PARTNER Trial Update

An overview of the PARTNER trial and an update on the ongoing studies of transcatheter aortic valve replacement.

BY JEAN-MICHEL PARADIS, MD, AND SUSHEEL KODALI, MD

Severe degenerative calcific aortic stenosis is an increasingly prevalent affliction among elderly patients, with a rate of mortality approaching 50% at 2 years in untreated symptomatic patients.[1] The current gold standard treatment is surgical aortic valve replacement, which has been proven to prolong survival and improve quality of life in good operative candidates.[2] However, in patients with multiple comorbidities, surgery is often prohibitive. Transcatheter aortic valve replacement (TAVR) is a new, less-invasive technique that is designed to be an alternative approach for high-risk patients with severe aortic stenosis. During this innovative procedure, a bioprosthetic valve is inserted via catheter from either the groin or through a small thoracotomy in patients with peripheral vascular disease. Using fluoroscopy and echocardiography, the valve is positioned and implanted within the native diseased aortic valve.

Figure 1. The Edwards Sapien THV.

The Sapien transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, CA) was first implanted in a human subject in 2002.[3] Since then, there has been rapid progression of its use throughout the world. The first implantation in the United States occurred in the setting of the REVIVAL I feasibility study on March 10, 2005. After seven implantations of the 23-mm valve via the transvenous antegrade approach, the REVIVAL I study was suspended due to procedural failures and poor outcomes. Major device modifications were made (the addition of a 26-mm size valve, a novel retrograde delivery catheter, and substitution of equine tissue with bovine tissue for the valve leaflet), and the nonrandomized REVIVAL II study was initiated to evaluate the outcomes after retrograde transarterial implantation of an aortic prosthesis via transfemoral cutdown in 55 patients.[4] Subsequently, a feasibility study evaluating transapical implantation of a transcatheter valve was initiated.[5] After completion of these feasibility studies, the US Food and Drug Administration allowed the initiation of the PARTNER trial.

THE PARTNER TRIAL

The pivotal PARTNER trial is the first randomized (1:1), controlled, multicenter study assessing the effectiveness and safety of any THV in patients with severe, symptomatic aortic stenosis who are at high risk for conventional surgery. The study device (Sapien) is available in 23- and 26-mm valve sizes and is delivered via a 22- or 24-F sheath for the transfemoral approach or a 26-F sheath for the transapical route. The balloon-expandable bioprosthesis is composed of a stainless steel frame inside which a trileaflet bovine pericardial valve is mounted (Figure 1).

In the PARTNER trial, the criteria used to define severe degenerative aortic valve stenosis were an aortic valve area of < 0.8 cm^2 (or aortic valve area index < 0.5 cm^2/m^2), a mean aortic gradient of > 40 mm Hg, or a peak aortic jet velocity of > 4 m/s. All patients had a New York Heart Association functional class ≥ 2. Some of the exclusion criteria included recent acute myocardial infarction (≤ 1 month), recent stroke or transient ischemic attack (within 6 months), congenital unicuspid or bicuspid aortic valves, a preexisting prosthetic heart valve in any position, severe ventricular dysfunction (left ventricular ejection fraction < 20%), renal insufficiency (creatinine > 3 mg/dL), and a life expectancy < 12 months.

Subjects enrolled were separated into two groups, and

each cohort was separately powered and analyzed (Figure 2). In the first group, called *cohort B,* which was composed of patients who were deemed to be unsuitable candidates for surgery, TAVR was measured against standard medical therapy. Inoperability was judged by a cardiac interventionist and two separate surgical investigators and was based on a 30-day probability of death or serious, irreversible condition > 50% after surgical valve replacement. In cohort A, TAVR was compared to surgical replacement in high-risk surgical candidates, which were characterized by a Society of Thoracic Surgeons risk score > 10% and the presence of comorbidities resulting in a ≥ 15% predicted 30-day mortality, as assessed by a cardiac surgeon. Depending on their eligibility for transfemoral access, cohort A patients were further assigned to either the transfemoral or transapical arm of the trial. Within each arm, patients were randomized between TAVR and surgical AVR. Subjects in cohort B without adequate vascular access were not enrolled in the study. The primary endpoint was all-cause mortality at 1 year, but patients will be followed for at least 5 years.

