2012 PARTNER Trial Update

A review of the data that are currently available, as well as the issues that will be addressed in the next iteration of the PARTNER trial.

BY D. SCOTT LIM, MD

As the first completed randomized clinical trial in the rapidly expanding field of transcatheter aortic valve replacement (TAVR) (Figure 1), PARTNER deserves both scrutiny and praise. This article focuses not only on the most recent 2-year follow-up data but also the future directions of the subsequent PARTNER II trial and next-generation iterations of the Sapien valve (Edwards Lifesciences, Irvine, CA).

THE PARTNER I TRIAL

The original PARTNER trial was really two trials of two different patient populations wrapped into one. PARTNER IB looked at the role of TAVR, using an early generation, balloon-expandable Sapien valve in patients for whom there were no other acceptable therapeutic options to treat their symptomatic, severe aortic stenosis (AS).[1] PARTNER IA used the same TAVR system and compared it to the surgical standard of care in patients who were considered to be at high operative risk.[2]

In both trials, the definition of AS was the same: severity was judged by echocardiography as an aortic valve area of < 0.8 cm^2 and either a mean gradient of 40 mm Hg or a maximum velocity of > 4 m/s. Although this definition comprises the majority of patients with severe AS, a few caveats must be noted. First, society guidelines have called for intervention in aortic valve areas of < 1 cm^2, which means that the PARTNER trial looked at a narrower population with more severe AS.[3] Unfortunately, this also created a small disparity between the regulatory and reimbursement guidelines in the United States, which were developed from the PARTNER trial and these national professional guidelines.

Second, the PARTNER severity guidelines looked at patients with a significant gradient. For patients with low-gradient, low flow (but still severe) AS, the PARTNER trial guidelines allowed the use of inotropic stress echocardiography to determine the presence of contractile reserve. If, with dobutamine augmentation, the impaired left ventricle (ejection fraction < 40%) was able to generate a gradient > 40 mm Hg or a maximum velocity of > 4 m/s, it was believed that the patient would likely benefit from aortic valve therapy. If not, it was believed that the ventricular dysfunction was prohibitive for therapeutic benefit. Of note, this does not account for the recently elucidated

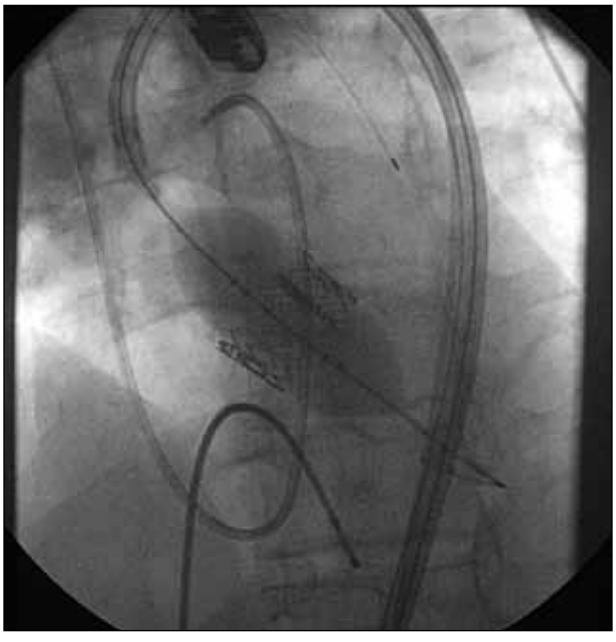

Figure 1. Transfemoral TAVR performed with the first-generation Sapien valve.

entity of low-flow, low-gradient but preserved ejection fraction AS.[4,5] Although it is possible that these patients would similarly benefit from TAVR, they were excluded from study and therefore represent a potential gap in the treatment strategy.

PARTNER IB

The PARTNER IB trial demonstrated that for patients with severe, symptomatic AS, TAVR had a remarkable benefit in comparison to medical therapy.[1,6] Unfortunately, medical therapy for severe AS has been shown not to alter the dismal prognosis of the disease; AS in this population is worse than many cancers with reputable mortality. Combining the extremely poor prognosis of AS with the treatment effect of TAVR in this population made for an outstanding result.

