The Conundrum of Permanent Pacemaker Implantation After Transcatheter Aortic Valve Implantation

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Transcatheter aortic valve implantation (TAVI) has matured into the preferred treatment modality for patients with severe aortic stenosis at extreme or high risk for conventional surgery and a valuable alternative for those at intermediate risk in view of similar or superior clinical outcomes and decreased rates of periprocedural adverse events.1-3 In this context, it remains unclear whether other procedure-related events—including atrioventricular conduction disturbances that require permanent pacemaker (PPM) implantation—are of prognostic relevance.

See Article by Mohananey et al

In the natural history of aortic stenosis, variable degrees of heart block may occur with calcium deposits expanding progressively from the left ventricular outflow tract to the atriocventricular conduction system. As matter of fact, a PPM is already present in ≈10% to ≈20% of patients with severe aortic stenosis at the time of transcatheter or surgical intervention.4 Because of its proximity to the aortic root, iatrogenic injury to the atriocventricular conduction system also occurs after surgical bioprosthesis implantation, with comparable PPM rates for TAVI and surgery reported in the PARTNER trials (Placement of Aortic Transcatheter Valves).2,5 Several patient- and procedure-related factors have been associated with PPM implantation after TAVI and include advanced age, male gender, atrial fibrillation, calcification of aortic and mitral annulus, small left ventricular outflow tract, pre-procedural or intra-procedural conduction disorders, balloon pre-dilation, and depth of prosthesis implantation.6,7 In addition, the type of transcatheter bioprosthesis plays an important role with rates of PPM implantation progressively increasing from balloon-expandable prostheses over self-expanding prostheses to mechanically deployed prostheses.8 Along this line, outer skirts and adaptive seals surrounding the inflow portion, designed to reduce paravalvular leaks, as well as features that allow for repositionability of the device within the aortic annulus, may modify the risk of atriocventricular conduction disturbances after TAVI.

Despite our present understanding of the putative mechanisms and predictors of PPM implantation after TAVI, the impact of this complication on clinical outcomes remains subject of debate. Among patients included in the PARTNER trial and registries, the presence of PPM (implanted prior or after TAVI) was independently associated with 1-year mortality.7,9 Similarly, periprocedural PPM implantation increased the risk of mortality and a composite of mortality and hospitalization for heart failure among 9785 patients included in the US Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy (TVT) registry.10 At variance with these studies, long-term survival after TAVI was unaffected by PPM implantation in most other reports.11,12

In this issue of Circulation: Cardiovascular Interventions, Mohananey et al13 provide more clarity by presenting new data of a meta-analysis including 23 studies with 20,287 patients who underwent TAVI stratifying outcomes by the need for new PPM implantation after the intervention. As important strength of the present analysis, patients with PPM implantation before TAVI were excluded. At 1-year follow-up, the risk of the primary outcome of all-cause mortality was not significantly increased among patients who received PPM (risk ratio, 1.03; 95% confidence intervals [CI], 0.92-1.16). Similarly, the risks of cardiovascular mortality, myocardial infarction, and stroke were comparable between patients requiring PPM implantation or not. However, patients without PPM implantation experienced a significantly greater improvement in left ventricular ejection fraction (standardized mean difference, 0.22; 95% CI, 0.12-0.32).

Despite these reassuring findings, some observations on the meta-analytic approach and the individual studies deserve consideration. The investigators used crude number of events to estimate the risk ratio for clinical outcomes. Although this approach is robust in the setting of meta-analyses of randomized trials with symmetrical loss to follow-up between groups, it becomes more challenging when losses to follow-up are asymmetrical as seen, for example, in the TVT registry14 that contributed to >40% of the pooled population. When analyzed naively, as done in the present meta-analysis, the results of the study by Fadahunsi et al15 indicate no increased risk of mortality in TAVI patients undergoing PPM implantation (risk ratio, 1.04; 95% CI, 0.88-1.24); however, when a time to event analysis is used to derive hazard ratio (HR), then a clinically relevant risk increase emerges, which, as originally published, was statistically significant (HR, 1.31; 95% CI, 1.09-1.58). The asymmetry in loss to follow-up is large and unexplained, therefore results by Fadahunsi et al15 are difficult to interpret. Because this is clearly the largest study published to date, results of the meta-analysis will, therefore, depend on the decision to use risk ratio or HR

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and on the decision to include or not the study by Fadahunsi et al.\textsuperscript{10} A reanalysis of included studies using HR, when available, shows an increased risk of death in patients with PPM (pooled HR, 1.15; 95% CI, 1.02–1.29), which disappears after exclusion of the study by Fadahunsi et al.\textsuperscript{10} (pooled HR, 1.05; 95% CI, 0.91–1.22).

