

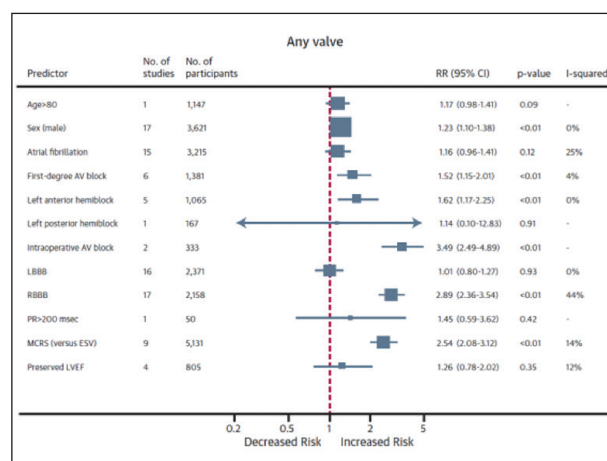
# Permanent Pacemaker Implantation After TAVR

Reviewing the current landscape of permanent pacemaker implantation post-TAVR and a look at the road ahead.

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**T**ranscatheter aortic valve replacement (TAVR) has been shown to be superior to medical therapy in inoperable patients with severe aortic valve stenosis and noninferior to surgical aortic valve replacement (SAVR) in patients at high or intermediate risk for surgery.<sup>1-4</sup> New data on TAVR in low-surgical-risk patients have also shown encouraging clinical outcomes. TAVR using a balloon-expandable prosthesis was found to be associated with significantly lower composite rates of death, stroke, or rehospitalization at 1 year,<sup>5</sup> while a self-expanding prosthesis was found to be noninferior to SAVR with respect to the composite endpoint of death or disabling stroke at 24 months.<sup>6</sup>

Despite improvements in TAVR outcomes with advanced technology, permanent pacemaker (PPM) implantation remains a frequent complication. The need for a PPM is related to conduction abnormalities arising from anatomic interaction between the valve prosthesis and the atrioventricular node and bundle of His. Clinical data regarding the impact of PPM requirement after TAVR have been disparate, with one study demonstrating reduced survival and increased hospitalization,<sup>7</sup> while another study showed no difference in mortality or heart failure at 2-year follow-up.<sup>8</sup> Although initial studies with earlier iterations of the balloon-expandable and self-expanding valves showed starkly higher PPM rates with a self-expanding prosthesis,<sup>9-11</sup> more recent data with newer-generation valves show comparable PPM rates between prosthesis types.<sup>7,12,13</sup> Several recent publications have highlighted criteria predictive of PPM implantation, including electrocardiographic, anatomic, and intraprocedural factors. As the TAVR pendulum moves toward low-risk patient populations, it is paramount to understand the causality and consequences of post-TAVR PPM implantation.



**Figure 1. Relative risks for each predictor of PPM implantation after TAVR (any valve).** Forest plot of summary crude risk ratios of each assessed predictor for patients receiving the Medtronic CoreValve Revalving System (MCBS) or Edwards Sapien Valve (ESV) prosthesis. Heterogeneity estimates ( $I^2$ ) are given for those predictors for which datasets from two or more studies were available. AV, atrioventricular; CI, confidence interval; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PR, PR interval. Reprinted with permission from Siontis GC, Jüni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVI: a meta-analysis. *J Am Coll Cardiol*. 2014;64:129-140.

## BASELINE ELECTROCARDIOGRAPHIC FACTORS

All TAVR patients should undergo preprocedural electrocardiography. The preprocedural electrocardiogram contains valuable information that may be predictive for post-TAVR PPM implantation. Post hoc and meta-analyses have examined the incidence of PPM

TABLE 1. BASELINE ECG CHARACTERISTICS PREDICTIVE OF THE NEED FOR PPM IMPLANTATION

|                                         | New PPM (n = 173) | No PPM (n = 1,800) | P Value |
|-----------------------------------------|-------------------|--------------------|---------|
| Electrocardiographic characteristics    |                   |                    |         |
| Sinus rhythm                            | 73.7              | 73.8               | .97     |
| Atrial tachyarrhythmia*                 | 22.8              | 23.6               | .82     |
| Bradycardia†                            | 4.1               | 1.5                | .02     |
| First-degree AVB                        | 18.8              | 14.4               | .12     |
| Intraventricular conduction disturbance |                   |                    |         |
| RBBB                                    | 47.6              | 12.8               | < .001  |
| Incomplete RBBB                         | 2.2               | 1.9                | .70     |
| LBBB                                    | 7.1               | 9.0                | .39     |
| Left anterior hemiblock                 | 16.5              | 8.5                | .009    |
| Left posterior hemiblock                | 0.0               | 0.1                | 1.00    |
| IVCD                                    | 3.3               | 7.4                | .14     |

Note: Values are % or mean  $\pm$  standard deviation.

