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EDITORIAL COMMENT

Conduction Abnormalities

The True Achilles' Heel of Transcatheter Aortic Valve Replacement?*

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Transcatheter aortic valve replacement (TAVR) has entailed a paradigm shift in the treatment of heart valve diseases. During the past decade we have witnessed a great technological development in the field of TAVR, as well as a marked improvement in the patient selection process, which have translated into progressive reductions of the main complications, including stroke, paravalvular leaks, vascular complications, and mortality (1). Concurrently, the use of TAVR has been expanded from patients ineligible for surgical aortic valve replacement to patients at lower risk (2), and the clinical indications have been broadened. Nowadays, TAVR is approved in the United States and Europe for the treatment of patients at intermediate risk, and several ongoing studies in patients at low surgical risk will determine whether this therapy may become the first-line treatment for severe aortic stenosis.

However, the high rate of conduction abnormalities post-TAVR remains a concern and probably represents one of the main limitations of this treatment compared with cardiac surgery. While the predictors of new-onset conduction abnormalities have been extensively studied, little is known about the specific predictive factors of these complications in patients receiving newer-generation devices. In addition, the real clinical effect of conduction abnormalities and the need for permanent pacemaker (PPM) implantation following TAVR remain controversial. Although limited data suggest a potential effect on mortality, studies assessing the outcomes of conduction abnormalities after TAVR have yielded conflicting results (3). Unfortunately, to date, no specific features have been incorporated into transcatheter heart valve (THV) systems to reduce the risk for these complications. On the contrary, an increased rate of conduction abnormalities has been reported associated with the use of most newer THVs, suggesting that the clinical relevance of these complications may increase in the near future (3).

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In this issue of *JACC: Cardiovascular Interventions*, 3 studies shed new light on post-TAVR conduction abnormalities. In the first study, Mauri et al. (4) looked carefully at the technical and anatomic predictors of PPM implantation in patients receiving the SAPIEN 3 THV (Edwards Lifesciences, Irvine, California). A total of 33 of 229 patients with no previous pacemakers (14.4%) received PPMs following the TAVR procedure. In addition to the presence of pre-existing right bundle branch block (RBBB), important calcification of the left ventricular outflow tract at the level of the left and right coronary leaflets and a deep implantation of the valve, defined as >25.5% of the stent frame below the aortic annulus at the level of the posterior leaflet on angiography (odds ratio: 15.7; $p < 0.001$), were independent predictors of PPM implantation. Importantly, patients with none of these risk factors had a rate of PPM placement of 1.1%, and reducing the depth of valve implantation by 3 mm resulted in a decrease of 52% in the need for PPM, without increasing the incidence of paravalvular leaks. Although other technical changes may have influenced such results, this study suggests that the increased rate of PPM

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implantation with the SAPIEN 3 THV appears to be driven mainly by technical rather than device-related factors and that significant reductions in the rate of PPM implantation can be obtained by modifying the implantation technique. The confirmation of these results in larger multicenter studies will represent a major step forward in reducing the rates of PPM associated with this new THV. However, the potential risks (i.e., valve embolization) of a high (more aortic) valve implantation strategy should not be underestimated.

