Impact of Preprocedural Aortic Valve Calcification on Conduction Disturbances after Transfemoral Aortic Valve Replacement

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Keywords
Transcatheter aortic valve replacement · Permanent pacemaker · Conduction disturbances · Aortic valve stenosis · Calcification

Abstract
Aim: The present study analyzes in depth the impact of different calcification patterns on disturbances of the conduction system in transcatheter aortic valve replacement (TAVR) patients. Methods and Results: A total of 169 preprocedural TAVR multislice computed tomography scans from consecutive transfemoral (TF) TAVRs performed between 2014 and 2017 using either Edwards SAPIEN or Medtronic Evolut R valves were retrospectively evaluated. The volume, distribution, and orientation of annular and valvular aortic valve calcification were measured and their impact on postoperative conduction disturbances was determined using linear and logistic regression analyses. The total volume of calcification and distribution at the aortic annulus or valve did not influence the conduction system. Oval calcification of the left aortic cusp was independently associated with an elevated risk for an increase in atrioventricular block degree (+0.6, \( p = 0.03 \)). Moreover, orthogonal calcifications at the level of the aortic annulus were associated with an increased risk for QRS prolongation (+26 ms, \( p = 0.004 \)) and an increased risk for permanent pacemaker implantation (OR 4.3, \( p = 0.03 \)) after TF TAVR. This was more pronounced in patients undergoing TF TAVR using a balloon-expandable Edwards SAPIEN 3 valve (QRS +38.195 ms, \( p < 0.001 \); OR permanent pacemaker 15.48, \( p = 0.013 \)). Conclusion: Orthogonal annular calcification confers an increased risk for conduction disturbances after TAVR. This is even more pronounced after implantation of balloon-expandable valves.

Introduction
Transcatheter aortic valve replacement (TAVR) has become an established treatment for patients at increased operative risk with severe aortic valve stenosis [1, 2]. While it was initially developed for inoperable patients, the indication has meanwhile expanded to intermediate-risk patients [3–5]. First randomized trials have investigated the

P.S. and J.S. contributed equally to this work.
efficacy of TAVR in patients at low operative risk [6]. However, concerns about the durability of TAVR valves and the higher need for a permanent pacemaker (PPM) hamper the extension of TAVR to younger patients. Especially for younger patients, a benefit from the minimally invasive TAVR procedure might be outweighed by chronic right ventricular pacing and a higher incidence of atrial fibrillation, heart failure, and long-term mortality [7–11].

The anatomic proximity of the membranous septum – in which the bundle of His is located more anteriorly, distally, and cranially than previously thought [12] – to the right coronary and noncoronary cusps of the aortic valve is a major cause of disturbances of atrioventricular (AV) conduction after TAVR [13]. Indeed, invasive electrophysiological studies have demonstrated infranodal AV block after TAVR, reflecting severe injury to the His bundle and/or the left bundle branch [14–17]. Thus, maneuvers which stress the conduction system – such as, for example, overstretching the left ventricular outflow tract (LVOT) by balloon predilatation, low implantation height, or oversized valves – should be avoided [18]. A further anatomical factor which is known to induce conduction disturbances after TAVR is annular calcification, which increases the risk for new-onset left bundle branch block (BBB) by a factor of 3 [19]. Calcification of the aortic valve cusps is the nature of degenerative aortic valve stenosis, and in TAVR it is crucial for fixation of the transcatheter aortic valve prosthesis. However, calcification at the level of the aortic annulus may transfer the radial force during implantation of the prosthetic valve to the membranous septum, thereby injuring the His bundle and/or the left bundle branch. Calcifications are removed in patients treated with surgical aortic valve replacement, but they remain in situ in patients treated with TAVR, which may explain the higher need for PPM implantations. Accurate knowledge of the distribution of aortic valve calcification may therefore help to predict or even prevent new conduction disturbances after TAVR and the need for a PPM.

The present study measures the detailed volumes, distribution, and orientation of aortic valve calcifications on preprocedural multislice computed tomography (MSCT), their impact on new AV conduction disturbances, and the need for postprocedural PPM implantation.

