EXPERT REVIEW

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Transcatheter Aortic Valve Replacement: Recent Evidence from Pivotal Trials

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AORTIC STENOSIS (AS) is the most common valve disease of the elderly.[1,2] Once symptoms develop, it is associated with a mortality rate as high as 50% within 5 years.[3,4] The morbidity and mortality advantages from surgical aortic valve replacement (SAVR) for severe AS have been well established for decades.[5,6] When considering the indications for SAVR, risk assessment has been classified as either low, intermediate, high, or prohibitive based on multiple measures such as the Society of Thoracic Surgeons (STS) perioperative risk of mortality (PROM) score, frailty, major organ system dysfunction, and procedure-specific considerations.[7-11] Since its inception in 2002, transcatheter aortic valve replacement (TAVR) has emerged as a reasonable alternative to SAVR in higher-risk patients with severe AS.[12,13]

In general, there are 2 types of transcatheter valves currently available: balloon-expandable (BE) and self-expanding (SE).[2,8,9] In the setting of severe AS, superior outcomes in patients with prohibitive risk were demonstrated with BE TAVR (first-generation Sapien valve; Edwards Lifesciences, Irvine, CA) compared with medical therapy, and equivalent outcomes in patients at high risk for surgery were shown at 1 and 2 years with the same BE TAVR compared with SAVR.[14-16] Based on these landmark randomized clinical trials (RCTs), initial expert consensus recommended BE TAVR for the following: (1) patients with prohibitive risk and (2) as a reasonable alternative to SAVR in high-risk patients.[17]

Even though current guidelines continue to support these initial recommendations, newer generations of devices are now available, techniques have improved, and complications have been reduced.[2,8,9] For example, a recent RCT comparing SAVR with TAVR with the newer CoreValve SE bioprosthesis (Medtronic Inc, Minneapolis, MN) in patients with severe AS at increased risk for surgery demonstrated, for the first time, a significantly lower 1-year mortality in the SE TAVR group.[18] In addition, observational studies of CoreValve SE TAVR have shown acceptable mortality outcomes in low- and intermediate-risk patients with severe AS.[19-23] To continue to evaluate these trends, 3 recent RCTs designed to determine the safety, efficacy, and comparability of TAVR versus SAVR in different target populations have been published.[24-26] These well-designed trials have further established TAVR as an alternative to SAVR in patients with AS.[24-26]

The purpose of this expert review was to summarize the study design, outcomes, and complications reported in the following 3 RCTs comparing TAVR with SAVR: (1) the PARTNER-1 (Placement of Aortic Transcatheter Valve) trial (TAVR *v* SAVR cohort) and its final 5-year clinical and valve performance outcomes with BE TAVR (first-generation Sapien valve) in high-risk surgical patients[24]; (2) the CoreValve Trial and its subsequent 2-year outcomes with the CoreValve SE TAVR in patients at increased risk for surgery[25]; and (3) the NOTION (Nordic Aortic Valve Intervention) trial and its 1-year outcomes with the CoreValve SE TAVR primarily in low-risk patients.[26]

TRIAL DESIGN

The PARTNER-1 Trial (TAVR v SAVR Cohort)

The PARTNER-1 trial reported 5-year outcomes for a cohort of BE TAVR versus SAVR in high-risk surgical patients.[24] This cohort originated from the initial Placement of Aortic Transcatheter Valve (PARTNER) trial, a multicenter RCT performed in 25 leading centers comparing the following 2 cohorts of patients with severe AS: (1) BE TAVR versus SAVR in high-risk surgical patients (n = 699)[16]; and (2) BE TAVR versus medical treatment in inoperable patients (n = 358).[14] For the purposes of this review, further discussion addresses only the BE TAVR versus SAVR cohort when referring to the PARTNER-1 trial. TAVR was performed with a BE bovine pericardial tissue valve (first-generation Sapien

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1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2015.12.027

Key words: transcatheter aortic valve replacement, surgical aortic valve replacement, aortic stenosis, randomized controlled trial, balloon-expandable prosthesis, self-expanding prosthesis, perioperative risk, PARTNER trial, CoreValve trials, NOTION trial, Society of Thoracic Surgeons, perioperative risk of mortality (PROM) score, European System for Cardiac Operative Risk Evaluation (EuroSCORE), Valve Academic Research Consortium, mortality, prosthetic valvular regurgitation, peripheral vascular disease, permanent pacemaker, general anesthesia, monitored anesthesia care

valve) using either a transfemoral (n = 244) or transapical (n = 104) approach. A total of 3,105 patients were screened, and 699 of those were classified as high risk and were enrolled. Patients then were assigned randomly either to TAVR (n = 348) or SAVR (n = 351) (Table 1). The primary endpoint was all-cause mortality at 5 years. A neurologist was not involved in the assessment of patients in this trial.

