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EDITORIAL COMMENT

3-Year Results of a TAVR Trial in High Surgical Risk Patients*

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For decades, surgical aortic valve replacement (SAVR) was the only durable approach available for the management of patients with severe aortic stenosis. The introduction of transcatheter aortic valve replacement (TAVR) in 2002 was a huge advance in the field and rapidly became the standard of care for inoperable/extreme risk patients (1-4).

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The PARTNER (Placement of Aortic Transcatheter Valves) trial was first to directly compare TAVR to SAVR head to head in high surgical risk patients. At 1 year, TAVR with the balloon-expandable Edwards Sapien valve (Edwards Lifesciences, Irvine, California) was noninferior for mortality compared with SAVR in this patient cohort (24.2% vs. 26.8%; $p = 0.001$ for noninferiority) (5). This was maintained at 5 years of follow-up (67.8% vs. 62.4%; $p = 0.76$) (6). Next came the CoreValve US Pivotal trial, comparing outcomes following TAVR with the self-expanding Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) to SAVR, the 3-year results of which are reported in this issue of the *Journal* by Deeb et al. (7). Briefly, patients with severe symptomatic aortic stenosis, who had an estimated 30-day mortality of ≥15% and a combined mortality and morbidity of <50%, were enrolled in this trial.

It is helpful to look at some key issues and differences that are highlighted by this landmark trial.

1. *All-cause mortality*: At 1 year, all-cause mortality was lower in the TAVR arm compared with SAVR (14.2% vs. 19.1%; $p < 0.001$ for noninferiority, $p = 0.04$ for superiority) (8). At 2 years, mortality was still lower with TAVR (22.2% vs. 28.6%; $p = 0.04$) (9). At 3 years, the difference is no longer statistically significant (32.9% vs. 39.1%; $p = 0.07$) (7). The initial superiority finding had been exciting yet surprising, and although numerous mechanisms had been suggested, none were felt to be entirely convincing (10). Even as we await longer-term results, the current 3-year results suggest that the finding may have been due to chance. Further, although landmark analyses are not provided, the curves and event rates appear to be fairly parallel after the 3- to 4-month mark. Nonetheless, even the finding that the 2 procedures are similar for mortality to 3 years is a big win for the field itself.

2. *Stroke*: At 1 year, stroke rates for TAVR versus SAVR were 8.8% versus 12.6% ($p = 0.10$) (7); at 2 years, rates were 10.9% versus 16.6% ($p = 0.05$) (8). Now, at 3 years, stroke rates are further lower in the TAVR arm (12.6% vs. 19.0%; $p = 0.03$). The curves continue to diverge over the 3-year follow-up period (7). In the PARTNER trial, comparable 3-year stroke rates for balloon-expandable TAVR versus SAVR were 8.2% versus 9.3% ($p = 0.76$) (11). Although not directly comparable across trials, these are impressive differences (~6.4% absolute difference between CoreValve TAVR and SAVR and ~10% absolute difference between the surgical arms of the 2 trials), and the reasons for the same will need to be clearly delineated in the future.

3. *New permanent pacemaker implantation*: Because this is felt to be due to a direct effect of the prosthesis on the conduction system, one would expect the rates to be highest in the periprocedural period. Indeed, the rates of permanent pacemaker implantation were highest within 30 days for TAVR compared with SAVR (19.8% vs. 7.1%; $p < 0.001$), and

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then stayed high at 1 year (22.3% vs. 11.3%; $p < 0.001$), 2 years (25.8% vs. 12.8%; $p < 0.001$), and now 3 years (28.0% vs. 14.5%; $p < 0.001$). Taking into account that ~22% of the study population was enrolled with an existing permanent pacemaker, these data suggest that 1 of every 2 CoreValve TAVR patients will likely have a pacemaker 3 years after the procedure. This drives up overall costs and resource utilization during index hospitalization (12), and may impact right ventricular function in the long term (13). This is an important consideration for physicians when choosing between the 2 strategies, particularly as the field moves toward TAVR in intermediate and lower-risk populations. A gradual yet tenacious need for pacemaker implantation beyond the initial 30-day period may have also have implications for routine screening protocols in patients receiving both TAVR and SAVR.

4. *Valve performance*: Very importantly, valve performance and hemodynamics were maintained over 3 years of follow-up. Mean gradient and effective orifice area were both better in the TAVR valves compared with SAVR. There was no evidence of clinical valve thrombosis or structural valve degeneration in either valve at 3 years. Given that the median lifespan of surgical bioprosthetic valves in this patient population is 10 to 15 years, longer-term follow-up of the TAVR valves is keenly awaited (14,15). This will be particularly important for lower-risk populations, where the risk of mortality from competing hazards will be significantly lower than noted in the current (CoreValve) and PARTNER trials.

Moderate to severe aortic regurgitation was mostly paravalvular in nature in the TAVR arm, and it remained at 5% to 8% from discharge through 3 years. At first glance, this suggests that paravalvular regurgitation rates were stable over time. However, there is progressive attrition in the sample size over the duration of follow-up due to a combination of death and missing 3-year follow-up data. Thus, a more accurate representation might be a composite of moderate to severe paravalvular regurgitation or death over time. Symptom benefit and outcomes are felt to be worse in patients with significant regurgitation following TAVR (16).

Long-term studies of rapidly evolving technologies can often be a Sisyphean task because the device studied may be outdated or iterations behind clinical practice by the time the follow-up is completed. This is true for this trial as well, because the current commercially available CoreValve platform (Evolut R, Medtronic Inc.) has several modifications over the platform studied here, such as smaller sheath size, recapturability, and an extended sealing skirt, which were specifically devised to address some of the limitations observed here. Clinical practice has also evolved because the design of this trial, and most TAVR operators today would not leave the procedure room without addressing severe paravalvular regurgitation following implantation (17).

The vast majority of cardiac surgeons have embraced TAVR as the go-to approach for high surgical risk patients, which has enabled a greater dispersion of this technology to patients that would have otherwise been turned down or had high perioperative mortality and morbidity (18). Overall, both TAVR and SAVR remain very good options for the management of complex aortic stenosis patients and the heart team approach ensures that the best possible decision is made for every patient, based on a sound understanding of each procedure's strengths and weaknesses. The 3-year CoreValve data presented here are thus a big step toward enabling this patient-centered, personalized decision-making process for the heart team. The biggest winner is the patient.

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