Subjects and Methods

Study Population

A total of 188 consecutive patients with severe aortic valve stenosis which underwent transfemoral (TF) TAVR either with the balloon-expandable Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) valve or the self-expandable Medtronic Evolut R (Minneapolis, MN, USA) valve between February 2014 and June 2017 at the University Heart Center Freiburg, Germany, were included in the study. Valve-in-valve procedures, other valve types, bicuspid valves, or direct access procedures were excluded. From the 188 patients, 18 were excluded due to impaired MSCT scan quality, and 1 TAVR procedure was not successful. An interdisciplinary heart team determined the treatment strategy. Baseline characteristics, procedural data, and follow-up data were collected retrospectively and transferred onto a Microsoft Excel (Redmond, WA, USA) spreadsheet.

Analysis of Aortic Valve Calcification

All MSCT scans were performed using a first-generation dual-source MSCT (SOMATOM Definition; Siemens Healthineers, Erlangen, Germany) with an ECG-triggered cycle and contrast agent, as described previously [20]. The data sets were transferred to 3mensio Structural Heart version 8.1 software (Pie Medical Imaging BV, Maastricht, The Netherlands), reconstructed, and analyzed. The threshold for relevant calcification was defined as >600 Hounsfield units (HU) and a size >1 mm³. If necessary, the HU threshold was adapted manually. Calcification of the aortic valve was measured within the range from 10 mm below the aortic annulus and 20 mm above. The calcification volume (complete valve) or area (annulus) was automatically measured by the 3mensio software and discriminated into different valve areas (LVOT, right coronary/left coronary/noncoronary cusp). Furthermore, the orientation (tangential or orthogonal to the aorta; within, across, or outside the annulus) and shape (round, oval, or long) of the calcification were determined. In 106 cases, a postprocedural MSCT was performed.

Endpoints

Differences in QRS time, new or increasing AV block degree (+1 means: +1 higher degree of AV block), or new PPM implantation were chosen as endpoints during the hospital stay. Patients with an existing PPM were excluded from the endpoint analysis. The indication for a PPM was made individually by a specialized cardiologist and the TAVR team according to current recommendations [13].

Statistical Analysis

The impact of the volume, distribution, and orientation of the annular and valvular aortic valve calcification on postoperative conduction disturbances (QRS time, BBB, AV block, or need for pacemaker implantation) was analyzed using linear or logistic regression analysis as appropriate. Due to the explorative nature of the study, p values are descriptive, and no adjustment for multiple testing was applied. All analyses were performed using Stata 15 (Stata Corp, College Station, TX, USA).

Results

Study Population, Baseline Characteristics, and Procedural Outcome

In all, 169 consecutive patients who underwent TF TAVR either with an Edwards SAPIEN 3 valve (n = 131) or a Medtronic Evolut R (n = 38) valve were retrospectively included in the study. The mean age was 81.8 years,
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with a mean STS score of 9.1. The rate of males was 41%, but it was lower among the patients undergoing TAVR using the Medtronic Evolut R valve (23.7%, \( p = 0.019 \)) (Table 1). After the procedure, the QRS time increased by 16.8 ms, without a significant difference between the patients undergoing TF TAVR with an Edwards SAPIEN 3 valve and those undergoing it with a Medtronic Evolut R valve. Naturally, the grade of oversizing and the number of postdilatations were higher among the patients receiving an Evolut R valve. 27.2% received a new PPM, again without a significant difference between SAPIEN 3 and Evolut R patients (Table 2).

