Implications of Contemporary Clinical Trials

The Placement of Aortic Transcatheter Valve (PARTNER) Trial
Clinical Trialist Perspective

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For several decades, surgical aortic valve replacement (sAVR) has been considered the therapeutic gold standard for the treatment of severe aortic stenosis (AS). Severe AS is a progressive disease with a long latency period, and despite significant strides in medical therapy for numerous other forms of cardiovascular disease, little progress has been made in medical therapy for AS. The mechanical effects of aortic valve obstruction induce burdensome hemodynamic consequences that are the sine qua non of severe AS. Thus, particularly in patients with comorbid conditions who are at high risk for complications with traditional sAVR, untreated AS was conventionally viewed as a terminal condition for patients refusing high-risk sAVR or those deemed not operative candidates by treating physicians.

The publication of the 1-year outcomes from the 2 cohorts of the Placement of Aortic Transcatheter Valve (PARTNER) Trial1,2 has redefined this conventional wisdom. The PARTNER trial established the alternative use of a novel, less invasive procedure, transcatheter aortic valve replacement (tAVR), in the sickest patients with AS. In patients deemed at high risk for standard sAVR and with similar rates of 1-year all-cause mortality compared with sAVR (24.2% versus 26.8%; \( P = 0.001 \) for noninferiority). In patients deemed not to be candidates for surgery (cohort B), tAVR was superior to standard therapy with reduced 1-year all-cause mortality (30.7% versus 50.7%; \( P < 0.001 \)). It is not often in clinical medicine that an early-stage less invasive technology demonstrates life-altering and life-saving impact on a common disease. Thus, it is instructive to examine several of the unique attributes of the landmark PARTNER trial that firmly established the evidence base for the role of tAVR in the treatment of AS. We focus here on a selected number of interesting facets of the trial from a clinical trialist’s perspective.

Power Calculations and Use of a Weighted Coprimary End Point

For any randomized trial, the power and sample size calculation are critical determinants of the overall success of the trial and the interpretation of findings. For PARTNER (particularly for patients in cohort B, a cohort of patients at such a high risk that very limited applicable published data were available to predict outcomes),3 the assumptions on overall event rates were difficult to validate a priori. Moreover, particularly for a study with a primary end point of all-cause mortality and enrolling a projected 650 patients based on a noninferiority assessment in cohort A and only 350 patients based on a superiority assessment in cohort B, the power of the study hinged on the accuracy of the projected event rates, which were significantly greater than those observed in most other contemporary trials in cardiovascular disease.

It is remarkable that given the limited contemporary data available in the PARTNER-like population of patients with AS, the actual event rates closely mirrored the projected rates (Table 1). For cohort A, event rates were 16% lower than expected, but given the absolute noninferiority margin of 7.5% on a baseline sAVR arm event rate of 26.7%, this represents a 28% relative margin for the upper limit of the 95% confidence interval of the treatment effect, which falls within accepted standards for noninferiority. For cohort B, there was a greater-than-expected overall event rate, which further increased the power of the study because power is more directly determined by the number of events rather than the total number of enrolled patients in a study. (In fact, in light of the admitted uncertainty in these projected rates during the design phase of the study, the protocol specified that a minimum of 150 deaths would have to be observed before enrollment was stopped, a useful way of avoiding underpowering the study.) The correlation between observed and expected event rates within PARTNER validates the sample size calculations that were made prior to study initiation. It also lends more credibility and confidence to the overall observed effect sizes for the primary end point of all-cause mortality in cohort B: a 20% absolute reduction with tAVR over standard therapy (which equates to a number needed to treat of 5 patients with tAVR to prevent 1 death in the first year after randomization).

In addition to prespecifying the total number of required events for cohort B, the PARTNER investigators included a coprimary composite end point for the trial: the hierarchical (or weighted) occurrence of all-cause death or repeat hospitalization for valve-related adverse events (especially wors-
Part of Death or Repeat Hospitalization in Cohort B of the PARTNER Trial

The unique attribute of this methodology is that time to death is prioritized (or weighted higher) over time to repeat hospitalization. This approach is relatively novel among trials in cardiovascular disease. The Finkelstein-Schoenfeld method, or an extension of this methodology as proposed by Pocock et al,6 performs a pairwise comparison of randomized patients (every tAVR patient is compared with a standard therapy patient), and the time to each specific component outcome is compared for each pair. The unique attribute of this methodology is that time to death is prioritized (or weighted higher) over time to repeat hospitalization (Table 2). The statistical significance of these pairwise comparisons can be assessed with a nonparametric test.

The findings of this analysis within PARTNER (P<0.001 for the comparison) bolstered the overall study findings and were consistent with the more conventional approach assessing the nonhierarchical composite of death or repeat hospitalization. Despite the attractiveness of the Finkelstein-Schoenfeld approach, the application of this methodology to future cardiovascular clinical trials depends to some extent on whether issues of interpretation (and the ability to graphically depict the results of such an analysis) can be resolved.

**Patient Selection and Standardization of Study Screening and Enrollment**

Another unique aspect of PARTNER related to the accurate assessment of patient risk that ultimately determined the eligibility of screened patients who were enrolled in the trial. Risk assessment was critical in PARTNER for 2 primary reasons: (1) the reliance of statistical power of the trial on accurate event rates (mortality) requiring the enrollment of only high-surgical-risk patients and (2) addressing the increasing awareness and demand for the tAVR procedure (as opposed to either standard therapy or sAVR) by patients and their referring physicians. There are several validated models of risk assessment for patients undergoing sAVR, yet these models were derived from cohorts of patients with substantially lower operative risk than those being considered for PARTNER. Additionally, more recent studies have demonstrated their limited use among patients undergoing tAVR.7,8 Thus, although the PARTNER protocol explicitly specified the overall risk categories of patients eligible for either cohort A or B, further efforts were necessary to limit treatment creep and to ensure sufficient patient risk within the trial.

