Who Is a TAVR Candidate in 2016?

The assessment of risk and patient selection.

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Since the first transcatheter aortic valve replacement (TAVR) procedure was performed by Alain Cribier and colleagues in 2002,¹ it is estimated that more than 200,000 people have been treated with transcatheter valve prostheses. The exponential uptake of this exciting treatment modality has been driven by many factors, including excellent trial and clinical results, patient preference, and physician comfort.

Aortic stenosis is predominantly a disease of age and is associated with senile calcific degeneration, particularly in developed nations. It is estimated that more than 4% of people older than 75 years have moderate or severe aortic stenosis, with increasing prevalence with advancing age.² This association with age results in a cohort with a significant burden of comorbidities and higher procedural risk, which prior to the introduction of TAVR, led to approximately 30% of patients not undergoing definitive operative management.³

Due to the increasing age of the population in most Western countries, the number of elderly patients with symptomatic severe aortic stenosis continues to increase. TAVR offers a less invasive means of definitive treatment with a robust evidence base showing it is superior to medical therapy⁴⁵ and at least equivalent, if not superior, to surgical valve replacement⁶⁷ in appropriately selected patients.

Increasing clinical use of TAVR has, however, been associated with a shift in treated patients toward a lower-risk cohort. It remains important that the technology is used to treat those patients who will receive the greatest clinical benefit, and it is imperative that TAVR be performed in accordance with contemporarytrial evidence or within a research framework that will advance the current evidence base.

COHORTS TREATED IN CLINICAL TRIALS

Clinical practice must be built upon a strong evidence base and hence, treated patients should mirror those proven to benefit within clinical trials. At the same time, detailed post hoc analysis of published trials aiming to identify patient subsets that do not benefit from treatment should also be utilized to further refine the clinical population.

PARTNER I Trials

The PARTNER I trials were the first randomized trials to assess the efficacy and safety of TAVR with the Sapien device (Edwards Lifesciences) in high-risk⁶ and extreme-surgical-risk⁴ patients with native valve stenosis. Patients were required to have a Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score of ≥ 10% or have comorbidities leading two independent surgeons to estimate a postoperative risk of death at 15% to 30%. The mean STS PROM score in the PARTNER I high-risk cohort undergoing TAVR was 11.8% ± 3.3%, whereas the STS PROM score in the PARTNER I extreme-risk cohort was 11.2% ± 5.8%.

Only patients with aortic stenosis affecting a tricuspid native valve were included, with exclusion criteria including bicuspid valve morphology, significant concomitant valve dysfunction, left ventricular ejection fraction < 20%, recent stroke, and severe renal impairment, resulting in a highly selected group with only 34% of site-screened patients accepted for randomization by the study’s patient review committee.

The trial results were impressive with observed rates of mortality lower than predicted by the STS PROM at 30 days: 3.4% in the high-risk cohort and 5% in the extreme-risk cohort. In this highly selected cohort, the rates of major complications such as stroke, pacing, and vascular injury were also acceptable. At 5 years however, only 32.2%⁸ of the high-risk TAVR cohort and 28.2%⁹ of the extreme-risk TAVR cohort remained alive. With an estimated procedural cost of $70,000,¹⁰ there is room to further improve patient selection.
CoreValve US IDE Trials

The CoreValve US Investigational Device Exemption (IDE) trials are contemporary studies assessing the efficacy of TAVR using the CoreValve prosthesis (Medtronic, Inc.) in high-risk and extreme-risk patients. The trial enrolled 394 people into a high-risk TAVR cohort (mean STS PROM, 7.3% ± 3%) and 489 people into the extreme-risk cohort (mean STS PROM, 10.3% ± 5.5%). The lower STS PROM score in the CoreValve US IDE trials may, in part, be due to the inclusion of the frailty assessment in combination with STS PROM in patient selection. Similar to the PARTNER trial, included patients were highly selected with 20% of patients presented to the patient review committee not reaching randomization; only patients with severe native trileaflet aortic stenosis were included. Patients with severe concomitant valve dysfunction, recent stroke, left ventricular ejection fraction < 20%, or severe renal dysfunction were excluded.