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 169)</th>
<th>SAPIEN 3 valve (n = 131)</th>
<th>Evolut R valve (n = 38)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>81.8±5.9</td>
<td>82.0±5.7</td>
<td>81.3±6.7</td>
<td>0.50</td>
</tr>
<tr>
<td>Male</td>
<td>70 (41.4)</td>
<td>61 (46.6)</td>
<td>9 (23.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5±5.1</td>
<td>26.6±5.2</td>
<td>26.2±4.4</td>
<td>0.70</td>
</tr>
<tr>
<td>STS score</td>
<td>9.14±7.41</td>
<td>8.88±7.19</td>
<td>10.01±8.16</td>
<td>0.41</td>
</tr>
<tr>
<td>NYHA class &gt;II</td>
<td>106 (64.6)</td>
<td>81 (63.8)</td>
<td>25 (67.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>CCS class &gt;II</td>
<td>29 (20.4)</td>
<td>24 (21.8)</td>
<td>5 (15.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Syncope</td>
<td>34 (20.1)</td>
<td>31 (24.0)</td>
<td>3 (8.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>97 (57.4)</td>
<td>78 (59.5)</td>
<td>19 (50.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>12 (7.1)</td>
<td>11 (8.4)</td>
<td>1 (2.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>47 (27.8)</td>
<td>38 (29.0)</td>
<td>9 (23.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>139 (82.7)</td>
<td>106 (81.5)</td>
<td>33 (86.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57 (33.7)</td>
<td>44 (33.6)</td>
<td>13 (34.2)</td>
<td>0.94</td>
</tr>
<tr>
<td>PAD</td>
<td>40 (23.7)</td>
<td>34 (26.0)</td>
<td>6 (15.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>23 (13.6)</td>
<td>21 (16.0)</td>
<td>2 (5.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>COPD</td>
<td>28 (16.6)</td>
<td>25 (19.1)</td>
<td>3 (7.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>72 (42.6)</td>
<td>58 (44.3)</td>
<td>14 (36.8)</td>
<td>0.42</td>
</tr>
<tr>
<td>Previous pacemaker</td>
<td>19 (11.2)</td>
<td>13 (9.9)</td>
<td>6 (15.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Oversizing, %</td>
<td>7.5 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>19.7 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postdilatation</td>
<td>9 (4.8)</td>
<td>2 (1.4)</td>
<td>7 (14.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values denote means ± SD or \( n \) (%) unless specified otherwise. BMI, body mass index; STS, Society of Thoracic Surgeons; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease.

### Table 2. Postprocedural changes in ECG and new PPM

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>SAPIEN 3 valve</th>
<th>Evolut R valve</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS time difference, ms</td>
<td>+16.77±26.88</td>
<td>+16.93±27.92</td>
<td>+16.23±23.17</td>
<td>0.90</td>
</tr>
<tr>
<td>AV block difference, °</td>
<td>+0.32±0.89</td>
<td>+0.29±0.92</td>
<td>+0.39±0.79</td>
<td>0.61</td>
</tr>
<tr>
<td>New BBB (n = 153)</td>
<td>48 (28.4)</td>
<td>36 (30.0)</td>
<td>12 (36.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>New PPM (n = 150)</td>
<td>46 (27.2)</td>
<td>37 (31.4)</td>
<td>9 (28.1)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

\( n = \text{(share %). AV, atrioventricular; BBB, bundle branch block; PPM, permanent pacemaker.} \)

Impact of Calcification Volume on the Conduction System

In order to measure the impact of the total calcification volume on the conduction system, the calcification volume was determined and correlated with QRS time and AV block degree before and after TF TAVR (QRS time before: 108.5 ± 23.1 ms; QRS time after: 125.4 ± 31.1 ms). The grade of calcification of the whole valve did not influence QRS time (\( p = 0.27 \)). Furthermore, the difference in AV block degree did not depend on the total calcification volume of the native stenotic valve (\( p = 0.27 \)) (Fig. 1). Accordingly, an increase in total calcification volume was...
not associated with a higher risk for the development of a new BBB or the need for a new PPM.

**Impact of Calcification Distribution on New AV Conduction Disturbances**

At the level of the device landing zone, the cardiac conduction system is located within the membranous septum. The distribution of aortic valve calcification may thus influence the impact of TAVR on the conduction system. Therefore, the calcification volume was determined at the level of the LVOT, defined as 10 mm below the annulus, and at the valvular level distinguished between the right coronary, left coronary, and noncoronary cusp. The amount of calcification in the different cusps was associated neither with an increase in QRS time nor with an increase in AV block degree after TF TAVR (Fig. 2). Consequently, the risk for a new BBB or new PPM did not depend on the distribution of calcifications in the aortic valve cusps (data not shown). The volume of calcification in the LVOT did not influence QRS time, any increase in AV block degree, any new BBB, or the need for a new PPM (Fig. 3). Furthermore, the shape of the calcification at the level of the annulus and cusps did not influence QRS time, any new BBB, and the need for a new PPM, except for an oval calcification at the left coronary cusp, which increased the risk for AV block.