The CoreValve Trial

The CoreValve trial reported the 2-year outcomes of the new CoreValve SE TAVR versus SAVR in patients at increased surgical risk.[25] This trial originated from the initial CoreValve trial that reported 1-year outcomes for all-cause mortality.[18]

The trial was conducted in the United States and was a multicenter, randomized, noninferiority trial design. TAVR was performed with the first-generation CoreValve SE bioprosthesis, but the 2-year data included 2 additional patients who received a smaller (23 mm) second-generation device that was not available earlier. The CoreValve device differs from the BE TAVR device in that it consists of a nitinol SE frame, with porcine pericardial cusps mounted on a porcine pericardial skirt. Its nitinol construction allows for significant elasticity and aids in repositioning, a crucial difference compared with the Sapien valve. A total of 797 patients (750 in the as-treated population) with severe AS at increased risk for surgery were assigned randomly to either CoreValve SE TAVR (n = 391) or SAVR (n = 359) (see Table 1). The primary endpoint was all-cause mortality at 2 years. Abnormalities in the neurologic evaluation triggered a neurology consultation.

The NOTION Trial

The (NOTION) trial, conducted at 3 centers (2 in Denmark and 1 in Sweden), was the first RCT to evaluate SE TAVR versus SAVR in patients with severe AS regardless of their predicted risk of death after surgery.[26] The enrollment of patients regardless of their predicted risk (all-comers) was intended to reflect the population most often referred for treatment in practice. As with the CoreValve trial in the United States, TAVR was performed with a CoreValve SE bioprosthesis primarily via a transfemoral (96.5%) approach with the patient under general (81.7%) or local anesthesia (18.3%).[26] A total of 280 patients ≥70 years old with severe AS and no significant coronary artery disease were randomly assigned to SE TAVR (n = 145) or SAVR (n = 135) (see Table 1). Of these patients, 81.8% were considered low risk, with a STS-PROM score <4%. At the time of the NOTION trial design, there were no other RCTs studying low- or intermediate-risk patients. The primary endpoint was the composite rate of death from any cause, stroke, or myocardial infarction at 1 year. Furthermore, all outcomes were defined according to standard criteria outlined in the Valve Academic Research Consortium-2 definitions.[27] When a neurologic lesion was suspected, an independent neurologist was consulted.

TRIAL INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were similar in all the trials. Patients had New York Heart Association (NYHA) class II or worse symptoms and severe AS with either a mean gradient >40 mmHg or peak aortic velocity >4 m/s.[24-26] However, the NOTION trial also included asymptomatic patients if they had left ventricular posterior wall thickness >17 mm, decreasing left ventricular ejection fraction, or new-onset atrial fibrillation. Exclusion criteria were very similar in the CoreValve and PARTNER trials.[24,25] Compared with these RCTs, the NOTION trial had fewer exclusion criteria, but notable differences were the exclusion of patients with prior cardiac surgery and those with stroke within 30 days.[24-26]

PATIENT POPULATION

Patient demographics in the PARTNER-1 trial were not significantly different between cohorts. Patients had a mean follow-up of 3.14 years, and mean age was 84.1 ± 6.6 years: 94% were NYHA class III or IV, and the mean STS-PROM score was 11.8% ± 3.3% in the TAVR cohort and 11.7% ± 3.5% in the SAVR cohort (p > 0.05).[24] The patient demographics in the CoreValve trial were not significantly different between cohorts with the exception of more diabetic patients in the SAVR group, but overall insulin requirements were no different between the groups.[25] The median follow-up was 24.4 months in TAVR and 24.2 months in SAVR, with a mean age of 83.2 ± 6.7 years: 86.1% were NYHA class III or IV, and the overall STS-PROM score was 7.4%. In the NOTION trial, patient demographics were not significantly different between cohorts, with a similar mean EuroSCORE (European System for Cardiac Operative Risk Evaluation): 81.8% of patients were considered low risk (STS-PROM score <4%).[26]

TRIAL OUTCOMES AND COMPLICATIONS

The outcomes of the PARTNER-1, the CoreValve, and the NOTION trials are reviewed in this section (Table 2, Figs 1–3).[24-26] Furthermore, this section reviews each trial with respect to the main complications associated with first-generation TAVR devices, including stroke, prosthetic valvular regurgitation (PVR), and vascular complications.[8,9,13] The focus on PVR has been derived from a recent meta-analysis that has suggested a strong correlation between this outcome and mortality.[28]

The PARTNER-1 Trial (TAVR v SAVR Cohort)

In high-risk surgical patients, the PARTNER-1 (TAVR *v* SAVR cohort) trial demonstrated that 5-year mortality remained equivalent with BE TAVR (67.8%) compared with SAVR (62.4%; p = 0.86).[24] Previously, the results of the original PARTNER trial demonstrated that mortality was equivalent with BE TAVR (24.2%) compared with SAVR both at 1 year (24.2% *v* 26.8%; p = 0.44)[16] and at 2 years (33.9% *v* 35%; p = 0.78).[15,16] In the TAVR cohort, multivariate predictors for all-cause mortality included PVR, peripheral vascular disease (PVD), renal failure, liver dysfunction, and body mass index (BMI). In the SAVR cohort, multivariate predictors for mortality included the STS-PROM score, significant mitral regurgitation, PVD, liver disease, and BMI. Further subgroup analysis noted that patients without pulmonary hypertension and those with PVD did better with SAVR compared with TAVR.