Abbreviations: AVB, atrioventricular block; ECG, electrocardiogram; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; PPM, permanent pacemaker; RBBB, right bundle branch block.

\*Atrial fibrillation, atrial flutter, or atrial tachycardia.

†Sinus bradycardia, sinus pauses, or junctional bradycardia.

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implantation after TAVR based on valve type (balloon expandable vs self-expanding). In a study examining the balloon-expandable Sapien transcatheter heart valve (Edwards Lifesciences), researchers performed an as-treated analysis of 1,973 patients who underwent TAVR in the randomized PARTNER trial and continued access registry.<sup>7</sup> In a multivariate analysis, the strongest electrocardiographic predictors for post-TAVR PPM included preexisting right bundle branch block (RBBB) and left anterior fascicular hemiblock (LAFB;  $P < .001$ ) (Table 1).<sup>7</sup> A separate meta-analysis of 41 studies, which included 11,210 TAVR patients who received either a balloon-expandable or self-expanding prosthesis, showed a 17% post-TAVR PPM rate and an increased risk of PPM in men (risk ratio [RR], 1.23;  $P < .01$ ), as well as those with baseline first-degree atrioventricular block (AVB) (RR, 1.52;  $P < .01$ ), LAFB (RR, 1.62;  $P < .01$ ), and RBBB (RR, 2.89;  $P < .01$ ).<sup>14</sup> The development of intraprocedural AVB carried the highest risk (RR, 3.49;  $P < .01$ ) (Figure 1).<sup>14</sup> However, these factors only remained significant in patients who received the self-expanding CoreValve system (Medtronic), with limited data on those who received the Sapien transcatheter heart valve.

## ANATOMIC AND INTRAPROCEDURAL FACTORS

Pre-TAVR multidetector CT (MDCT) is crucial for the assessment of the aortic valve complex, left ventricular outflow tract (LVOT), and peripheral vasculature. Several patient-specific anatomic variables have been prospectively and retrospectively examined in those requiring PPM after TAVR. In recent years, the assessment of membranous septum (MS) length on pre-TAVR MDCT has been a particular focus. MS length approximates the distance between the aortic valve annular plane and the bundle of His. In a study by Hamdan et al, MDCT was used to assess MS length in 73 patients who underwent TAVR with the CoreValve self-expanding prosthesis. The reported post-TAVR PPM rate was 28%.<sup>15</sup> A multivariate logistic regression analysis of those 73 treated patients showed that MS length was the strongest preprocedural predictor of high-degree AVB (odds ratio [OR], 1.35;  $P = .01$ ) and PPM implantation (OR, 1.43;  $P = .002$ ).<sup>15</sup> Based on pre- and postprocedural parameters, the difference between MS length and valve implantation depth was shown to be the most powerful independent predictor of high-degree AVB and PPM (OR, 1.4 and 1.39, respectively;

**TABLE 2. CALCIUM VOLUME IN PATIENTS WHO REQUIRED NEW PPM IMPLANTATION (COMPARED WITH THOSE WHO DID NOT) AFTER THIRD-GENERATION BALLOON-EXPANDABLE TAVR**

