Implications of Contemporary Clinical Trials

The Placement of Aortic Transcatheter Valve (PARTNER) Trial
The View of a Cardiologist

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The Placement of Aortic Transcatheter Valves (PARTNER) trial randomized inoperable patients with severe symptomatic aortic stenosis (AS) to medical therapy versus transcatheter aortic valve replacement (TAVR) in 1 arm (PARTNER B) and high-surgical-risk AS patients to surgical aortic valve replacement (SAVR) versus TAVR in the other arm (PARTNER A).1,2 TAVR was far superior to medical therapy in PARTNER B, and TAVR had a mortality similar to that of SAVR in PARTNER A.

The impact of PARTNER is hard to overestimate. It was an elegant randomized trial in an area of cardiology noted for its dearth of such trials.3 It reiterated the gravity of symptomatic AS and demonstrated the power of a previously unavailable therapy for AS, yet it also expressed caution in the application of this exciting new therapy.

Randomized Trials in Valvular Heart Disease
The very fact that PARTNER was a randomized, controlled trial is by itself noteworthy. The American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease are unique among all of the American College of Cardiology/American Heart Association guidelines in that only a single recommendation (balloon mitral valvotomy for mitral stenosis) was based on a Level of Evidence A (0.3% of the total). Seventy-five percent of the recommendations were supported by only a Level of Evidence C (consensus of opinion). Although a half-million patients with coronary disease and/or heart failure have been enrolled in randomized controlled trials, only a hundredth of that number have been enrolled in randomized controlled trials aimed at therapy for valvular heart disease. Thus, PARTNER by itself increases the number of randomized valve patients by ≈17%. PARTNER vitiates many of the reasons given to explain why until now so few patients have been randomized—too hard to recruit, high variability in therapeutic techniques, too expensive, etc—by showing that such a trial can be performed and be performed well.

Impact on the Patient With AS
The lethality of symptomatic AS has been recognized for decades; the disease kills at the rate of ≈2%/mo, so 75% will have died in 3 years after the onset of symptoms if left untreated by valve replacement.4–6 It has often been written that there is no medical therapy for AS, and the medical arm of PARTNER (which even allowed balloon valvotomy) confirmed the very high mortality rate for patients treated medically. Indeed, for the foreseeable future, a medical therapy that relieves this mechanical problem (outflow obstruction) seems quite unlikely, although a medical therapy that prevents or reduces valve calcification seems plausible.

At the same time, the trial provided evidence of an exciting option for inoperable patients. TAVR reduced mortality by 50% compared with medical therapy, and much of the mortality that did occur was unrelated to TAVR but was instead due to the very sick nature of the patients enrolled. Importantly, there was also an impressive improvement in symptoms. Thus, patients lived longer and with a better quality of life after TAVR compared with medical therapy.

The trial also demonstrated a potential alternative for high-surgical-risk patients who might choose this less invasive therapy (when available for this indication) over SAVR. TAVR and SAVR had nearly identical midterm mortality rates, but it must be noted that the morbidities of the 2 procedures were quite different; TAVR had an excess stroke risk and excess risk of paravalvular leak, whereas SAVR had an excess bleeding risk.

The impact of PARTNER is made yet greater by the exceptional quality of trial. There are now well over 5000 randomized controlled trials in cardiovascular medicine, but few have the impact of PARTNER. The weight of PARTNER stems from several qualities: (1) The magnitude of superiority for TAVR versus medical therapy was exceptional; (2) the patients included in the trial are those routinely faced by the clinician and thus there is “real-world” impact; (3) the data were presented in an extensive fashion and the statistical analysis was robust, leaving little doubt about the veracity of the conclusions made; and (4) authorship was a balance of respected cardiologists and cardiac surgeons, assuaging any worry about professional or provincial bias.

Thus, there is now a proven, less invasive mechanical therapy for inoperable AS patients and an encouraging less invasive strategy for high-surgical-risk patients.
Patient Selection

Symptomatic AS is a fatal disease, and now we have a new therapy for treating it. Does this mean that every inoperable patient with symptomatic AS should receive TAVR? The answer is a resounding “no.” It is almost impossible to reach a Society of Thoracic Surgeons risk of mortality in the 15% range that many would define as inoperable from cardiac abnormalities alone (Figures 1 and 2). An 80-year-old man with an ejection fraction of 30% undergoing a second cardiac operation that includes SAVR plus coronary bypass has a Society of Thoracic Surgeons risk of 6%, and that number probably overestimates risk.7,8 For the risk score to reach inoperability, severe lung disease and renal disease are usually also present, often in concert with diabetes mellitus. An inoperable patient with severe dyspnea and advanced lung disease receiving home oxygen may not benefit from TAVR despite relief of severe AS. Thus, before TAVR is contemplated, there must be a reasonable expectation that the patient’s symptoms are due to AS and that relief of AS will lead to a substantial improvement in both longevity and quality of life.