It is important to note that as impressive as these results are, they were based on a narrowly defined group of patients with AS. Many of the comorbid risk factors that allowed a patient to fall into the category of "inoperable" can easily tip the patient over into the so-called cohort C—patients dying with AS rather than from AS. Drilling down on the PARTNER data demonstrated that the best outcomes occurred in patients without extreme comorbidities.[6] The distinction between these two subsets of patients can be easily blurred by confounding issues but is a very important one to keep in mind.

Other points to be taken from the PARTNER trial were the importance of vascular access and the issue of neurologic events. Given that the PARTNER trial evaluated an early generation, large-bore delivery system from a transfemoral approach, patients needed to have adequate-caliber vessels. For patients with vessels that were borderline small or diseased, major vascular complications occurred in approximately 16% when pushing the 25- to 28-F outer diameter of the delivery system. Survival at 12 months in patients who then had a major vascular complication was 47.2%, which was similar to that of patients randomized to the medical control arm. These results drive home the point of careful patient selection, with attention to vascular access routes.[6]

Another issue that has raised much attention from the PARTNER data was that of neurologic complications. In the inoperable AS patients of PARTNER, there was an early hazard for strokes in patients undergoing TAVR compared to the medical control arm, predominantly occurring < 30 days, at a rate for all stroke/transient ischemic attack of 6.7% versus 1.7%.[1] Early mortality was also equated with patients who had a major periprocedural stroke (66.7% at 12 months). However,

Figure 2. Transapical approach for TAVR performed using the second-generation Sapien XT valve.

when this was compared as an analysis of stroke or mortality, there still remained a substantial benefit for those undergoing TAVR after 6 months out to 2 years.[7] Following the periprocedural period, there appears to be a constant hazard for stroke that is mainly related to the extent of the underlying cardiovascular disease burden.[8] Although speculation has also centered on whether the stent of the Sapien valve, by pinning the native leaflet tissue into the sinuses, creates areas of stasis and thrombosis risk, the optimal antiplatelet/anticoagulation strategy after TAVR is unclear. There are also significant resources being put into neuroembolic protection devices to be used adjunctively in TAVR, but at present, no randomized clinical trial data have been reported to support their use.[9]

These remarkable results of the PARTNER IB trial data, in a group of patients normally faced with a dismal outcome, led to a rapid (and appropriate) regulatory approval of this technology. It remains, however, a note of caution that appropriate patient selection, with avoidance of vascular and neurological complications, is paramount to success.

PARTNER IA

In contrast, the PARTNER IA trial evaluated a different group of patients—those at high risk for conventional surgical aortic valve replacement (SAVR). Therefore, PARTNER IA was a trial of patients with lesser degrees of comorbidities and in which a first-generation technol-

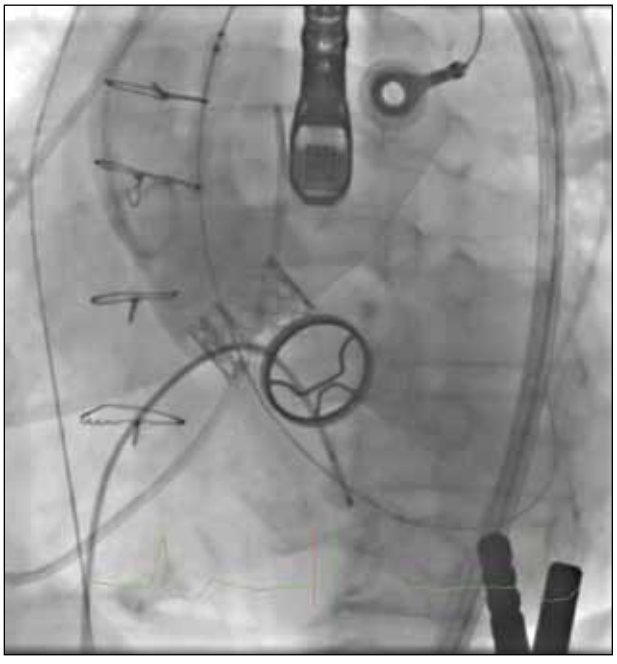

Figure 3. Evolution in valve replacement therapy is seen in this patient, from the surgically implanted single tilting-disc mitral prosthesis to TAVR with the Sapien valve in the aortic position.

