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EDITORIAL COMMENT

Mortality in the PARTNER Trials

Transfemoral Is Better*

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Severe aortic stenosis (AS) is the most frequent form of valvular heart disease in Western countries, and symptomatic AS has become an increasing health problem for their growing elderly populations. The lethality of symptomatic AS has been recognized for decades; it has a high and rapid rate of mortality in untreated patients that approaches 50% over the first 2 years (1). Aortic valve replacement (AVR) is still the current gold standard of treatment for these patients; it has been proven to prolong and improve quality of life in good operative candidates and can be performed with acceptable mortality in elderly patients. However, surgery is often prohibitive in patients with multiple or severe comorbidities and high operative risk (2).

The PARTNER (Placement of AoRTic TraNscathetERValve Trial Edwards SAPIEN Transcatheter Heart Valve) trials were a fundamental breakthrough in this field. The PARTNER-B trial investigated the safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients deemed unsuitable for surgical AVR by randomizing inoperable patients with severe symptomatic AS to medical therapy or TAVR (3). In the PARTNER-A trial, patients who had severe, symptomatic AS and were considered to be at high risk for surgery were randomized to TAVR or standard AVR (4). TAVR was far superior to medical therapy in the PARTNER-B trial and was not inferior to surgery in the PARTNER-A trial.

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In this issue of the *Journal*, Svensson et al. (5) compare when and how deaths occurred in both the PARTNER-A and PARTNER-B trials. A total of 3,105 patients were evaluated for potential inclusion in the PARTNER trials; 699 patients were considered to be at high risk for open surgery (PARTNER-A trial), and 358 patients were considered inoperable (PARTNER-B trial). Before randomization, it was determined whether each patient was suitable for a transfemoral (TF) approach (n = 244) or a transapical (TA) approach (n = 104), depending on vascular access. In addition, 351 patients were randomized to AVR. The baseline patient characteristics were similar among the subsets in the PARTNER-A trial and between the treatment arms in the PARTNER-B trial. Median follow-up was 2 years and 1.3 years for patients in the PARTNER-A and PARTNER-B trials, respectively. Deaths were categorized as cardiovascular, noncardiovascular, or uncategorizable.

In the PARTNER-B trial, the rates of death were 56.9% in the TAVR group and 75.4% in the standard therapy group; the corresponding rates of cardiac death were 39.2% and 49.6%, respectively. There was an early peak of instantaneous risk of death among patients randomized to standard therapy that was prolonged beyond 6 months, possibly related to balloon aortic valvuloplasty (BAV). In fact, 114 patients assigned to standard therapy underwent BAV during the 30 days after randomization and 36 patients underwent BAV more than 30 days after randomization. Patients who underwent BAV, compared with those who did not, appeared to have more favorable outcomes for at least the first 6 months after randomization to standard therapy (6). Regardless, the patients in the standard therapy group remained at considerably higher risk compared with the general population throughout the 2.5 years of follow-up, and the instantaneous risk of cardiovascular death remained elevated well above the risk after randomization of patients to TAVR. Patients

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treated with TAVR had markedly improved overall survival compared with standard therapy. Survival diverged between the 2 trial arms within 30 to 60 days, and the gap widened thereafter. The net lifetime added by TF-TAVR over standard therapy was on average a half-year within 2.5 years of randomization. When considering the magnitude of the reduction in mortality seen after TAVR, absolute mortality remained a sobering 56.9% after a median follow-up of 1.3 years. Therefore, it would be worthwhile to identify the patients excluded from surgery who would derive little or no long-term benefit from TAVR due to coexisting conditions or comorbidities that would limit their life expectancy. In a subgroup analysis of mortality outcomes according to surgical risk (on the basis of Society of Thoracic Surgeons [STS] score) by Makkar et al. (6) on 2-year data, the mortality benefit with TAVR decreased with increasing STS score. Therefore, TAVR should be considered the standard of care for selected inoperable patients with an expected survival commensurate with or better than that of the general population. On that basis, the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease (7) recommends TAVR for high-risk patients with severe symptomatic AS who are unable to undergo surgical AVR because of a prohibitive surgical risk to improve survival and reduce symptoms (Class I, Level of Evidence: B).

In the PARTNER-A trial, the rates of death were lower with no significant difference between the surgery group (39.6%) and the transcatheter group (39.0%); however, there was a difference in overall mortality between the TF-TAVR group (36.9%) and the TA-TAVR group (44.2%). The corresponding rates of cardiac death were 36.7% in the TF-TAVR group, 21.7% in the TA-TAVR group, and 33.1% in the AVR group. The TA-TAVR group had 37% uncategorized deaths. The instantaneous unadjusted risk of death peaked early after randomization in both the AVR and TA-TAVR groups, falling within 3 to 6 months to a low level commensurate with that of matched U.S. population estimates; conversely, the instantaneous risk of death of TF-TAVR was only modestly elevated from the date of randomization. This pattern of early risk resulted in separation of TF-TAVR survival curves from those of AVR and TA-TAVR. The conditional probability of dying was higher with the surgical approach and lower with transcatheter procedures, mostly if performed with the TF approach. The treatment effect was greater in the first 30 days. After the first month, only a slight difference was seen, with confidence intervals quite comparable in width. Interestingly, patients undergoing surgical procedures and patients undergoing TA-TAVR were at higher risk for noncardiovascular events. Twenty patients died between randomization and the procedure, including 3 patients assigned to TAVR (1 patient assigned to TA-TAVR) and 17 patients assigned to AVR, but only 7 of these patients died within the first 30 days after randomization. Considering that patient allocation was performed using a random process and baseline features were matched to prevent selection bias, it should be inferred that the increased noncardiovascular mortality was related to the surgical and TA approach; although the early risk of cardiovascular death was higher with TF-TAVR, it was related to periprocedural factors and probably due to the difference between access sites. The TA procedure is performed via an anterolateral minithoracotomy in the fifth or sixth intercostal space to obtain straight access to the left ventricular apex. Notably, 15% of all deaths in patients undergoing TA-TAVR were related to respiratory failure, which was significantly higher than with TF-TAVR (3.3%) and AVR (6.4%). In addition, the use of the TA approach involves the puncture and the introduction of a large catheter through the ventricular apex (≥24-F, with external diameter ≥7.9 mm). This has been associated with a greater increase (up to 4 times higher) in cardiac biomarkers of myocardial injury with the presence of significant myocardial necrosis at the level of the left ventricular apex in such patients as well as less improvement in left ventricular ejection fraction during follow-up (8). As a result, 0.13 year of lifetime was gained within 2.5 years by TF-TAVR over AVR, 0.22 year by TF-TAVR over TA-TAVR, and 0.087 year by AVR over TA-TAVR. The PARTNER-B trial supports the use of TAVR as an alternative to surgery in selected high-risk patients with AS, and the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease (7) recommends the use of TAVR as a reasonable alternative to surgical AVR but restricted to patients with a high-risk surgical profile given the limited known long-term outcomes and valve durability (Class IIa, Level of Evidence: B).

In patients at high risk for surgery, TA-TAVR and AVR were associated with elevated periprocedural risk more than TF-TAVR, particularly for noncardiovascular death. Therefore, when feasible, TF-TAVR should be considered a less invasive approach and the standard of care for the implantation of balloon-expandable transcatheter aortic bioprosthesis. In the near future, with improvements in valve and sheath technology, more and more patients with a

lower risk profile will most likely be treated with TF-TAVR. However, it is still important to evaluate whether other proximal, less invasive, alternative approaches to TF-TAVR, such as axillary and direct aortic approaches, will lead to better results than TA-TAVR.

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