# TAVR is Noninferior to Surgical AVR in High-Risk Patients with Aortic Stenosis: Results from the PARTNER Trial

As many as one-third of patients with severe aortic stenosis are considered unsuitable candidates for surgical aortic valve replacement (AVR) and subsequently have a grave prognosis. An earlier report from the Placement of Aortic Transcatheter Valve (PARNTER; NCT00530894) randomized clinical trial (Cohort B) [Leon MB et al. *New Engl J Med* 2010] demonstrated that transcatheter aortic valve replacement (TAVR) in inoperable patients dramatically reduced the risk of death over standard medical care (HR, 0.55; 95% CI, 0.4 to 0.74; p<0.001; number needed to treat of 5 patients to prevent 1 additional death at 1 year). Among survivors at 1 year, the rate of cardiac symptoms was also lower in the patients who underwent TAVR. However, these benefits were associated with a significantly increased risk of stroke (5.0% vs 1.1%; p=0.06) and major vascular complications (16.2% vs 1.1%; p<0.001) that were associated with TAVR.

The PARTNER trial now reports that TAVR was noninferior to surgical AVR, the current standard of care, in preventing mortality at 1 year in high-risk patients with symptomatic severe aortic stenosis (Cohort A). The results were presented by Craig R. Smith, MD, Columbia University, New York, New York, USA.

The primary hypothesis was that TAVR would be noninferior to surgical AVR in patients who were deemed high-risk surgical candidates for all cause mortality at 1 year. The study was designed to compare the safety and efficacy of TAVR by either a transfemoral (TF) or transapical (TA) vascular access approach with surgical AVR and was additionally powered to consider the efficacy and safety of TF TAVR individually as a secondary analysis. Patients were required to have symptomatic severe aortic stenosis and be at high surgical risk (ie, a 30-day predicted operative mortality risk ≥15%, as estimated by their Society of Thoracic Surgeons (STS) score). A total of 3105 high-risk patients were screened, and 1057 were enrolled in a 2:1 ratio in the operable (A) and inoperable (B) cohorts of the PARTNER trial. Teams of cardiologists and cardiothoracic surgeons worked together to determine the eligibility of patients and manage their care.

Of the 699 patients who were enrolled in the PARTNER A trial, 492 with adequate femoral/iliac vessel diameter (≥7 mm for the #23 mm valve and ≥8 mm for the #26 mm valve) were randomized to either TF TAVR (n=244) or surgical AVR (n=248). Those with inadequate peripheral vessels (n=207) were randomized to either TA TAVR (n=104) or surgical AVR (n=103).

The primary study endpoint was all-cause mortality at 1 year. Safety endpoints included neurological events (stroke and stroke or transient ischemic attack [TIA]), major vascular complications, major bleeding, repeat hospitalization, new pacemaker requirement, new-onset atrial fibrillation (AF), procedural events, and surgical complications. Cardiac symptoms, 6-minute walk test, and echo assessment of valve performance were used to measure clinical effectiveness. All patients were followed for at least 1 year, and only 2 patients were lost to follow-up. All analyses were considered by intention-to-treat, although 42 patients were not treated as assigned.

Randomized patients appeared to represent those with severely symptomatic aortic stenosis well (mean valve area was 0.7 $cm^2$ and mean aortic valve gradient was 43 mm Hg) and were well balanced between treatment groups. Patients were of advanced age (mean 84 years), and there were nearly equal numbers of women and men. The mean STS score was 11.8, and over 90% had NYHA class III or IV cardiac symptoms with a mean left ventricular ejection fraction of 53%. The vast majority of patients had prior coronary artery disease, almost one-third of patients had prior cerebrovascular disease, 43% had undergone prior coronary artery bypass

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grafting, and 42% had prior peripheral vascular disease. On average, TAVR reduced procedure time by 2 hours and intensive care unit stay by 2 days.

Mortality at 1 year was 26.8% in those who received surgical AVR compared with 24.2% for TAVR (HR, 0.93; 95% CI, 0.71 to 1.22; p=0.001 for noninferiority; p=0.62 for superiority). Among those within the TF subgroup, TAVR was noninferior compared with surgical AVR (22.2% vs 26.4%; HR, 0.83; 95% CI, 0.60 to 1.15; p=0.002 for noninferiority, p=0.25 for superiority). The TA TAVR comparison with surgical AVR was underpowered; however, there was a trend toward increased mortality with TA TAVR, and the investigators did not report the preliminary p-value for noninferiority (29.0% vs 27.9%; HR, 1.22; 95% CI, 0.75 to 1.98; p=0.41 for superiority). Mortality rates at 30 days were lower than expected in both treatment groups, with a trend toward a lower rate with TAVR (3.4%, which is the lowest reported to date for this novel procedure) versus 6.5% for surgical AVR (p=0.07). The operative mortality risk that was estimated by these patients' STS scores was expected to be higher (11%).

