Transcatheter Heart Valve Selection and Permanent Pacemaker Implantation in Patients With Pre-Existent Right Bundle Branch Block

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Background—Right bundle branch block is an established predictor for new conduction disturbances and need for a permanent pacemaker (PPM) after transcatheter aortic valve replacement. The aim of the study was to evaluate the absolute rates of transcatheter aortic valve replacement related PPM implantations in patients with pre-existent right bundle branch block and categorize for different transcatheter heart valves.

Methods and Results—We pooled data on 306 transcatheter aortic valve replacement patients from 4 high-volume centers in Europe and selected those with right bundle branch block at baseline without a previously implanted PPM. Logistic regression was used to evaluate whether PPM rate differed among transcatheter heart valves after adjustment for confounders. Mean age was 83±7 years and 63% were male. Median Society of Thoracic Surgeons score was 6.3 (interquartile range, 4.1–10.2). The following transcatheter valve designs were used: Medtronic CoreValve (n=130; Medtronic, Minneapolis, MN); Edwards Sapien XT (ES-XT; n=124) and Edwards Sapien 3 (ES-3; n=32; Edwards Lifesciences, Irvine, CA); and Boston Scientific Lotus (n=20; Boston Scientific Corporation, Marlborough, MA). Overall permanent pacemaker implantation rate post-transcatheter aortic valve replacement was 41%, and per valve design: 75% with Lotus, 46% with CoreValve, 32% with ES-XT, and 34% with ES-3. The indication for PPM implantation was total atrioventricular block in 98% of the cases. Lotus was associated with a higher PPM rate than all other valves. PPM rate did not differ between ES-XT and ES-3. Ventricular paced rhythm at 30-day and 1-year follow-up was present in 81% at 89%, respectively.

Conclusions—Right bundle branch block at baseline is associated with a high incidence of PPM implantation for all transcatheter heart valves. PPM rate was highest for Lotus and lowest for ES-XT and ES-3. Pacemaker dependency remained high during follow-up. (J Am Heart Assoc. 2017;6:e005028. DOI: 10.1161/JAHA.116.005028.)

Key Words: aortic stenosis • bundle-branch block • pacemaker • predictors • right bundle branch block • transcatheter aortic valve implantation • transcatheter aortic valve replacement

Patients with severe aortic stenosis and a higher operative risk for mortality are good candidates for transcatheter aortic valve replacement (TAVR).1–4 TAVR involves placement...
Knowledge of the respective PPM rates for different THV designs in patients with RBBB may guide patient-tailored THV selection. This multicenter collaboration sought to further elucidate TAVR-related PPM rates in patients with pre-existent RBBB and categorize for different THV designs.

**Methods**

**Patient Selection**

Between May 2008 and February 2016, 2845 patients underwent TAVR in 4 tertiary care European institutions. All patients were screened for RBBB (and absence of a PPM) before the TAVR procedure and were included in a joint database collecting: baseline demographics; TAVR procedure characteristics; new conduction disorders within 24 hours; PPM at 30 days; and electrocardiographic and clinical-follow-up data at 30 days and 1 year. THV selection was per institution’s discretion. A minimum of 10 available cases per THV was a predefined requirement for further analysis, to secure solidity of data. The 4 THVs used were CoreValve (Medtronic, Minneapolis, MN), Sapien XT (ES-XT) and Sapien 3 (ES-3; Edwards Lifesciences, Irvine, CA), and Lotus (Boston Scientific Corporation, Marlborough, MA). Figure 1 displays the patient flow diagram. All patients provided written informed consent for the procedure and data analysis for research purposes per institutional review board approval.

**Outcomes**

The primary outcome was implantation of a PPM within 30 days after the TAVR procedure. Secondary outcomes were new-onset conduction disturbances within 24 hours: (1) third-degree atrioventricular block (AV3B) and (2) alternating bundle branch block (ie, change from RBBB to LBBB). The decision for PPM was per treating physician’s discretion, but, in general, in compliance with contemporary European Society of Cardiology Guidelines on PPM. Clinical outcomes were reported using the revised Valve Academic Research Consortium criteria.

**Statistical Analysis**

Continuous variables are presented as mean±SD or median (interquartile range; IQR). Distribution of continuous variables was assessed for normality with histograms and the Shapiro–Wilk test. Continuous variables were compared using a Student t test or Mann–Whitney U test, when applicable. Categorical variables are expressed as percentages plus absolute numbers and were tested with the chi-square test for trend.