Four Problems to Be Solved as TAVR Evolves

PARTNER presents the results of an early (but remarkable) model of the Edwards SAPIEN valve. Surely this valve and other types of TAVR will evolve as technology evolves, likely producing even better results that will almost certainly address the following problems.

Stroke

In PARTNER cohort A, the risk of stroke for TAVR exceeded that for SAVR. Stroke is a potentially devastating complication, especially in this older age group for whom independence is perhaps the major issue in their quality of life. It is likely that delivery of the relatively bulky TAVR past the head vessels leads to detachment of atherosclerotic debris from the aorta, causing subsequent carotid embolization. Smaller delivery systems and possibly carotid protection devices may ameliorate the TAVR stroke risk in the future. However, the stroke rate in both TAVR and SAVR continued to increase after valve implantation, pointing to the high stroke risk inherent in the population being treated. Thus, stroke risk is likely to be lower in lower-risk groups.

Delivery

In the United States, the Edwards SAPIEN valve is delivered through either a 24F or a 28F sheath, creating obvious access problems, which in turn lead to vascular complications. Although currently approved only for femoral access, transaortic, transaxillary, and transapical approaches should help obviate access complications in the future, as will technology that permits access with smaller sheaths. Delivery through an 18F sheath is available in Europe, and even smaller devices will likely be available in the future.

Aortic Regurgitation

Early data from Europe indicate that postimplantation outcome is impaired if there is more than trivial aortic regurgitation after the procedure.9 This is not surprising because the left ventricle in AS develops concentric hypertrophy, leading to impairment of diastolic filling, which in turn accommodates the volume overload of aortic regurgitation poorly. Post-TAVR aortic regurgitation is usually paravalvular and stems either from residual annular calcium that prevents proper valve seating or from the fact that the TAVR is geometrically round whereas some aortic annuli are more oval. An obvious solution is to develop a valve that can conform more easily to the patient’s annulus, but how such a valve can be constructed is still unclear.

Durability

For the patients currently undergoing AVR in PARTNER, the presence of severe comorbidities makes it likely that the patient will succumb to those illnesses before the structural valve deterioration that sometimes accompanies biological
valves becomes an issue. However, if implantation becomes common in less afflicted patients, valve durability will become an important variable. So far, no tendency toward early deterioration has been detected, but only the passage of time can give us a true appraisal of the durability of TAVR.

**Extension of TAVR to Lower-Risk Patients: Implications for the Referring Cardiologist and the Role of the Heart Team**

The experience with TAVR demonstrated in PARTNER represents an early experience with a technique that used a large delivery device in very ill patients. Inevitably, technology will advance and delivery will become more miniaturized and more facile, presumably leading to fewer complications during insertion. As availability becomes common knowledge to our patients, there will be a greater demand from them for this less invasive technique. How will we proceed? Will we push beyond the scope of the data, using TAVR for progressively less stringent indications while waiting for new data to become available, forgetting the proven track record of SAVR? Or will we act responsibly, weighing risk and benefit from the data we have at hand?

In my view, the best way to give our patients the best advice is to use what I call the “tumor board” strategy. When a patient presents with cancer, practitioners of the 3 major treatment modalities—radiation oncology, surgical oncology, and medical oncology—view the specifics of the case together and, using existing data, decide formally as a group called a tumor board on which treatment strategy is best for the patient. This concept translated to mechanical therapy for valvular heart disease is often referred to as a heart team, but the concept is the same. Cardiac surgeons, vascular surgeons, interventional cardiologists, referring cardiologists, and imagers view the case together and by consensus decide on the best therapy for the patient. This strategy simultaneously provides the patient the benefit of a wealth of experience not available from any 1 specialist while avoiding the potential bias of self-interest. If we move forward in this fashion, we will give our patients the best therapy while using the exciting outcome of PARTNER to its fullest potential.

**Disclosures**

None.

**References**


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