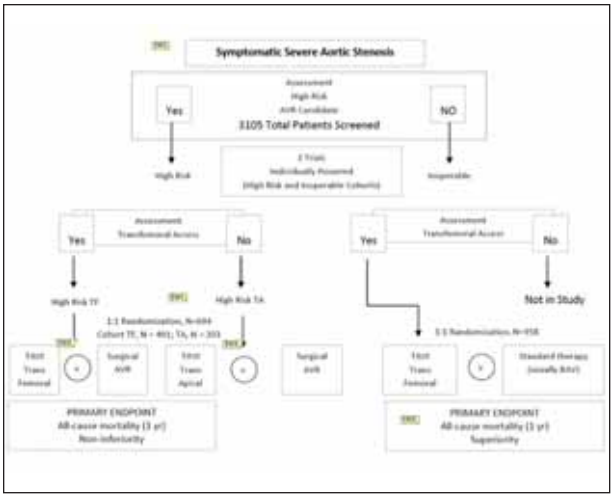

Figure 2. Overall PARTNER trial design.

PARTNER Trial Cohort B

Study population. The PARTNER cohort B trial was a superiority trial with a primary endpoint of all-cause mortality at 1 year. There was a coprimary endpoint that was a composite of mortality and repeat hospitalization.[6] Between May 11, 2007, and March 16, 2009, 21 sites from the United States, Canada, and Germany enrolled 358 patients. Of these, 179 patients were randomized to standard medical therapy, and 179 patients were assigned to TAVR. The overall population was at high risk, as demonstrated by a mean age of 83 years and a mean Society of Thoracic Surgeons score of 11.6% (± 6%). Although generally well balanced, the logistic EuroSCORE was significantly higher in the control group (30.4% vs 26.4%; *P* = .04). Moreover, the standard therapy group had numerically higher proportions of subjects with the following risk factors: coronary artery disease (74.3% vs 67.6%; *P* = .20), previous myocardial infarction (26.4% vs 18.6%; *P* = .10), previous coronary artery bypass graft (45.6% vs 37.4%; *P* = .17), chronic obstructive pulmonary disease (52.5% vs 41.3%; *P* = .04), oxygen dependence (25.7% vs 21.2%; *P* = .38), elevated creatinine > 2 mg/dL (9.6% vs 5.6%; *P* = .23), and atrial fibrillation (48.8% vs 32.9%; *P* = .04). On the other hand, peripheral vascular disease (30.3% vs 25.1%; *P* = .04), extensively calcified aorta (19% vs 11.2%; *P* = .05), and chest wall deformity (8.4% vs 5%; *P* = .29) were numerically more prevalent in the TAVR group. Baseline echocardiographic findings were similar between the two groups.

Of the 179 patients allocated to TAVR, two patients died before the procedure, two patients had unsuccessful transfemoral access, and two patients had an intraprocedural annulus measurement > 25 mm that precluded TAVR. It is also important to mention the heterogeneity of treatment options in the standard medical therapy control group. Indeed, 83.8% of the control subjects received balloon aortic valvuloplasty, 6.1% underwent surgical AVR, 3.3% had apical-aortic conduits, 2.2% underwent TAVR at a nonparticipating center outside of the United States, and only 7.9% underwent no invasive procedure and were on medical therapy alone.

Outcomes. At 1-year follow-up, the rate of death from any cause was significantly lower in the TAVR group as compared with the standard therapy group (30.7% vs 50.7%; hazard ratio, 0.55; 95% confidence interval [CI], 0.4–0.74; *P* < .001). Additionally, the 1-year rate of death from cardiovascular causes was also less in the TAVR group than in the control arm (20.5% vs 44.6%; hazard ratio, 0.39; 95% CI, 0.27–0.56; *P* < .001). The rate of death from any cause or repeat hospitalization at 1-year follow-up was 42.5% in the TAVR arm as compared with 71.6% in the medical treatment group (hazard ratio, 0.46; 95% CI, 0.35–0.59; *P* < .001). Furthermore, there was a significant reduction in symptoms and a significant improvement in the distance covered during the 6-minute walking test in patients in the TAVR arm.

However, there were significant complications associated with the TAVR procedure. The 30-day risk of any neurologic events was higher in the TAVR group (6.7% vs 1.7%; *P* = .03), which was maintained at 1 year (10.6% vs 4.5%; *P* = .04). The PARTNER trial did not have a prespecified neurologic assessment. Major stroke was retrospectively adjudicated by the clinical events committee and was defined as a focal or global neurologic deficit associated with a modified Rankin score of 2 or higher. The rate

of major stroke was higher in the TAVR arm at 30 days (5% vs 1.1%; *P* = .06) and 1 year (7.8% vs 3.9%; *P* = .18). Nonetheless, the 1-year rate of the composite of death from any cause or major stroke was still in favor of the TAVR group (33% vs 51.3%; hazard ratio, 0.58; 95% CI, 0.43–0.78; *P* < .001).