At 30 days, the observed mortality in the high-risk cohort was 3.3% and 8.4% in the extreme-risk cohort. At 12 months, the observed rates were 14.2% and 24.3%, respectively, with superiority over surgical valve replacement demonstrated in the highly selected, high-risk cohort.

The CoreValve US IDE and PARTNER trial 1-year results differed in a number of important areas, such as stroke rates and all-cause mortality. Although the CoreValve US IDE trial achieved superiority of the TAVR arm compared to surgical AVR, while the PARTNER IA trial achieved noninferiority, direct comparison between these trials is difficult and potentially misleading. As previously mentioned, the mean STS PROM scores were significantly lower in the CoreValve US IDE trials, particularly in the high-risk cohort. The CoreValve trial commenced enrolling patients nearly 4 years after the PARTNER trials started and a year after the PARTNER trial results were released. It is possible that lessons learned from the PARTNER trials led to improvements in patient selection, awareness of the importance of minimizing paravalvular leak, and attention to access site management, all contributing to the outstanding results seen in the CoreValve US IDE trial.

Nonrandomized Next-Generation Device Clinical Trials

A number of newer-generation TAVR devices are entering trial and clinical use. With design features purposed to reduce procedural complications and improve outcomes, most have been studied in single-arm trials with comparative US IDE trials currently enrolling. These trials have included highly selected cohorts with inclusion and exclusion criteria similar to the PARTNER and CoreValve US IDE trials, although with a trend to lower reported STS PROM scores (Figure 1).

The Lotus Valve system (Boston Scientific Corporation) was studied in the single-arm REPRISE suite of trials.

The REPRISE II trial enrolled 120 patients with a mean STS PROM score of 7.1%. The Direct Flow prosthesis (Direct Flow Medical) was studied in the DISCOVER trial that enrolled 100 patients with a mean STS PROM score of 9.7%. The CoreValve Evolut R device (Medtronic, Inc.), an iteration of the CoreValve was studied in a first-in-human CE Mark trial of 100 patients, with a mean STS PROM score of 7%.

These trials have seen a gradual trend to include patients who are deemed high-risk, despite a lower average STS PROM score. This is due to assessment of a number of additional variables, such as STS Plus risk factors, frailty indices (ie, hand grip, gait speed, Katz Index), and the Charlson Comorbidity Index when selecting appropriate patients. This trend reflects an acknowledgement that these additional factors have been shown in analyses of previous study and registry cohorts to offer additional predictive benefit over surgical risk scores alone.

COHORTS TREATED IN CLINICAL REGISTRIES

While the majority of clinical trials published to date have focused on TAVR for treatment of native trileaflet aortic stenosis in elderly high- and extreme-surgical-risk patients, the large number of clinical registries have provided evidence for treatment of a number of additional cohorts, often without the strict inclusion and exclusion criteria of clinical trials. Registries offer a view of real-world practice.

Risk Cohorts

The creep of STS PROM scores toward a lower-risk cohort, seen in contemporary clinical trials, has been
Aortic Valve

Bioprosthetic Valve Dysfunction

Bioprosthetic Valve Dysfunction

Aortic Regurgitation

The evidence for efficacy of TAVI in the treatment of native aortic valve regurgitation is largely limited to registry data. Coexisting aortoventricular interface dilatation and lack of aortic valve calcification may lead to difficulty in achieving prosthesis stability and is likely to have contributed to the relatively high frequency of ectopic valve deployment and the need for valve-in-valve therapy, as seen in the few published cohorts. The JenaValve (JenaValve Technology), which uses a clipping mechanism to grasp the valve leaflets and overcome the difficulty of anchoring a transcatheter prosthesis in a noncalcified annulus, has demonstrated some efficacy in native valve regurgitation and has obtained CE Mark approval for the treatment of aortic stenosis and regurgitation. While the clipping mechanism has distinct advantages in noncalcified valves, the ability to clip heavily calcified leaflets, particularly with protuberant nodules, may be more difficult. The clip, similar to a paperclip, can function even if the clip components are held apart by a significant amount of tissue. While this could conceivably increase the risk of paravalvular regurgitation, the ongoing JUPITER postmarket registry will provide a larger sample size to further assess safety and efficacy in patients with aortic regurgitation and aortic stenosis.

