A comprehensive review of the PARTNER trial

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Objective: Percutaneous transcatheter aortic valve replacement was introduced in 2002, but its effectiveness remained to be assessed.

Methods: A prospective, randomized trial (the Placement of Aortic Transcatheter Valves, or PARTNER) was designed with 2 arms: PARTNER A (n = 699) for high-risk surgical patients (Society of Thoracic Surgeons score >10%, surgeon assessed risk of mortality >15%) and PARTNER B (n = 358, patients inoperable by assessment of 2 surgeons). PARTNER A patients were divided into femoral artery access transcatheter aortic valve replacement or none (n = 207), and then randomized to open aortic valve replacement (n = 351) or device (n = 348). Inclusion criteria included valve area <0.8 cm^2, gradient >40 mm Hg or peak >64 mm Hg, and survival >1 year. The end point of the study was 1-year mortality.

Results: Thirty-day mortality for PARTNER A was 3.4% for transcatheter aortic valve replacement and 6.5% for aortic valve replacement; 1-year mortality was 24.2% and 26.8%, respectively ($P = .001$ for noninferiority). The respective prevalence of stroke was 3.8% and 2.1% ($P = .2$), although for all neurologic events, the difference between transcatheter aortic valve replacement and aortic valve replacement was significant ($P = .04$), including 4.6% for femoral artery access transcatheter aortic valve replacement versus 1.4% for open aortic valve replacement ($P = .05$). For PARTNER B—transcatheter aortic valve replacement versus medical treatment—30-day mortality was 5.0% versus 2.8% ($P = .41$), and at 1 year, mortality was 30.7% versus 50.7% ($P < .001$), respectively. Hospitalization cost of transcatheter aortic valve replacement for PARTNER B was $78,542, or $50,200 per year of life gained. Analysis of PARTNER A strokes showed that hazard with transcatheter aortic valve replacement peaked early, but thereafter remained constant in relation to aortic valve replacement. Two-year PARTNER A data showed paravalvular regurgitation was associated with increased mortality, even when mild ($P < .001$). Continued access to transapical transcatheter aortic valve replacement (n = 853) showed a mortality of 8.2% and decline in strokes to 2.0%. Of the 1801 Cleveland Clinic patients reviewed to December 2010, 214 (12%) underwent transcatheter aortic valve replacement with a mortality of 1%; in 2011, 105 underwent transcatheter aortic valve replacement: 34 transapical aortic valve replacement, with no deaths, and 71 femoral artery access aortic valve replacement with 1 death.

Conclusions: The PARTNER A and B trials showed that survival has been remarkably good, but stroke and perivalvular leakage require further device development. (J Thorac Cardiovasc Surg 2013;145:S11-6)

H.R. Andersen first obtained a patent for an intra-aortic valve metal-stent balloon expandable valve with internal biologic leaflets.[1–6] Subsequently, Cribier, Leon, and Moses persisted with developing the technology using a femoral transvenous approach.[1–6] A transapical (TA) transcatheter aortic valve replacement (TAVR) approach was then developed, followed by a transarterial femoral (TF) approach and, more recently, transaortic and transaxillary approaches. Two initial feasibility trials were performed in the United States for both TA-TAVR and TF-TAVR.[1-23]

The PARTNER trial (Placement of Aortic Transcatheter Valves) was designed as a multicenter randomized trial comparing open standard aortic valve replacement (AVR) with TAVR in high-risk patients, and also TAVR versus standard medical treatment.[1,2,5,6] In addition, cost analysis, 2-year data analysis, and stroke analysis have been done, as well as analysis of continued access for TA-TAVR.[1,2,4,21]

METHODS

A total of 3105 patients were presented to a Web-based review panel for potential inclusion in the trial (Figure 1). Ultimately, 12% were enrolled; however, the number of patients reviewed at sites but not presented was

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Dr Svensson holds stock in Cardiosolutions and ValveXchange and receives royalties from Post-Thorax. Dr Roselli is a consultant for Medtronic and Edwards Lifesciences, and is a teacher and speaker for Cook Medical and Terumo Medical. Dr Gillinov is a consultant for Edwards Lifesciences and Onyx Lifesciences, and receives research support from St. Jude Medical and Medtronic. Dr Sabik is a consultant for Medtronic and ValveXchange, and receives lecture fees from Edwards Lifesciences. Drs Tuzcu, Kapadia, Blackstone, and Lytle have nothing to disclose with regard to commercial support.

Read at The American Association for Thoracic Surgery Aortic Symposium, New York, New York, April 26-27, 2012.

Received for publication April 26, 2012; revisions received Aug 10, 2012; accepted for publication Nov 28, 2012.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.11.051

Abbreviations and Acronyms

AVR = aortic valve replacement
BMI = body mass index
COPD = chronic obstructive pulmonary disease
FDA = Food and Drug Administration
PARTNER = Placement of Aortic Transcatheter Valves
STS = Society of Thoracic Surgeons
TA = transapical
TAVR = transcatheter aortic valve replacement
TF = transarterial femoral

considerably higher. For example, as of December 2010 at Cleveland Clinic, we had reviewed 1801 patients who were considered potential trial participants. If patients presented for potential enrollment but clearly were not candidates based on inclusion and exclusion criteria, they were then reviewed for surgery, balloon dilatation, or medical treatment. Hence, of the 1801 patients reviewed formally and discussed at our weekly Tuesday morning meeting, 193 went on to surgery and 214 went on to enrollment into TAVR studies. During the same period, the number of patients who underwent open AVR was noted.

