Implications of Contemporary Clinical Trials

The Placement of Aortic Transcatheter Valve (PARTNER) Trial
The Surgeon’s Perspective: Celebration and Concern

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The Placement of Aortic Transcatheter Valve (PARTNER) Trial is a very well-designed, meticulously executed, prospective randomized trial that demonstrated that transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN valve was superior to medical therapy in the treatment of inoperable patients with aortic stenosis (cohort B) and that it was not inferior to standard surgical aortic valve replacement in patients with advanced symptomatic aortic stenosis who are high risk for surgical therapy (cohort A).1,2 The trial involved both surgeons and cardiologists from the beginning. Every patient enrolled in the trial was discussed by conference call before enrollment was accepted. Enrolling sites were centers of excellence in surgical valve replacement and in interventional cardiology. The trial demonstrated a 20% survival advantage in the nonoperable cohort A patients at 1 year. This level of benefit is rare in medical device therapy. In the high-risk surgical patients, TAVR and surgical valve replacement each demonstrated equivalent 1-year mortality (TAVR, 24.2%; surgical aortic valve replacement, 26.8%) and equivalent 1-year relief of symptoms.2 The results of the trial led to approval by the Food and Drug Administration of the device for commercial use in inoperable patients. Use of the device in the United States for high-risk surgical patients is under consideration. This therapy is of great benefit to patients who are similar to those enrolled in the trial. Certainly, this is cause for celebration.

The celebration associated with PARTNER is tempered by concerns, however. The procedure remains a major interventional undertaking requiring transit of large-bore catheters across often-diseased vascular structures and deployment of a valve with precision in carefully selected patients. Patients and families of inoperable patients seeking TAVR focus on the 20% 1-year survival benefit. Sometimes lost in their consideration is the fact that in this very ill group of patients, the 1-year mortality was 30% in patients who received the device.1 As we use this device commercially, it is important that in the process of shared decision making, the risks of the procedure are adequately explained to our patients and that these risks are not overwhelmed by our enthusiasm for this potentially lifesaving therapy.

As we consider the risk benefit analysis of TAVR, it is important to understand the risks of the alternatives. Clearly, in nonoperative patients with advanced symptomatic aortic stenosis, medical therapy, including balloon valvuloplasty, offers little that can either prolong life or improve the quality of the patient’s life. In the high-risk surgical patients, however, surgical outcomes are much better than “historical controls.” The Society of Thoracic Surgeons (STS) risk calculator projects that the 30-day mortality for an 80-year-old man undergoing an uncomplicated aortic valve replacement is only 1.5% with a predicted stroke rate of 1.2%. Morbidity, especially pain, has been dramatically reduced by new incisions and attention to detail. Cohort A of PARTNER was remarkable for the quality of the results in the surgically treated patients. Operative mortality, predicted to be 11%, was only 8%. TAVR patients recovered more quickly and quality of life at 3 months was higher in the TAVR group, but quality-of-life outcomes were essentially equivalent at 1 year.2

What complications need to be discussed with patients and their families as one considers TAVR? The Valve Academic Research Consortium (VARC) has defined standardized end points for transcatheter aortic valve implantation trials.3 The VARC safety end points at 30 days include all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury, periprocedural infarction, major vascular complications, and repeat procedure for valve-related dysfunction (repeat surgical or interventional therapy). A meta-analysis of outcomes after TAVR included 3519 patients from 17 studies. These patients were roughly equivalent to the PARTNER patients with an STS-predicted risk of mortality of 8.7% and a mean age of 81.5 years. All-cause 30-day mortality was 7.8%; stroke rate at 30 days was 3.2%; major vascular event rate at 30 days was 11.9%; major bleeding was 22.3% (life-threatening bleeding was 15.6%); periprocedural myocardial infarction was 1%; and permanent pacer at 30 days was 4.9% with the Edwards system and 29% with the Medtronic CoreValve system. Conversion to surgery was 1.3%. Valve embolization was 1.7%, and the requirement for a valve-in-valve deployment was 2.3%.4
Results from the PARTNER Trial also suggest that the VARC safety end points are relatively common. In cohort B, major vascular complications occurred in 16.2% and major bleeding occurred in 16.8%. Both the PARTNER Trial cohort B and registry data have demonstrated that major vascular complications are associated with an ~2-times increase in mortality over the first 12 months. In cohort A (the high-risk surgical patients), the stroke rate was twice as high with TAVR compared with surgical aortic valve replacement (6.1% versus 3.0%; \(P=0.07\)). The difference when transient ischemic attacks and strokes were considered together was statistically significant \((P=0.04)\).