Bioprosthetic Valve Dysfunction

Although native valve regurgitation is associated with intrinsic difficulties for transcatheter treatment, the presence of rigid sewing rings and frames on bioprostheses offers a platform for transcatheter prosthesis anchoring. The Valve-in-Valve International Data registry was established to assess the safety and efficacy of TAVR prostheses for the treatment of bioprosthetic valve dysfunction.

Reported surgical bioprosthesis failure rates vary from 10% to 30% at 10 years and 30% to 60% at 15 years, with durability affected by variables such as age at implantation, type of prosthesis, and comorbidities. Valve failure can be due to stenosis from calcific degeneration, pannus formation, or subclinical leaflet thrombosis, or due to regurgitation from leaflet wear or infection, or a combination of stenosis and regurgitation. Traditionally, valve failure was treated by repeat surgical valve replacement though increasing age at the time of valve failure; additional comorbidities and the complexities of repeat sternotomy may result in prohibitively high morbidity and mortality. In this population, TAVR has provided an alternate treatment modality for patients with either stenosis or regurgitation.

In 459 patients treated at 55 centers, the 1-year survival after valve-in-valve procedures was 83.2%, with baseline predictors of mortality including stenosis as the mode of bioprosthesis failure and small initial bioprosthesis size. These data add weight to the implantation of surgical bioprostheses rather than mechanical prostheses in a slightly younger cohort than that traditionally selected, with the understanding that should the bioprosthesis fail, TAVR is a safe and effective second procedure.

TRIAL EVIDENCE FOR TREATMENT OF LOWER-RISK PATIENTS

The PARTNER II Sapien 3 intermediate-risk cohort enrolled 1,076 patients with a mean STS PROM score of 5.3%. This was an elderly cohort with a mean age of 81.9 years. At 30 days, there was a low 1.1% rate of mortality...
and a 2.6% incidence of stroke. Longer-term follow-up has not yet been reported, and comparative safety and efficacy outcomes with surgical AVR (SAVR) remain to be studied. The PARTNER IIa trial will randomize a similar intermediate-risk cohort (STS PROM ≥ 4%) to receive treatment by TAVR with the Sapien XT prosthesis (Edwards Lifesciences) or SAVR. The results of this trial will provide randomized data regarding the safety and efficacy of TAVR in a lower-risk cohort.

The SurtAVI clinical trial similarly aims to determine the safety and efficacy of the CoreValve device compared to SAVR in patients with an estimated 30-day perioperative mortality of 3% to 15%. Recruitment was initially slow, which was at least partially attributed to patient and physician preference for treatment by TAVR in the non-trial clinical setting, rather than potential randomization to surgery if they were to enter the study.

The NOTION trial randomized an all-comer population of 280 patients aged > 70 years to treatment by TAVR using the CoreValve device versus SAVR. The mean STS PROM score was 2.9% in the TAVR arm and 3.1% in the SAVR arm. The primary outcome measure of all-cause death, stroke, or myocardial infarction at 12 months was not significantly lower in the TAVR arm (13.1% vs 16.3%; \( P = .43 \)). There were, however, significantly lower rates of major bleeding, stage II/III kidney injury, and post-procedural atrial fibrillation, but higher rates of new pacemaker implantation. Echocardiographic data demonstrated a statistically, although potentially not clinically, higher effective orifice area and lower mean transprosthetic gradient after TAVR.

What remains elusive from trial evidence is long-term follow-up and demonstration of equivalent treatment durability. While the PARTNER I trial has reported 5-year results, the inclusion of elderly high-risk patients has resulted in nearly 70% mortality and hence an insufficient cohort to prove treatment longevity. Evidence is still a number of years off and will come from ongoing follow-up of large registries, which included treatment of younger and lower-risk patients and even more distant results from lower-risk trials such as NOTION, SurtAVI, and PARTNER II.

**LIMITATIONS OF SURGICAL RISK SCORES**

With the frequent categorization of patients into low-, intermediate-, high-, and extreme-procedural-risk groups, it would seem an easy feat to identify those best served by each treatment modality; however, surgical risk scores have a number of limitations. The STS and EuroSCORE were designed to predict perioperative mortality and were formulated from, and validated in, surgical cohorts. There is no weight given within these scoring systems to frailty or many comorbid conditions, which are of increasing frequency in an aging cohort.