Briefly, PARTNER A patients were required to be high risk for conventional open valve surgery.[1,5] This was determined by a minimal Society of Thoracic Surgeons (STS) score of 10% for death, and the surgeons' assessment of the risk as >15%. In addition, patients were required to have symptomatic aortic valve stenosis with an area <0.8 cm^2, and gradients either > a mean of 40 mm Hg or a peak of 64 mm Hg, the latter equivalent to a velocity of 4 m/second. The list of exclusions included recent myocardial infarction, stroke, infections, creatinine level >3.0 mg/dL, and patients not likely to survive a year. For PARTNER B,[2,6] patients approved for the study were required to have 2 cardiac surgeons agree that they were inoperable based on a combined risk of death and irreversible severe morbidity >50%.

Data on hospital costs were also collected. After completion of the trial, patients could be enrolled in continued access to TAVR in PARTNER A and PARTNER B. Furthermore, after 1 year, surviving patients were allowed to cross over in PARTNER B. PARTNER B patients listed as having died from unknown causes underwent careful review to determine cause of death.

The trial was designed by members of the PARTNER executive committee and the sponsor (Edwards Lifesciences), with additional input and approval from the U.S. Food and Drug Administration (FDA). In June 2006, the proposal for a randomized trial with 2 arms for either inoperable or high-risk surgical patients was proposed by 3 of us (L.G.S., E.H.B., and B.W.L.) and other surgeons, with the high-risk surgical patients randomized to open AVR, TF-TAVR, or TA-TAVR. The final trial was designed based on extensive discussion, and TA-TAVR was dropped from randomization in patients with femoral access. The executive committee and principal investigators had full access to all the data after the database was locked. An independent clinical events committee arbitrated events and complications. For PARTNER B deaths and neurologic events in PARTNER A, clinical events committee records were reviewed in detail. An independent echocardiography core laboratory assessed echocardiographic outcomes.

The device used for the study consisted of a stainless steel tubular mesh stent with internal bovine pericardial leaflets (Edwards LifeSciences' Sapien valve). The device was loaded onto an inflatable balloon within a loader. A balloon dilatation was performed first and then, when the device was positioned correctly, the balloon was inflated during rapid pacing of the heart, usually at 180 to 200 beats per minute. Transesophageal echocardiography was used to check correct position, supplemented as needed by root aortography. Technical steps for device insertion have been described previously. The study end points were 1-year survival, with documentation of complications and their effects on 1-year survival.

For PARTNER A, the trial was designed for noninferiority of TAVR versus open AVR and, furthermore, the TF-TAVR group assignment was powered to compare TF-TAVR noninferiority with open surgery. This was not done for TA-TAVR. Based on this design, 650 patients were required for PARTNER A with at least 85% power to show noninferiority of TAVR assuming a 1-year mortality of 29% for TAVR and 32% for AVR. Similarly, 450 patients were required for TF-TAVR power. For PARTNER B, the trial was for superiority of TF-TAVR versus medical treatment in the control arm. To achieve 85% power to show superiority, 350 patients were required, assuming 37.5% mortality in the control subjects and 25% in the TAVR patients. In the case of PARTNER B, to analyze the nonprimary end point of both death and repeat hospitalization, the Finkelstein-Schoenfeld nonparametric method was used.[20] To do this, all patients had multiple pairwise comparisons performed, first with respect to time to death and to repeat hospitalization, if the latter occurred.

RESULTS

For PARTNER A, 351 patients were assigned to AVR and 348 to TAVR, of whom 244 were TF-TAVR and 104 TA-TAVR.[1,5] Variables were mostly well balanced between AVR and TAVR, and the mean STS score was 11.8%. Actual AVR mortality was 8%, a 0.68 observed-to-expected ratio compared with STS score. Patients in the non-TF-TAVR were considered for TA-TAVR; however, they had more previous coronary artery bypasses, percutaneous coronary interventions, cerebrovascular disease, previous carotid endarterectomies, peripheral arterial disease, porcelain aortas, radiation heart disease, and severe aortic valve stenosis, the latter a risk factor for neurologic events. Forty-two patients did not undergo treatment as assigned.

For TAVR, 3 patients died during the procedure, 16 had the procedure aborted or converted to open operation, 7 had multiple valves inserted (3 patients died), and another 7 were aborted because of valve embolization, for a total of 33 procedure failures (9.5%). Thirty-day mortality for intention to treat for was 3.4% for TAVR and 6.5% for AVR ($P = .07$); for TF-TAVR, mortality was 3.3% versus 6.2% with AVR ($P = .13$). For TA-TAVR, 30-day mortality was 3.8% and control AVR was 7.0% ($P = .32$, intention to treat). At 1 year, mortality was 24.2% for TAVR and 26.8% for AVR, with no significant difference, meeting noninferiority. Prevalence of neurologic events for TAVR versus AVR at 30 days was 5.5% versus 2.4% ($P = .04$); major strokes was 3.8% versus 2.1% ($P = .2$). For all neurologic events, TF-TAVR versus open AVR was 4.6% versus 1.4% ($P = .05$). Subgroup analysis showed that women fared better with TAVR and patients undergoing reoperations fared better with open AVR, contrary to expectations, and not fully explained. Other events included more vascular