Other frequent complications included vascular and bleeding events. Both major vascular complications (16.2% vs 1.1%; *P* < .001) and major bleeding events (16.8% vs 3.9%; *P* < .001) were more frequent at 30 days in the TAVR group. The rate of new pacemaker implantation was similar in the two groups. In patients who underwent TAVR, multiple valve implantations occurred in 6.3%, whereas the percentage of valve-in-valve procedures was 2.3%.

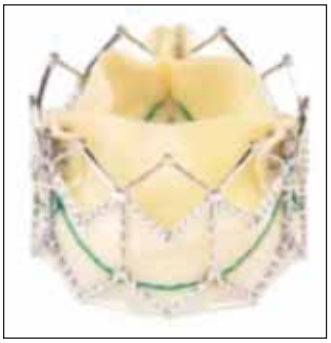

Figure 3. The new Edwards Sapien XT THV.

Echocardiographic data. After TAVR, the mean valve area was 1.5 ± 0.3 cm^2, and the mean gradient was 11.1 ± 6.9 mm Hg. These results were sustained at 1-year follow-up, indicating an excellent hemodynamic performance of the valve without evidence of deterioration in the short term. Moderate or severe paravalvular aortic regurgitation was present in 10.5% at 1 year. On the other hand, moderate or severe transvalvular aortic regurgitation was noted in 4.2% of TAVR patients at 1 year as compared with 15.2% in the control group.

PARTNER Trial Cohort A

Study population. PARTNER cohort A[7] was a noninferiority trial composed of 699 patients with severe aortic stenosis who were deemed to be high-risk surgical candidates. All patients were recruited between May 11, 2007, and August 28, 2009, in 26 centers in the United States, Canada, or Germany. Patients included in the trial were then randomly assigned to surgical AVR (351 patients) or TAVR (348 patients) via either transfemoral placement (244 patients) or transapical implantation (104 patients). The baseline characteristics of the patients assigned to TAVR were similar to those allocated to surgical replacement. However, within the TAVR arm, the rates of previous coronary artery bypass grafting (52.9% vs 39.4%; *P* < .001), cerebral vascular disease (35.7% vs 25.4%; *P* = .01), and peripheral vascular disease (60.2% vs 34.9%; *P* < .001) were higher in patients in the transapical cohort as compared with patients in the transfemoral group. In the surgical control group, 38 randomized patients (10.8%) were not treated. The main reasons for nontreatment were refusal to undergo surgery in 17 subjects, withdrawal from the trial in 11 patients, and death before the procedure in five individuals. In comparison, only four patients (1.1%) in the TAVR group were not treated. Perhaps, the longer interval between randomization and treatment in the surgical group partially explains the nontreatment statistics.

Outcomes. In the TAVR group, there were three intraprocedural deaths, whereas there was one intraprocedural death in the surgical AVR group. Multiple transcatheter valves were implanted in seven patients. Residual significant aortic regurgitation was the reason for placing the second valve in five patients, whereas valve embolization was the cause in two subjects. No coronary obstruction secondary to a transcatheter valve procedure was reported during this trial. In the TAVR arm, the rate of conversion to an open surgical procedure was 2.6%.

The rate of death from any cause at 1 year in the TAVR group was 24.2% as compared with 26.8% in the surgical group, a 2.6% difference that fit well within the prespecified noninferiority margin. The rate of death in the surgical cohort was also comparable to each individual mortality rate in the transfemoral cohort and the transapical cohort when analyzed separately.

Similar to cohort B, neurologic complications were more frequent in the TAVR arm. At 30 days, the rate of all strokes and transient ischemic attacks was greater in the TAVR group than in the surgical AVR arm (5.5% vs 2.4%; *P* = .04). This difference was maintained at 1 year (8.3% vs 4.3%, *P* = .04). At 1 year, 5.1% of subjects in the TAVR group and 2.4% in the surgical cohort had suffered from a major stroke, which was retrospectively adjudicated by the clinical events committee. This doubling in the rate of stroke seems consistent with the findings of PARTNER cohort B trial and recent data showing a high incidence of new silent neurological embolic events after both transfemoral and transapical TAVR.[8] Nevertheless, there was no difference between the two arms at 1 year in the rates of a composite of death from any cause or major stroke (6.9% vs 8.2%; *P* = .52).

The 1-year rate of all vascular complications was higher in the TAVR group (18% vs 4.8%; *P* < .001), whereas the rate of major bleeding was higher in the surgical arm (14.7% vs 25.7%; *P* < .001). The authors of the PARTNER trial also noticed two other clinical benefits with TAVR, a shorter length of stay in the intensive care unit (3 days vs 5 days; *P* < .001) and a shorter index hospitalization (8 days vs 12 days; *P* < .001). Symptom improvement (New York Heart Association class and 6-minute walking test) at 1 year was comparable in the two groups.