Logistic regression was performed to identify predictors for the primary outcome (ie, PPM). THVs were included in the univariate analysis plus potential confounders in regard to the primary outcome. The number of variables in the univariate model was limited by the established rule of thumb of 10 events per variable. All selected variables were evaluated using univariate logistic regression for inclusion in the multivariate model, considering a P value of <0.20 as an entry criterion. These variables remained in the multivariate model, regardless of P value after adjustment. We controlled for the interaction between valve type and alternative access, because alternative access was seldom used with CoreValve and Lotus. All statistical analyses were performed with SPSS software (version 21.0.01; IBM Corp, Armonk, NY). A 2-sided value of P<0.05 was considered statistically significant.

**Results**

A total of 2845 consecutive patients underwent TAVR at 4 European centers. For the purpose of this study, 306 (11%)...
patients with pre-existent RBBB (without a PPM in situ) were extracted and further analyzed (Figure 1). Patient characteristics are listed in Table 1. Mean age was 83±7 years, the majority was male (194; 63%), and the median predicted risk of mortality (Society of Thoracic Surgeons [STS] score) was 6.3% (IQR, 4.1–10.2). The CoreValve and Sapien-XT were used in the majority of patients (42% and 41%, respectively). An alternative access was used in ≈20% with the balloon expandable ES-XT and ES-3 and 9% with CoreValve and not with Lotus. Antiarrhythmic agents were commonly used; 13% of patients used amiodarone and 4% digoxin.

Clinical Outcomes

All-cause mortality—within 48 hours following the procedure—was 3% (n=10). Thirty-day mortality rate was 7% (n=20) and 30-day stroke rate was 2% (n=5). One-year mortality rate was 18% (n=44).

PPM Implantation

Conduction changes are summarized in Table 2. The primary outcome—PPM implantation within 30 days—occurred in 41% of patients. The univariate analysis is summarized in Table S1. The following variables were included in the multivariate analysis: valve type; alternative access; body mass index (BMI); sex; and an interaction term for valve type x alternative access (because alternative access was not applied with Lotus). Results from the multivariate analysis are displayed in Figure 2. By multivariate analysis, PPM was more common with Lotus than with the other THVs. Lotus was associated with a significantly higher PPM rate than all other individual transcatheter heart valves (Lotus versus CoreValve: odds ratio [OR], 3.69 [95% CI, 1.13–12.04]; P=0.030; Lotus versus ES-XT: OR, 6.79 [95% CI, 2.05–22.52]; P=0.002; Lotus versus ES-3: OR, 5.24 [95% CI, 1.30–21.25]; P=0.020). On the contrary, PPM rate was lower with the ES-XT valve versus CoreValve and Lotus (ES-XT vs CoreValve: OR, 0.54 [95% CI, 0.31–0.95]; P=0.033; ES-XT vs Lotus: OR, 0.15 [95% CI, 0.04–0.49]; P=0.002). PPM rate between the balloon expandable valves did not differ (ES-XT vs ES-3: OR, 0.91 [95% CI, 0.40–2.07]; P=0.820). Another independent predictor for PPM in the multivariable model was a higher BMI before TAVR (multivariable OR, 1.08 per 1 kg/m² increment [95% CI, 1.02–1.14]; P=0.013). Alternative access was associated with a lower rate of PPM in the univariate model (OR, 0.32 [95% CI,
**Discussion**

The present study showed that tailored valve choice may reduce rates of PPM implantations in patients with pre-existent RBBB. Overall PPM rate post-TAVR in patients with RBBB was 41% and was highest with Lotus (75%). More than 80% of patients with a PPM remained pacemaker dependent at 30-day and 1-year follow-up.

Prevalence of RBBB in the general population ranges from 0.5% to 1.5%, has a male predominance, and increases with age to 2.2% in patients above 55 years old. Prevalence of pre-existent RBBB is 4% in patients undergoing surgical aortic valve replacement (SAVR) with a mean age of 69 years and is 10% in patients undergoing TAVR with a mean age of 81. RBBB is a dominant predictor for PPM after both TAVR and SAVR. Not unexpectedly, patients with pre-existent RBBB are more vulnerable for high-grade AV block given that the conduction system is already impaired. With TAVR, the radial force of a stented frame may impose pressure on the conduction system embedded in the interventricular septum within a couple of millimeters from the aortic annulus and may further compromise the left bundle branch. Before patients with RBBB evolve toward total AV block, an alternating bundle branch can sometimes be recognized, as illustrated in Figure 3. In our population, an alternating bundle branch block within 24 hours post-TAVR could be detected in 8% of patients.