ogy was being compared against a standard of care for which the surgical community has refined their results to a remarkable degree. If nothing else, the PARTNER IA trial confirmed the outstanding results of SAVR, with a lower observed-to-expected mortality ratio.[2] In this group of patients, TAVR results at 2 years were ultimately noninferior to SAVR, leading to the consideration of TAVR as an acceptable alternative.[7]

Unlike the PARTNER IB trial, inadequate femoral/iliac arterial access was not a limitation, because there was an option for a transapical delivery of the balloon-expandable Sapien valve (Figure 2). There was a significant learning curve for TAVR and, in particular, a very steep learning curve for the transapical approach.[10] However, there is a documented benefit to training and educating newer transapical operators, which can lead to early results that are comparable to those of more experienced centers. The transapical route, however, still exposes the patient to the morbidity of a chest incision, potential for lung retraction, and left ventricular injury from the large delivery sheath. Data from the PARTNER trial demonstrated that patients who underwent transapical TAVR had improvement in quality-of-life indices that were similar to SAVR but no better. This was in contrast to patients undergoing transfemoral TAVR who had substantial quality-of-life improvements greater than that experienced by those undergoing SAVR.[11]

> "PARTNER trial data demonstrated that patients who underwent TAVR had improvement in quality-of-life indices that were similar to SAVR but no better."

The 2-year follow-up data from the PARTNER IA trial shed light on the importance of perivalvar aortic regurgitation.[6] The first question that this raises is whether perivalvar aortic regurgitation is associated with a worse prognosis or if it causes a worse prognosis. Fundamentally, balloon-expandable TAVR is an attempt to place a circular device in a potentially noncircular aortic outflow. Patients with greater disease burden may have increased calcium and, therefore, increased irregularity of the aortic valve. By placing a circular and nonconforming Sapien valve into this irregularity, there is an increased likelihood of aortic insufficiency. However, it also appears that optimal sizing of the prosthesis to the aortic annulus can decrease the incidence of perivalvar aortic regurgitation and that three-dimensional methods of annulus measurement are superior to two-dimensional echocardiography.[12]

The PARTNER IA trial data have shown TAVR to be an acceptable alternative to SAVR in this high-risk group of patients with AS. Improvements still need to be achieved in areas of perivalvar aortic regurgitation and lower morbidity vascular access.

FUTURE DIRECTIONS

The next-generation trial, PARTNER II, is already underway, and as with PARTNER I, it is actually two trials in one. PARTNER IIB has completed enrollment and was designed to evaluate the next version of the Sapien valve (Sapien XT) in inoperable patients. The valve and delivery system have been improved to have greater stent radial strength in a smaller delivery package, thereby allowing a smaller delivery sheath (18- and 19-F inner diameter vs 22 and 24 F for the earlier Sapien valve).

The PARTNER IIA trial is underway and is evaluating TAVR in an intermediate-risk population (defined as a Society of Thoracic Surgery risk calculator score of > 4% for predicted mortality). It allows for concomitant therapy of coronary artery disease, such that patients may be randomized between TAVR and percutaneous

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coronary intervention versus SAVR and coronary artery bypass grafting. Due to the outstanding results of conventional surgery in this lower-risk group of patients, it remains to be seen whether the previous concerns of neurologic complications and perivalvar aortic regurgitation, as seen in PARTNER I, will limit the benefit for patients randomized to TAVR in PARTNER IIA.

Future iterations of the Sapien valve platform have been publicly presented, with design changes to address perivalvar aortic regurgitation, vascular access issues, and deployment.

CONCLUSION

Just as the previous decade has witnessed a maturity in transcatheter approaches to coronary artery disease, this next decade will see a tremendous evolution in transcatheter therapy for aortic valve disease (Figure 3). The PARTNER trials were the first and likely most significant randomized clinical trial steps in this direction. The high bar set by these trials will need to be duplicated for future trials in this area, to the benefit of patients with AS. ■

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