Echocardiographic data. From an echocardiographic standpoint, TAVR conferred an advantage over surgical AVR with respect to mean valve area (1.59 cm^2 vs 1.44 cm^2; $P = .002$) and mean aortic valve gradient (10.2 mm Hg vs 11.5 mm Hg; $P = .008$), probably because of the less-bulky support frame. On the other hand, rates of moderate or severe paravalvular regurgitation, which is increasingly recognized as an important predictor of subsequent events,[9] were higher in the TAVR group versus the surgical group at 30 days (12.2% vs 0.9%; $P < .001$) and at 1 year (6.8% vs 1.9%; $P < .001$).

PARTNER II TRIAL

A second prospective, randomized, multicenter trial, the PARTNER II trial, is currently ongoing and was designed to investigate the procedural clinical performance and outcomes after TAVR with the next-generation Edwards Sapien XT THV, as well as the new 18-F NovaFlex system (Edwards Lifesciences) in patients deemed to be nonoperable. The Sapien XT valve has several key differences from the previous-generation device, including a cobalt chromium frame and modified leaflet design that may improve durability (Figure 3). Given the results of the cohort B control patients in the PARTNER trial, it has been judged that a study against a medical management control group is no longer possible. Consequently, an "old device" versus "new device" noninferiority trial was designed. In this manner, each of the PARTNER II randomized trial arms will receive a valve implant. The primary endpoint is a composite of death, stroke, and repeat hospitalization at 1 year.

Cohort B of the PARTNER II trial will include a minimum of 500 randomized patients and a total of up to 600 patients (including roll-in patients and those who have previously consented). Study patients will undergo clinical follow-up at discharge, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years after the procedure. The initial enrollment began in January 2011, and the anticipated enrollment completion date is estimated to be December 2011.

It is anticipated that cohort A of the PARTNER II trial will be randomizing patients between TAVR with the Sapien XT valve and surgical AVR in moderate- to high-risk patients. This trial will enroll patients with a lower surgical risk score than the PARTNER trial.

CONCLUSION

With proven higher survival rates and improved valvular function compared with standard medical therapy in the PARTNER trial, TAVR is the appropriate care for inoperable patients with severe symptomatic aortic stenosis. In the cohort of subjects who are at high surgical risk but are still deemed operative, similar rates of survival at 1 year were achieved in the TAVR and surgical AVR groups. In these patients, the benefits of a less invasive-therapy must be weighed carefully against the potential risks and benefits of TAVR.

The numerous exclusion criteria in the PARTNER trial might limit the applicability of the trial results in a real-world cardiology practice that may frequently encounter patients with low ejection fraction, renal dysfunction, and cerebrovascular and peripheral arterial disease. In addition, the unknown long-term durability of the prosthetic valves used in TAVR will mandate longer follow-up duration. In the future, surgeons and interventional cardiologists, in collaboration, will need to set up a multidisciplinary heart teams to decide which procedure is best for each patient and to ensure appropriate and evidence-based use of TAVR. With more operator experience, standardized training, smaller delivery systems, improvement in devices, procedural changes, and embolic protection devices, TAVR may establish itself as a sustainable treatment option for a larger range of patients. Additional randomized trials, including the ongoing PARTNER II study, will certainly help to shed light on some of these issues. ■

Jean-Michel Paradis, MD, is with the Columbia University Medical Center–New York Presbyterian Hospital in New York. He has disclosed that he has no financial interests related to this article. Dr. Paradis may be reached at jp3153@columbia.edu.

Susheel Kodali, MD, is with the Columbia University Medical Center–New York Presbyterian Hospital in New York. He has disclosed that he is a consultant to Edwards Lifesciences and St. Jude Medical, and is on the Medical Advisory Board for Thubrikar Aortic Valve. Dr. Kodali may be reached at sk2427@columbia.edu.

1. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1-148.
2. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation. 1982;66:1105-1110.
3. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106:3006-3008.
4. Kodali SK, O'Neill WW, Moses JW, et al. Early and late (one year) outcomes following transcatheter aortic valve implantation in patients with severe aortic stenosis (from the United States REVIVAL trial). Am J Cardiol. 2011;107:1058-1064.
5. Svensson LG, Dewey T, Kapadia S, et al. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. Ann Thorac Surg. 2008;86:46-54; discussion 54-55.
6. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-1607.
7. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-2198.
8. Rodes-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol. 2011;57:18-28.
9. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011;123:299-308.