According to a recent meta-analysis, TAVR with the self-expanding CoreValve is associated with a higher PPM rate compared with the balloon expandable ES-XT. PPM rate with newer-generation THVs varies and definitely remains a clinical issue, in particular with the mechanically expanded Lotus.

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**Table 2. Permanent Pacemaker Implantations and Conduction-Related Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=130)</th>
<th>ES-XT (N=124)</th>
<th>Lotus (N=20)</th>
<th>ES-3 (N=32)</th>
<th>Overall (N=306)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New AV3B &lt;24 hours, n (%)</td>
<td>48 (39)</td>
<td>30 (27)</td>
<td>13 (68)</td>
<td>10 (39)</td>
<td>101 (36)</td>
<td>0.004</td>
</tr>
<tr>
<td>Alternating BBB &lt;24 hours*, n (%)</td>
<td>10 (8)</td>
<td>7 (6)</td>
<td>3 (17)</td>
<td>3 (12)</td>
<td>23 (8)</td>
<td>0.457</td>
</tr>
<tr>
<td>New PPM, n (%)</td>
<td>60 (46)</td>
<td>40 (32)</td>
<td>15 (75)</td>
<td>11 (34)</td>
<td>126 (41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Indication for PPM, n (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV3B</td>
<td>59 (98)</td>
<td>39 (97)</td>
<td>14 (93)</td>
<td>11 (100)</td>
<td>123 (98)</td>
<td>0.489</td>
</tr>
<tr>
<td>AV2B</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Ventricular paced rhythm at 30 days‡</td>
<td>38 (81)</td>
<td>24 (92)</td>
<td>9 (69)</td>
<td>8 (73)</td>
<td>79 (81)</td>
<td>0.275</td>
</tr>
<tr>
<td>Ventricular paced rhythm at 1 year‡</td>
<td>21 (91)</td>
<td>15 (94)</td>
<td>2 (67)</td>
<td>3 (75)</td>
<td>41 (89)</td>
<td>0.415</td>
</tr>
</tbody>
</table>

Categorical variables are displayed as counts (percentages) and differences were tested using a chi-square test for trend. Continuous variables are displayed as median [IQR] and were tested with a Mann–Whitney U test. AV2B indicates second-degree atrioventricular block; AV3B, third-degree atrioventricular block; BBB, bundle branch block; ES-3, Edwards Sapien3; ES-XT, Edwards Sapien XT; IQR, interquartile range; PPM, permanent pacemaker.

*Alternating bundle branch block was considered as a new left bundle branch block in this patient population with pre-existent RBBB.

†Percentage indicates the proportion of patients who received a permanent pacemaker.

‡Follow-up electrocardiograms were missing in 29 patients (23%) at 30 days and in 80 (64%) at 1 year.
Also, the latest balloon expandable ES-3 THV has a higher reported PPM rate compared with its predecessor, ES-XT.\textsuperscript{25}

Prevalence of RBBB in this study was similar to what has been reported in the literature. Our findings demonstrate a higher incidence of PPM in patients with pre-existent RBBB compared to what generally is reported in a random TAVR population. In patients with pre-existent RBBB treated with CoreValve in this study, almost half required a PPM as compared to 20% in the randomized US CoreValve High Risk Study and 28% in the meta-analysis by Siontis et al.\textsuperscript{7,26} PPM rate in patients with ES-XT was 31% and is significantly higher than the 6% in the meta-analysis and 9% in the randomized PARTNER 2 (Placement of Aortic Transcatheter Valves 2) trial.\textsuperscript{3} In our study, also with newer generation THVs in patients with pre-existent RBBB, the PPM rate was consistently higher than what is reported in high-risk TAVR patients: ES-3 34% versus 10\%\textsuperscript{27} and Lotus 75% versus 27\%\textsuperscript{9} respectively.

Multivariate analysis confirmed a higher incidence of PPM with Lotus than with other THV designs. Conversely, ES-XT was associated with the lowest PPM risk. Interestingly, a higher BMI before TAVR also predicted PPM implantation, although the effect was modest. Previous studies reported the impact of BMI on outcomes post-TAVR, but did not show an enhanced rate of PPM implantations.\textsuperscript{4,28} The exact pathophysiology is unclear. However, BMI may pose particular hurdles from a procedure execution perspective and maybe result in less-accurate (and maybe deeper) valve implants. Alternative access (ie, transsubclavian or transapical access) was associated with a lower PPM rate in the univariate model. However, this effect was absent in the multivariate model, suggesting the effect of the balloon expandable valves that were used in the majority (75\%) of alternative access procedures.

