand. All annular sizes are amenable to surgery. Harder to fully quantitate and understand is excessive left ventricular outflow tract (LVOT) calcium, which was excluded in both trials for presumed

poor TAVR outcomes and potential paravalvular leak. These bars of LVOT calcium are easily handled with SAVR. In both trials, the patients were initially seen by the local expert heart team where they had to verify inclusion criteria with no exclusion criteria. Additionally, the surgeons and cardiologists on these teams had to verify that the anatomy seen was acceptable for both TAVR with the trial valve and SAVR. One might expect from this local expert review that when presented to the national screening committees of these trials, the vast majority would be accepted for treatment. However, in the BEV trial 34% and in the SEV trial 14.8% of patients were rejected at this level. One might argue as to why these patients were not accepted, but these clearly do not reflect all-comer real-world experiences that we see in our clinics.

Associated procedures such as mitral valve repair, tricuspid valve repair, ascending aortic replacement or MAZE procedure were not allowed (although some were done which might introduce unexpected bias). Not infrequently we have seen patients with severe AS with associated significant primary mitral regurgitation (MR) referred with a proposed plan of TAVR and see if the MR improves, with a mitral clip procedure to be considered if the MR does not improve. Although acceptable in a high-risk patient, surgical repair of primary MR is currently still the gold standard in patients with lower surgical risks, and mitral valve clipping is approved only in high-risk patients.

Aside from considerations of the population that was randomized, one may also question what might happen if the TAVR fails in younger patients. A TAVR in TAVR may be possible in some but is anatomically difficult or dangerous in many. Those unsuitable for TAVR in TAVR are sometimes counseled that they can then have SAVR similar to if it had been the first procedure done. Unfortunately, the current data suggests that the Hazard Risk for TAVR explant and SAVR is 2 to 3 times that of primary SAVR (19). When planning lifetime management of a younger patient who could potentially require more than one lifetime procedure, this remains an important discussion point.

Surgery has not remained static since the completion of the low-risk trials. In the Partner 3 BEV low-risk trial, for the first time, surgery had superior hemodynamics to TAVR. When asked why this occurred, the presenter noted that surgeons had learned to place larger surgical valves, despite both trials having an annular enlargement rate of <5%. With the advent of the Y annular enlargement described by Yang of the University of Michigan, surgeons can now routinely achieve three valve sizes larger than originally measured (20). In our practice, we obtain a TAVR computed tomography angiography (CTA) on all patients with planned SAVR. We then calculate an area derived annular diameter and chose a valve with an internal diameter that fits this. This has led to annular enlargement in our practice now being used in over 40% of our cases. This technique was not available during the low-risk trials and may have resulted in a more favorable surgical outcome had it been available.

Planned ancillary procedures outside of CAB as well as severe MR were protocol exclusions in the randomized trials. There were also limits on ascending aorta size that excluded patients needed ascending repair. Atrial fibrillation however was not an exclusion. The Cox Maze operation was shown early on to be safe when added to CAB or SAVR (21). More recent data suggests that addition of a Maze procedure to those with paroxysmal atrial fibrillation undergoing SAVR both increases the rate of normal sinus rhythm and improves survival (22,23). This should be considered along with the data that SAVR had a significantly higher rate of post procedure atrial fibrillation than TAVR in both low-risk trials.

The randomized TAVR trials have fundamentally changed our approach to severe AS. We believe that in appropriate patients, this represents a marked advance for our patients. We also understand that patients will always want the less invasive procedure as long as the outcomes are reasonably close. SAVR however remains the best choice based on the available data in some of these patients and surgeons need to be able to explain, based on data, why this is the best choice. We encourage surgeons to remain active participants in the TAVR field and help guide the expansion of TAVR based on data and not just a desire for the procedure (24).

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Footnote

Conflicts of Interest: M.J.R. served as national PI for the Medtronic SURTAVI and Evolut low risk trials. The authors have no other conflicts of interest to declare.

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