| Location           | Calcium Volume (mm <sup>3</sup> ) |                     | P Value |
|--------------------|-----------------------------------|---------------------|---------|
|                    | PPM Implantation                  | No PPM Implantation |         |
| Total leaflet: all | 271.3 (186.6–398.6)               | 156.3 (69.6–299.8)  | < .001  |
| NCC                | 110.2 (44.2–226.3)                | 65.5 (26.0–150.5)   | .03     |
| RCC                | 69.5 (43.8–127.0)                 | 28.8 (10.2–77.1)    | < .001  |
| LCC                | 78.0 (28.3–152.8)                 | 42.2 (13.6–86.8)    | .004    |
| Upper leaflet: all | 243.0 (170.0–398.1)               | 143.8 (61.7–276.3)  | .001    |
| NCC                | 74.2 (40.5–185.1)                 | 60.9 (24.8–137.5)   | .95     |
| RCC                | 67.5 (43.6–124.2)                 | 26.5 (9.0–74.2)     | < .001  |
| LCC                | 71.3 (22.2–139.8)                 | 32.2 (9.4–74.4)     | .002    |
| DLZ: all           | 39.0 (16.2–86.9)                  | 14.1 (2.5–40.3)     | < .001  |
| NCC                | 17.4 (1.2–51.6)                   | 0.8 (0.0–12.2)      | < .001  |
| RCC                | 0.1 (0.0–5.0)                     | 0.1 (0.0–3.5)       | .76     |
| LCC                | 5.8 (0.4–15.1)                    | 3.6 (0.1–18.8)      | .70     |
| LVOT: all          | 11.7 (1.3–24.9)                   | 0.8 (0.0–8.6)       | < .001  |
| NCC                | 0.8 (0.0–11.9)                    | 0 (0.0–0.08)        | < .001  |
| RCC                | 0 (0.0–0.3)                       | 0 (0.0–0.0)         | .005    |
| LCC                | 0 (0.0–11.5)                      | 0 (0.0–3.7)         | .39     |

Note: Values are median (interquartile range).

Abbreviations: DLZ, device landing zone; LCC, left coronary cusp; LVOT, left ventricular outflow tract; NCC, noncoronary cusp; PPM, permanent pacemaker; RCC, right coronary cusp; TAVR, transcatheter aortic valve replacement.

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$P < .001$ ).<sup>15</sup> Thus, a shorter MS length was associated with increased PPM rates after TAVR.

A retrospective analysis of 240 patients who received the Sapien transcatheter heart valve between 2013 and 2015 demonstrated a 14.6% PPM rate, with several key findings: patients who required a new PPM after TAVR tended to have shorter MS length ( $6.4 \pm 1.7$  mm vs  $7.7 \pm 1.9$  mm;  $P < .001$ ) and a larger valve implantation depth ( $0.60 \pm 2.9$  mm vs  $2.5 \pm 2.4$  mm;  $P < .001$ ).<sup>16</sup> Additionally, in the lower regions of the aortic valve leaflets, the noncoronary cusp device landing zone calcium volume (measured in mm<sup>3</sup> on the pre-TAVR MDCT scan) is an independent predictor of new PPM requirement (Table 2).<sup>16</sup> In fact, multivariate analysis from this study showed that the combination of baseline RBBB, a low or negative valve implantation depth, and significant noncoronary cusp device landing zone

calcium volume is highly predictive of post-TAVR PPM (Table 3).<sup>16</sup>

With regard to valve sizing, oversizing does not affect new PPM rates; however, the ratio of the valve diameter to LVOT diameter has a trend toward statistical significance, with every 0.1 increment conferring a 1.29 odds increase in the likelihood of needing a new PPM ( $P = .07$ ).<sup>16</sup> Intraprocedurally, the key variable that has been shown to predict post-TAVR PPM is valve implantation depth. In a report on 867 patients treated with the Sapien transcatheter heart valve, valve implantation depth  $> 6$  mm was associated with a significant increase in new PPM (OR, 2.03;  $P = .0092$ ).<sup>17</sup> Before and during TAVR, patient-specific assessment of the risk of new PPM requirement should include all of the aforementioned variables to anticipate the risk and fully inform the patient.