Neurological events at 30 days and 1 year were significantly higher in those who underwent TAVR (stroke or TIA occurred in 5.5% vs 2.4% at 30 days; p=0.04; 8.3% vs 4.3% at 1 year; p=0.04), driven predominantly by stroke (Table 1).

**Table 1. Secondary Endpoints.**

| | TAVR (n=348) n (%) | Surgical AVR (n=351) n (%) | p value |
|---|---|---|---|
| **All stroke or TIA, no. (%)** | | | |
| **30 days** | 19 (5.5) | 8 (2.4) | 0.04 |
| **1 year** | 27 (8.3) | 13 (4.3) | 0.04 |
| **Stroke, no. (%)** | | | |
| **30 days** | 16 (4.6) | 8 (2.4) | 0.12 |
| **1 year** | 20 (6.0) | 10 (3.2) | 0.08 |
| **Major stroke*, no. (%)** | | | |
| **30 days** | 13 (3.8) | 7 (2.1) | 0.20 |
| **1 year** | 17 (5.1) | 8 (2.4) | 0.07 |
| **Major vascular complications** | 38 (11) | 11 (3.2) | <0.01 |
| **Major bleeding** | 32 (9.3) | 67 (19.5) | <0.01 |
| **New-onset AF** | 30 (8.6) | 56 (16.0) | <0.01 |
| **Rehospitalization** | 15 (4.4) | 12 (3.7) | 0.64 |
| **New pacemaker** | 13 (3.8) | 12 (3.6) | 0.89 |

TAVR=transaortic valve replacement; AVR= aortic valve replacement; TIA=trans ischemic attack; Defined as Rankin Score >2; this was a post hoc analysis.

Cardiac symptoms by NYHA functional class and distance on the 6-minute walk test showed marked improvement at all time points in both groups. Mean echo gradients at 1 year were clinically similar, with paravalvular aortic regurgitation being greater with TAVR.

The PARTNER trial is a groundbreaking study in the minimally invasive management of valvular heart disease, with the potential to change the standard of practice within cardiology in a manner that has not been seen since the introduction of the coronary stent. If these preliminary results can be replicated with similar clinical effectiveness in routine practice, then transcatheter surgical AVR may be an acceptable alternative therapy to surgical AVR for high-risk patients in the near future. The significance of the trade-off between adverse events that are associated with TAVR versus surgical AVR short and long term requires further exploration.

## Results from the Randomized PARTNER Trial (Cohort B)

For patients with inoperable severe aortic stenosis, the incremental cost per life-year gained (LYG) for transcatheter aortic valve replacement (TAVR) is in line with values for other cardiovascular (CV) technologies. Matthew R. Reynolds, MD, MSc, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, presented these findings, which are based on a cost-effectiveness study of the PARTNER trial (Cohort B).

Data for Cohort B of the PARTNER trial showed that TAVR offers substantial clinical outcome benefits, compared with standard care, for patients who are unsuitable for surgical aortic valve replacement (AVR) [Leon MB et al. *NEJM* 2010]. The economic analysis was designed to compare the two treatment approaches with respect to short-term and long-term costs and lifetime cost-effectiveness.

This study included all 358 subjects in Cohort B. The primary endpoint was the lifetime incremental cost-effectiveness ratio (ICER), expressed as cost per LYG. The secondary endpoint was lifetime incremental cost per quality-adjusted life-year gained (QALY).

The mean initial cost of TAVR was $78,540, which represented the procedural costs, nonprocedural costs, and estimated physician fees. Within the 12-month period of the PARTNER trial, the total follow-up cost (excluding the initial cost) was significantly lower for TAVR ($29,352) than for standard therapy ($52,724)—a difference of $23,372 (p<0.001). The greater follow-up cost that was associated with standard therapy was related to a significantly higher hospitalization rate (2.15 vs 1.02; p<0.001). This higher rate was due entirely to admissions for CV causes. The greater hospitalization