The use of surgical risk scores to select patients also tends to rely heavily on the potential for peri-procedural mortality to select patients. However, for many elderly patients, mortality may not be as important a complication as morbidity and the potential impact on quality of life.

**FRAILTY**

Acknowledging the limitations of surgical risk scores, frailty has emerged as a strong predictor of procedural risk and is increasingly incorporated into patient selection. Frailty is the risk of significant decline a person is exposed to due to declining health and physical reserve, often seen in and associated with aging. Because frailty is a syndrome, diagnostic criteria are varied and not universally agreed upon. A number of metrics have, however, been attempted to quantify frailty; these metrics include 5-m gait speed, hand-grip strength, physical activity questionnaires, exhaustion questionnaires, self-reported weight loss, serum albumin levels, and activities of daily living dependency.

Although frailty may be an indication for percutaneous, rather than surgical, valve replacement, it is also a predictor of morbidity and mortality and hence, a discriminator for those who are at too high risk even for TAVR. This appears to hold true regardless of the means of frailty assessment. The ABC study demonstrated that slow 5-m gait speed led to a two- to threefold increase in the rate of mortality or major morbidity after surgery regardless of baseline STS PROM score. Similarly, a substudy from the PARTNER cohort demonstrated that elevated frailty assessed by albumin, gait speed, grip strength, and activities of daily living dependency was independently predictive of mortality.

Even when frailty is not formally assessed by using any of these suggested metrics, a subjective ‘end-of-bed’ assessment of frailty by the treating clinician has proven to be an independent predictor of late mortality after TAVR.

The frailty assessment, together with the burden of comorbidities, must be used to identify patients who are at too high risk for surgical valve replacement, but also to identify patients who are also at too high risk for TAVR. Essentially, patients who are dying from aortic stenosis and who would benefit from treatment must be differentiated from those who are dying from other comorbidities with aortic stenosis.

**HEART TEAM**

Given the complexity involved in assessing all domains that contribute to a patient’s suitability for TAVR, the involvement of a heart team is essential. The use of a heart team is recommended in both European and American guidelines and, in many countries, it is linked to the funding
of the procedure. However, what constitutes a heart team is varied, with many heart teams made up of only the treating physician and surgeon. We would argue that the more diverse the team, the more successful it will be in selecting appropriate patients and, potentially more importantly, excluding patients who are best served by medical therapy, surgery, treatment of other comorbidities, or even palliative management.

WHO IS A TAVR CANDIDATE IN 2016?

In 2016, TAVR has proven efficacy in elderly high- and extreme-risk patients with symptomatic severe native trileaflet aortic stenosis. The treatment of patients who have lower STS PROM scores, but who are deemed to be at high risk by a heart team due to comorbidities and/or frailty, is also appropriate and supported by registry and increasing trial evidence. The treatment of patients with bicuspid aortic stenosis, predominant aortic regurgitation, or bioprosthesis dysfunction when they have appropriate aortoventricular interface anatomy, and are deemed to be at high risk for surgical intervention by a heart team is also appropriate, although supported by a lower level of registry evidence. The treatment of patients with these conditions should be performed by experienced operators and centers where specific preprocedural assessments, devices, and procedural techniques are required. For example, device sizing in bicuspid anatomy requires assessment of metrics, such as intercommissural distance, while specific TAVR devices with annular sealing mechanisms may be more appropriate in pure aortic regurgitation.

Treatment of “intermediate-risk” elderly patients is likely safe and effective, although the long-term durability of results cannot be ensured at present. This is of greater concern in a population with a longer life expectancy. In 2016, we would recommend that these patients, if treated by TAVR, are treated in a clinical trial or properly reported registry framework in order to build the required evidence base to prove safety, efficacy, and longevity in these cohorts.

Perhaps more importantly, in 2016, we must do more to identify who is not a candidate for TAVR. Within the PARTNER I trial, at 5 years, more than 70% of the cohort was deceased. While TAVR may have allowed a number of these patients to enjoy improved quality of life, a significant number of people in contemporary trials do not report quantitative or qualitative improvement in function or quality of life. Until a well-validated, TAVR-specific mortality and morbidity score is created, it remains essential that an experienced heart team is available to make a comprehensive patient assessment of benefit versus futility.

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