Several novel trial processes were implemented in PARTNER both at the local (site) level and across sites at the Executive Committee level. Before randomization, all potential candidates were evaluated at each enrolling center by a collaborative team of physicians, the so-called heart team. Importantly, the explicit collaboration between these coprincipal investigators (a designated interventional cardiologist and a designated cardiac surgeon) at each site was formalized a priori in the design phase of PARTNER as expressed in the protocol and as administered through the site selection process by the sponsor and executive committee. For patients eligible for cohort A, the site coprincipal investigators had to concur that the predicted risk of operative mortality was ≥15% with a minimum Society of Thoracic Surgeons risk score of 10 (later changed to 8). For selected patients not meeting the Society of Thoracic Surgeons risk score criteria, at least 2 surgeon-investigators (not including the enrolling surgeon) were required to document that the patient’s predicted risk of operative mortality was ≥15%. Patients eligible for cohort B required formal agreement by a cardiologist and 2 cardiovascular surgeons that medical factors precluded operation based on a documented conclusion that the probability of death or serious, irreversible morbidity exceeded the probability of meaningful improvement (probability of death or serious, irreversible morbidity >50%). This definition of inoperable patients was devised by consensus within the physician Executive Committee and was meant to characterize a patient population deriving more risk (death or irrevers-
urable morbidity) than benefit from the standard treatment (sAVR). The requirement for close collaboration of treating physicians as formalized within the PARTNER protocol was a clinical trial process originally implemented to ensure rigorous study conduct and sufficient patient risk within the trial. However, this team-based process, as implemented within PARTNER and other recent trials, has subsequently evolved to encapsulate a paradigm shift toward disease-based systems of care for patients with advanced cardiovascular disease even outside clinical trials. It was in fact recently embraced in a consensus document on tAVR released by 4 leading interventional and surgical societies.  

Beyond the fostering of a local collaborative approach in PARTNER, additional novel advances in information technology were implemented in PARTNER to further standardize clinical trial processes across sites. After site-based assessments of patient eligibility, twice-weekly conference calls were conducted by the study Executive Committee to review and approve the selection of individual patients considered for randomization. In these calls, baseline characteristics of every eligible patient, including Society of Thoracic Surgeons risk scores (with relevant subcomponents) and relevant imaging studies (with actual images of echocardiographic, computed tomographic, and angiographic data), were shared through the use of an Internet-based Web conference methodology. These important but time- and labor-intensive Web calls facilitated standardization of study processes across sites to a degree not previously observed in clinical trials. Specific aspects addressed at various points during these screening calls included (1) standardizing the more subjective aspects of the inclusion/exclusion criteria, (2) standardizing vascular access screening and determining the patients not suitable for femoral arterial access, (3) addressing concomitant coronary artery disease and the need for revascularization, (4) assessing echocardiographic and computed tomography–based annulus sizing and eligibility for the available investigational devices, and (5) making suggestions to the site operators based on the collective shared experience of the executive committee for ways to improve the safety and efficacy of the scheduled procedure (both tAVR or sAVR).

The use of collaborative team-based study processes in PARTNER unquestionably improved the standardization of risk assessment and study conduct within the trial. In addition, implementation of these evaluative processes before enrollment likely also limited the number of study withdrawals and unsanctioned crossovers, especially in the control sAVR and standard therapy arms. During the period of recruitment within PARTNER, there was accelerating patient and physician demand for tAVR procedures because of accumulating favorable results and subsequent approval of tAVR outside the United States. Nonetheless, the rate of crossover in cohort B from standard therapy to either non-protocol tAVR (outside the United States) or high-risk sAVR was only 11.7%. Furthermore, in cohort A, only 6.0% of randomized patients did not undergo the assigned procedure (10.8% in the sAVR arm). It can be argued that without assiduous attention to risk assessment, screening, and enrollment before randomization, greater numbers of patients would have either withdrawn (especially for cohort A) or been treated outside the protocol (for cohort B).

Summary of the Real-World Implications of a Clinical Trial Evaluating a Novel Disease-Altering Therapy

As 2 individually powered parallel multicenter randomized clinical trials, the overall PARTNER experience represents the highest standard of clinical evidence demonstrating the relative value of tAVR for the treatment of severe symptomatic AS. The presentation and publication of the PARTNER trial results were met with worldwide acclaim and allowed many patients with previously untreatable or high-surgical-risk AS to be evaluated and treated with tAVR. Thus, PARTNER has satisfied the primary goal of a well-designed clinical trial: to assist in the objective evaluation of therapeutic alternatives with the aim of improving clinical outcomes and quality of life for patients. Through implementation of rigorous study processes in both the design and analysis phases of the trial as described above, the results appear robust and credible. Yet, although these and other trial processes no doubt contributed to the overall rigor and subsequent effectiveness of the PARTNER trial, it has been argued that to replicate the results of the PARTNER investigators in a real-world patient population, replication of the site selection process, training requirements, and collaborative study processes will be required. Thus, going forward, the clinical real-world applicability of the PARTNER results will be examined closely because this is the ultimate charge that follows after completion of all randomized trials: to demonstrate that the high standard of clinical evidence established within the trial can subsequently be translated into routine clinical practice.

Disclosures

Dr Leon is a member of the executive committee of PARTNER (unpaid). Dr Kirtane reports no conflicts.

References


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