In addition to the different methodological approaches, other clinical aspects should be considered when assessing the clinical significance of PPM implantation after TAVI.

**Indications and Timing of PPM Implantation After TAVI**

The absence of specific recommendations for PPM implantation after TAVI explains at least in part the considerable variability on the reported indications for permanent pacing across the studies of the present meta-analysis. They include variable degrees of atrioventricular block, sinus node dysfunction with symptomatic bradycardia, atrial fibrillation with inadequate ventricular response, and left bundle branch block. Although persistent new-onset left bundle branch block has been associated with an increased risk of high-degree atrioventricular block and sudden death suggesting a protective impact of PPM implantation within the first 30 days after TAVI,\textsuperscript{14} the prognostic significance of other procedure-related conduction disturbances remains unclear. Moreover, restoration of atrioventricular conduction has been reported in up to 50% of patients who have undergone PPM implantation after TAVI.\textsuperscript{15} The resolution of edema and inflammation as a result of the traumatic injury incurred during transcatheter bioprosthesis implantation may explain the dynamic nature of TAVI-related atrioventricular conduction abnormalities in analogy to what has been observed after surgical aortic valve replacement. Societal guidelines for device-based therapy of cardiac rhythm abnormalities, indeed, recommend PPM implantation in patients with post-operative atrioventricular block only if the conduction abnormality persists at least 7 days after cardiac surgery or is not expected to resolve.\textsuperscript{16} Further efforts are needed to identify patients who benefit from PPM implantation with the analysis of factors associated with persistent pacemaker dependency and the appropriate timing.

**Impact of Pacing on Left Ventricular Function**

Chronic pacing has been associated with impaired survival and higher rates of hospital readmissions among patients with depressed or preserved left ventricular ejection fraction.\textsuperscript{17} Right ventricular apical pacing results in asynchronous electrical activation of the left ventricle resembling that of left bundle

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**Figure.** Permanent pacemaker implantation among patients undergoing transcatheter aortic valve implantation (TAVI). AV indicates atrioventricular.
branch block. Moreover, loss of atrioventricular synchrony in case of single chamber pacing is associated with important hemodynamic alterations. These factors may trigger changes in myocardial structure, impair regional perfusion, and ultimately affect left ventricular function and atrial remodeling. In addition, PPM are prone to device-specific adverse events, including lead failure that require careful long-term monitoring. The current study describes a lack of improvement in left ventricular function among patients undergoing PPM implantation after TAVI. However, it should be noted that the majority of patients had normal or preserved left ventricular ejection fraction at baseline explaining the apparent disconnection between the lack of recovery in left ventricular function in the PPM group and clinical outcomes in terms of all-cause mortality. Early reduction of left ventricular mass as result of ventricular unloading after TAVI has been associated with a reduced risk of rehospitalization for heart failure. The specific anatomic features of bicuspid aortic valve that are more prevalent among young patients may also affect the risk of pacing-induced cardiomyopathy as consequence of long-term exposure to right ventricular pacing may gain importance. The specific anatomic features of bicuspid aortic valve that are more prevalent among young patients may also affect the risk of pacing-induced cardiomyopathy as consequence of long-term exposure to right ventricular pacing may gain importance. The specific anatomic features of bicuspid aortic valve that are more prevalent among young patients may also affect the risk of pacing-induced cardiomyopathy as consequence of long-term exposure to right ventricular pacing may gain importance.

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**Future Outlook**

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The Figure provides an overview of our current understanding related to the need and impact of PPM implantation among patients undergoing TAVI and identifies areas of ongoing research efforts. In this context, the findings of the study by Mohananey et al. are an important contribution to the field because of the reassurance that PPM implantation after TAVI among octogenarians seems not to be associated with a measurable adverse impact on long-term clinical outcomes. Continued efforts should aim to refine our ability to identify patients at risk before TAVI to modify the procedure with the aim to minimize injury to the atrioventricular conduction system during the intervention, to design transcatheter aortic bioprosthetic devices that minimize the risk for periprocedural atrioventricular conduction block, and careful clinical guidance for appropriate indications for PPM implantation after TAVI.

**Disclosure**

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**References**


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