The high rate of PPM with Lotus could hypothetically be caused by (1) a higher radial force of the stented frame compared to other THVs, which potentially forces the native annulus in a circular shape, and (2) the Lotus frame remains in contact with the wall of the left ventricular outflow tract throughout the process of foreshortening and locking, which could be more harmful to the conduction system. Depth of transcatheter valve implantation is an established predictor for CoreValve, ES-XT, and ES-3,\textsuperscript{29–31} in particular with an implantation depth of more than 6 mm below the native aortic

Figure 2. Forest plot displaying odds ratios (OR) for permanent pacemaker implantation after multivariate analysis. The following variables were included in the multivariate model: valve type, sex, body mass index (BMI), alternative access, and an interaction term valve type \(\times\) alternative access. \textsuperscript{*Odds ratio per 1 kg/m\textsuperscript{2} increment of BMI. \textsuperscript{†}An interaction term for the interaction between alternative access and valve type was included in the model to adjust for the fact that alternative access was not applied with Lotus. ES-3 indicates Edwards Sapien 3; ES-XT, Edwards Sapien XT; NA, not applicable; PPM, permanent pacemaker.

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valve. Methodology to determine depth of implantation is not standardized and was not collected in this study. However, depth of implantation could affect the need for PPM with any THV and warrants further detailed analysis.

Previous reports suggested the transient nature of TAVR-induced conduction disorders given that up to half of patients with new pacemakers post-TAVR were no longer pacemaker dependent at follow-up.13,32,33 In contrast, our study demonstrates a paced rhythm in 89% of patients at 1 year in patients who received a PPM, underscoring a less-resilient conduction system in these patients. Similarly, patients with pre-existent RBBB who developed AV3B within 24 hours after the procedure received a PPM in 91% of the cases, with 1 in 4 receiving the pacemaker more than 4 days post-TAVR, underscoring the persistence of this conduction disorder. In aggregate, conduction recovery post-TAVR in patients with pre-existent RBBB is unlikely, and therefore the decision to proceed with PPM implantation could be made early after TAVR to minimize hospital stay.

In our study—involving patients with pre-existent RBBB and a relatively high rate of PPM implantations—the mortality rate (7% at 30 days and 18% at 1 year) is on par with recently published trials and registry data.26,31,34–38 Conflicting data link new conduction disorders in general and PPM implantation in particular to impaired TAVR-related outcome, including less improvement in LV function or quality of life, more rehospitalizations, and increased 1-year mortality.13,39–41 Hypothetically, PPM implantation in patients with RBBB levels out mortality attributed to the high incidence of—potentially lethal—total heart blocks.

Limitations
This multicenter study has an observational design and may suffer from inherent bias in terms of THV selection and confounders. Depth of implantation—which is known to be associated with PPM—was not collected in this study. Indeed, given that balloon expandable devices have less TAVR-related conduction disorders, operators may already favor this THV for patients with pre-existent RBBB and avoid mechanically expanded valves on the other hand. Nonetheless, only THVs with at least 10 patients in the database were eligible for further analysis, and the number of events was sufficient to allow for adequate multivariate analysis to adjust for confounders. We acknowledge that the Lotus valve is relatively under-represented in the present study, and therefore avoidance of this valve cannot be strongly recommended. However, we believe that there is a clear signal that this valve is associated with the highest PPM rate. The decision to implant a PPM was at the treating physician’s discretion, but was most often for high-degree AV block and thus conforms to current international guidelines.17

Conclusion
Postprocedural PPM rate in this cohort of patients with pre-existent RBBB was consistently higher than described in the literature for all THVs. PPM rate was highest with Lotus and lowest with the balloon expandable ES-XT and ES-3. Pacemaker dependency remained high at both 30-day and 1-year follow-up.

Sources of Funding
Dr Van Mieghem has received research grants from Claret Medical, Boston Scientific, Medtronic, and Edwards Lifesciences.

Disclosures
Prof Dr De Jaegere is proctor for Boston Scientific. The remaining authors have nothing to disclose in relation to this topic.

References
TAVR in RBBB

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SUPPLEMENTAL MATERIAL
Table S1. Predictors for permanent pacemaker implantation.