The risk of stroke with TAVR deserves special comment. Many practitioners are focusing on this complication, and progress is being made with smaller devices, preoperative evaluation of the aortic arch, and exploration of filter devices. In addition to a stroke rate that is twice as high with TAVR compared with surgical aortic valve replacement, it is notable that the neurological events that occur with TAVR during the first year occur ~50% of the time within 2 days of the procedure and the remainder occur thereafter, most within the first 10 to 15 days. This implies that there may be either delayed release of emboli or development of platelet or fibrinous thrombus around the device with embolization in the interval between 2 and 15 days. Neuroimaging has confirmed the increased frequency of new lesions on diffusion-weighted magnetic resonance imaging compared with surgical aortic valve replacement. New lesions occur in 60% to 90% of patients undergoing TAVR, approximately twice the frequency of new lesions seen with surgical aortic valve replacement.6

In addition to the short-term concerns about complications within the first 30 days, it is important to keep in mind potential long-term problems with TAVR. Thus far, durability up to 3 years seems very encouraging.7 We must remember, however, that a 3- to 5-year durability, while suitable for the 80-year-old patients currently undergoing TAVR, is certainly inadequate for extension of the procedure to younger patients, particularly because younger patients with surgical valve replacement have accelerated calcification and structural valve deterioration with biological tissue. A second longer-term concern is the occurrence of moderate to severe paravalvular regurgitation, which in the PARTNER Trial persisted in 7% of patients at 1 year. Registry data have indicated that persistent moderate or severe regurgitation is associated with reduced long-term survival benefit.8,9

The PARTNER Trial focused on a “transfemoral first” approach to TAVR therapy with transapical access used only when the transfemoral technique was deemed to be unsafe. It is notable more than half the patients enrolled in the continued-access registry in the United States have undergone transapical access. This is related at least in part to a focus on the problems with vascular complications that have occurred with the larger first-generation Edwards SAPIEN devices used in the PARTNER trial. Transapical TAVR in the continued-access cohort has been successful and indeed has achieved outcomes numerically better \((P=NS)\) than the transapical therapy reported in the PARTNER trial (1-year mortality, 29.1% versus 25.3% versus 23.6% for PARTNER A transapical, PARTNER A surgical aortic valve replacement, and continued-access transapical, respectively). In addition to encouraging mortality, there has been an improvement in stroke rate in the continued-access transapical patients (10.8% versus 7% versus 3.7% at 12 months, PARTNER A transapical versus PARTNER A surgical AVR versus continued-access patients).10 Transapical access in experienced institutions is continuing to improve. In addition, other alternative access routes for this particular device such as transaortic access and even transcra- rotid access now offer potential advantages over transapical access in selected patients. As the continued-access registry demonstrates, there are many patients for whom nontransfemoral access offers an attractive reasonable alternative for TAVR, and continued evaluation of these nontransfemoral access routes is important.

The PARTNER Trial is a landmark investigation firmly establishing the utility of TAVR in high-risk patients. This group of patients represents patients from the upper 10% of risk among patients currently undergoing surgical aortic valve replacement. PARTNER II, the follow-up study, is an extension of this evaluation to patients with an STS-predicted risk of mortality >4. This represents the upper 25% of patients currently undergoing surgical aortic valve replacement. This progressive evaluation of lower-risk patients is appropriate in a measured and scientific manner. As techniques improve and as complications are progressively reduced with TAVR, one would expect that the technique will become applicable to a wide range of patients with aortic stenosis. There are currently data justifying the use of this device in patients at high risk, but long-term concerns and short-term complication issues certainly proscribed extension of this technique to lower-risk and younger patients without data from clinical trials—trials, we hope, as well designed and well executed as PARTNER.

Disclosures

None.

References


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