TABLE 3. PREDICTIVE RISK FACTORS FOR PPM IMPLANTATION

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | AUC   | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------|-----------------|---------|---------|
| <b>Preprocedural</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |       |                 |                 |         |         |
| One risk factor                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |       |                 |                 |         |         |
| RBBB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.739 | 60.0            | 98.8            | 45.7    | 98.8    |
| MS length                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.700 | 62.9            | 70.1            | 26.5    | 91.7    |
| NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.702 | 51.4            | 80.9            | 31.6    | 90.7    |
| Two risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |                 |                 |         |         |
| RBBB + MS length                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.825 | 68.6            | 83.3            | 41.4    | 94.0    |
| RBBB + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.852 | 85.7            | 72.1            | 34.1    | 96.7    |
| MS length + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.780 | 54.3            | 92.2            | 54.3    | 92.2    |
| Three risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |       |                 |                 |         |         |
| RBBB + MS length + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.875 | 77.1            | 87.7            | 50.9    | 95.7    |
| <b>Pre- and postprocedural</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |       |                 |                 |         |         |
| One risk factor                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |       |                 |                 |         |         |
| RBBB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.739 | 60.0            | 98.8            | 45.7    | 98.8    |
| ΔMSID                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.795 | 77.1            | 75.6            | 34.7    | 94.5    |
| NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.702 | 51.4            | 80.9            | 31.6    | 90.7    |
| Two risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |                 |                 |         |         |
| RBBB + ΔMSID                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.857 | 80.0            | 87.3            | 51.9    | 96.2    |
| RBBB + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.852 | 85.7            | 72.1            | 34.1    | 96.7    |
| ΔMSID + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.864 | 74.3            | 85.8            | 45.5    | 94.6    |
| Three risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |       |                 |                 |         |         |
| RBBB + ΔMSID + NCC-DLZ CA                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.916 | 94.3            | 83.8            | 49.3    | 98.8    |
| Abbreviations: AUC, area under the curve; MS, membranous septum; ΔMSID, valve implantation depth; NCC-DLZ CA, noncoronary cusp device landing zone calcium volume; NPV, negative predictive value; PPM, permanent pacemaker; PPV, positive predictive value; RBBB, right bundle branch block. Reprinted with permission from Maeno Y, Abramowitz Y, Kawamori H, et al. A highly predictive risk model for pacemaker implantation after TAVR. JACC Cardiovasc Imaging. 2017;10:1139–1147. |       |                 |                 |         |         |

## PREVENTION, CHALLENGES, AND CONSEQUENCES

In order to make informed decisions on patient care, reduce post-TAVR morbidity, lower costs, and deliberate on the merits of TAVR versus SAVR in certain lower-risk patients, it is important to mitigate the rate of post-TAVR PPM. Accordingly, it is necessary to understand the electrocardiographic, anatomic, and intraprocedural factors that contribute to PPM implantation. However, the challenge lies in the fact that many of the aforementioned predictors are non-modifiable. Previously unidentified ischemia or injury

aside, baseline electrocardiographic factors are typically not amenable to change or improvement. Furthermore, depending on whether a patient is undergoing TAVR with a balloon-expandable or self-expanding prosthesis, predictability and depth of valve deployment are subject to interoperator variability or experience. In real-world clinical practice, the intention to avoid low deployment can be thwarted by intraprocedural anatomic and hemodynamic factors.

Nevertheless, more refined deployment techniques, rapid-controlled transvenous pacing with self-expanding prostheses, and comprehensive preprocedural

imaging assessment are powerful tools to prevent avoidable PPM implantation. The long-term impact of a PPM in a TAVR population is unclear and there are mixed data on whether post-TAVR PPM leads to increased all-cause mortality at 1 year. A systematic review of more than 7,000 patients showed that there may be a protective effect from PPMs, with signals toward a reduction in cardiac death over 1-year follow-up.<sup>18</sup> However, new post-TAVR left bundle branch block was associated with an increased rate of cardiac death and all-cause mortality at 1 year.<sup>18</sup> To complicate matters further, there are several studies demonstrating that nearly 50% of patients who receive a post-TAVR PPM are no longer pacemaker dependent at 1 year.<sup>7,18</sup> This suggests that certain patients may experience recovery of their atrioventricular nodal function after the initial mechanical or ischemic conduction system injury immediately after TAVR. With regard to health care costs, receiving a new PPM after TAVR has been reported to significantly increase per-patient costs and hospital length of stay, particularly when the PPM is implanted more than 24 hours after TAVR.<sup>19</sup>

Ultimately, attention must be paid to minimizing the need for post-TAVR PPM in cases where it can be prevented. However, several electrocardiographic, anatomic, and procedural variables may be immutable. As we migrate toward lower-risk patients, preprocedural predictors of PPM after TAVR will be critical in navigating patient discussion and heart team clinical decision-making. ■

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