<table>
<thead>
<tr>
<th>Type of THV</th>
<th>Univariate OR [95% CI]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lotus vs. CoreValve</strong></td>
<td>3.50 [1.20-10.20]</td>
<td>.022</td>
</tr>
<tr>
<td><strong>Lotus vs. ES-XT</strong></td>
<td>6.30 [2.14-18.55]</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Lotus vs. ES-3</strong></td>
<td>5.73 [1.65-19.94]</td>
<td>.006</td>
</tr>
<tr>
<td><strong>CoreValve vs. ES-XT</strong></td>
<td>1.80 [1.08-3.00]</td>
<td>.024</td>
</tr>
<tr>
<td><strong>CoreValve vs. ES-3</strong></td>
<td>1.64 [0.73-3.67]</td>
<td>.232</td>
</tr>
<tr>
<td><strong>ES-XT vs. ES-3</strong></td>
<td>0.91 [0.40-2.07]</td>
<td>.820</td>
</tr>
</tbody>
</table>

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR [95% CI]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative access</strong></td>
<td>0.32 [0.15-0.69]</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Baseline atrial fibrillation</strong></td>
<td>0.79 [0.44-1.42]</td>
<td>.429</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>1.08 [1.02-1.14]</td>
<td>.006</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>1.49 [0.93-2.39]</td>
<td>.098</td>
</tr>
<tr>
<td><strong>Medication Amiodarone</strong></td>
<td>0.87 [0.43-1.75]</td>
<td>.690</td>
</tr>
<tr>
<td><strong>Medication Digitalis</strong></td>
<td>0.86 [0.25-3.00]</td>
<td>.813</td>
</tr>
<tr>
<td><strong>NYHA - class ≥ III</strong></td>
<td>0.92 [0.54-1.58]</td>
<td>.765</td>
</tr>
<tr>
<td><strong>Prior SAVR</strong></td>
<td>0.40 [0.08-1.95]</td>
<td>.256</td>
</tr>
</tbody>
</table>

Results from univariate logistic regression analysis. Variables in italic were included in the multivariate analysis. *Odds ratio per 1 kg/m² increment of body mass index. Abbreviations: CI = confidence interval; ES-3 = Edwards sapien valve 3; ES-XT = Edwards Sapien XT; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; THV = transcatheter heart valve.
Table S2. Predictors for new total atrioventricular block <24h.

<table>
<thead>
<tr>
<th>Type of THV</th>
<th>Univariate OR (95% CI)</th>
<th>P-Value</th>
<th>Multivariate OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lotus vs. CoreValve</strong></td>
<td>3.43 (1.22-9.63)</td>
<td>.019</td>
<td>3.80 (1.25-11.52)</td>
<td>.018</td>
</tr>
<tr>
<td><strong>Lotus vs. ES-XT</strong></td>
<td>5.92 (2.06-16-99)</td>
<td>.001</td>
<td>6.01 (1.93-18.67)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>Lotus vs. ES-3</strong></td>
<td>3.47 (0.99-12.09)</td>
<td>.051</td>
<td>3.88 (1.02-14.82)</td>
<td>.047</td>
</tr>
<tr>
<td><strong>CoreValve vs. ES-XT</strong></td>
<td>1.73 (0.99-3.00)</td>
<td>.053</td>
<td>1.58 (0.88-2.85)</td>
<td>.128</td>
</tr>
<tr>
<td><strong>CoreValve vs. ES-3</strong></td>
<td>1.01 (0.42-2.41)</td>
<td>.981</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ES-XT vs. ES-3</strong></td>
<td>0.59 (0.24-1.43)</td>
<td>.240</td>
<td>0.17 (0.05-0.52)</td>
<td>.002</td>
</tr>
</tbody>
</table>

**Patient characteristics**

| Alternative access               | 0.51 (0.21-1.23)       | .133    | 0.48 (0.13-1.81)         | .281    |
| Baseline atrial fibrillation     | 1.00 (0.53-1.86)       | .987    |                          |         |
| **Body mass index**              | 1.04 (0.99-1.10)       | .126    | 1.04 (0.98-1.10)         | .218    |
| **Female sex**                   | 1.39 (0.84-2.29)       | .200    | 1.30 (0.77-2.20)         | .326    |
| Prior surgical aortic valve replacement | 0.89 (0.22-3.63)   | .868    |                          |         |

Results from uni- and multivariate logistic regression for new onset third degree atrioventricular block within 24 hours. Variables in italic were included in multivariate regression. Abbreviations: CI = confidence interval; ES-XT = Edwards Sapien XT; ES-3 = Edwards Sapien 3; OR = Odds Ratio; THV = transcatheter heart valve.
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