The second study, by Fadahunsi et al. (5), is an analysis of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, evaluating the clinical effect of PPM implantation post-TAVR. TAVR was performed in 9,785 patients with no previous PPMs and 651 patients (6.6%) needed a PPM post-TAVR. Patients receiving PPMs had slightly longer hospital (7 days vs. 6 days; $p < 0.001$) and intensive care unit (56 h vs. 45 h; $p < 0.001$) stays. In addition, PPMs were associated with an increased risk for all-cause mortality (24.1% vs. 19.6%; hazard ratio: 1.31; $p = 0.003$) and the composite endpoint of mortality and admission for heart failure (37.3% vs. 28.5%; hazard ratio: 1.23; $p < 0.001$) at 1 year. These results are in agreement with those reported in a substudy of the PARTNER (Placement of Aortic Transcatheter Valves) trial (6) and will likely place PPM implantation post-TAVR at the eye of the storm. However, several important limitations of this study should be highlighted. First, patients receiving PPMs were older and more frequently were male and exhibited pre-procedural conduction abnormalities and severe comorbidities, leading to a higher risk profile. Although the results were adjusted, they may still be biased by potential residual confounding. Second, administrative data may have limitations regarding the allocation of events. In addition, although missing data were treated using multiple imputation techniques, the rate of missing data (in particular missing outcomes) is not reported. Third, the rate of PPM implantation in this study is strikingly low, especially in the subgroup of patients receiving balloon-expandable valves (4.3%). Reasons for this very low rate of PPM implantation, one-half of that observed in the PARTNER 1 and 2 trials (~8.5%) (6,7), are not fully understood. Fourth, and importantly, no data are provided regarding causes of death, types of pacemakers, and long-term pacing rates.

A recent meta-analysis including more than 7,000 patients (8) and the majority of previous studies of TAVR did not find a negative effect of PPM implantation after TAVR or cardiac surgery in all-cause mortality (9–12). Moreover, longer periods of follow-up (definitely longer than 1 year) have been necessary to detect the detrimental effect of long-term pacing in patients with heart failure (13). Considering that patients receiving PPMs in this study had a higher risk profile, one might speculate that the need for a PPM could be a marker rather than a cause of increased mortality. Such a hypothesis might be supported by the findings of the third study published in this issue regarding conduction abnormalities and TAVR. Watanabe et al. (14) evaluated the prognostic effect of pre-existing RBBB in patients undergoing TAVR in a substudy of the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention) registry. Of 749 patients included, 102 (13.6%) had pre-existing RBBB. The main baseline characteristics and procedural complications were similar in both groups except for the prevalence of cerebrovascular disease, the rate of life-threatening bleeding, and the rate of PPM implantation, which were higher in the RBBB group. Patients with pre-existing RBBB had a trend toward a lower 30-day survival rate (96.0% vs. 98.6%; $p = 0.09$). At 1-year follow-up, patients in the RBBB group had a higher rate of all-cause mortality (18% vs. 9%; $p = 0.03$) and cardiovascular mortality (10% vs. 3%; $p < 0.01$) and pre-existing RBBB was an independent predictor of cardiovascular mortality (hazard ratio: 2.59; $p = 0.021$). Interestingly, patients with RBBB and without PPMs were at higher risk for cardiovascular mortality in the early phase after discharge, whereas patients with RBBB receiving PPMs had higher mortality in the midterm outcomes. No increased cardiovascular mortality was observed in patients receiving PPMs without RBBB. Although multiple prior studies have already identified the presence of RBBB as the main factor determining the need for PPM post-TAVR (3), this study highlights the potential role of this conduction disturbance in increasing the rate of major adverse events and underscores the need for further studies in TAVR candidates with pre-existing conduction abnormalities, particularly RBBB. However, it should be noted that the study was not powered for this analysis of subgroups, and these results need to be interpreted with caution.

These studies provide new insight into the conundrum of conduction abnormalities in TAVR. If confirmed, these results urge engineers, device manufactures, and physicians to make efforts to reduce the rate of PPM implantation after TAVR. In some cases, this may be at the price of longer hospitalization. In addition, in patients at very high risk for PPM (e.g., those with RBBB), surgical aortic valve replacement may be considered. However, much

remains to be elucidated. Future studies should determine the causes of death in patients receiving PPMs after TAVR, identify patients at higher risk for poorer outcomes, and determine the potential benefit of resynchronization therapies, new pacing algorithms, and new type of pacemakers. Meanwhile, the outcomes of patients requiring PPMs post-TAVR should be scrutinized in ongoing trials including patients who are at low surgical risk.

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