**Impact of Calcification Orientation on Pacemaker Implantation Rate**

We evaluated the impact of the position and orientation of the calcification at the level of the aortic annulus on the conduction system. Calcification completely inside or outside the annular ring had no impact on the development of a new BBB or the need for a new PPM. Calcifications crossing the annular ring increased the appearance of an AV block (AV block +0.99, p = 0.03) and tended to increase the risk for a new BBB or new PPM (without reaching statistical significance).

Calcifications orientated tangentially to the annular ring did not impact QRS time, a new BBB, or the need for a new PPM. In contrast, orthogonal calcifications significantly increased QRS time (+26 ms, p = 0.004), tended to increase the risk for a new BBB (OR 3.2, p = 0.06), and quintupled the risk for a new PPM (OR 4.9, p = 0.03) (Fig. 4).

**Different Valve Types in Annuli with Orthogonal Calcifications**

Orthogonal annular calcifications were detected in 6.5% of the patients undergoing TF TAVR (11 of 169). None of these plaques were located near the membranous septum; they were mostly located under the left coronary cusp. Consequently, two-thirds of all patients with orthogonal annular calcifications required a PPM after TAVR. Eighty-six percent of the patients (6 out of 7) after Edwards SAPIEN 3 valve treatment received a PPM. Two patients receiving an Edwards SAPIEN 3 valve already had a permanent PPM before TAVR. Thus, the OR for

![Fig. 1. Impact of calcification volume on the conduction system.](image_url)

**Fig. 1.** Impact of calcification volume on the conduction system. a Total valve calcification (mm³) was determined using the 3mensio software and correlated with QRS time difference between before and after (QRS time at discharge) transcatheter aortic valve replacement. b The difference in atrioventricular (AV) block between before and after was correlated with the total calcification volume. A representative picture of low- and high-grade calcification is shown below.
patients with orthogonal annular calcification undergoing TF TAVR with the Edwards SAPIEN 3 valve was 15.5 (p = 0.01). Furthermore, the QRS time difference between before and after TF TAVR increased significantly, by 38.2 ms, in the patients receiving the Edwards SAPIEN 3 valve with orthogonal calcifications (p < 0.001) (Table 3). Only 2 patients with orthogonal annular calcifications received a Medtronic Evolut R valve. Here, no PPM was needed and the QRS time difference was not significantly changed between before and after TF TAVR.

Fig. 2. Impact of annular calcification distribution on the conduction system. Valve calcification (mm$^3$) was determined using the 3mensio software at the noncoronary, left coronary, and right coronary cusp and correlated with QRS time and atrioventricular (AV) block difference between before and after (QRS time/AV block at discharge) transcatheter aortic valve replacement.

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Discussion

The present study evaluated the impact of different calcification patterns on the conduction system after TAVR. The study population was at high operative risk according to the guidelines valid between February 2014 and June 2017 [21], with a mean STS score > 9 and a mean age of 82 years. Unlike other complications after TAVR, the rate of PPM implantation failed to decrease during the last years [13, 22]. At our center, the PPM implantation rate after TF TAVR was slightly increased compared to other real-world data from larger collectives [23]. Interestingly, there was no difference in need for a new PPM between the Edwards SAPIEN 3 and the Medtronic Evolut R valve at our center, despite large registries having observed higher pacemaker rates after implantation of self-expandable valves [24]. Since the indication for TAVR has spread towards younger patients at lower operative risk, complications such as PPM implantation that may be associated with an impaired long-term outcome after TAVR need to be prevented [11, 25]. About 10% of patients suffer from short- or long-term complications after PPM implantation [26]. One prevention strategy is optimal planning of the TAVR procedure. For instance, it is well established that valve implantation height and valve overexpansion are associated with the need for a PPM in patients undergoing TAVR [22, 27, 28].

A pre-procedural MSCT is mandatory for planning TAVR procedures [3]. Several studies have investigated the impact of the calcification volume measured in pre-procedural MSCT on the PPM transplantation rate after TAVR. In line with these studies, we found that the calcification volume of the aortic valve before TAVR was no predictor of new AV conduction disturbances or the need for new PPM implantation [29, 30]. The same was true for calcification of the aortic cusps: the volume of calcification in the noncoronary, left coronary, or right coronary cusp had no impact on QRS time, AV block, new BBB, and new PPM transplantation.

The impact of the annular calcification load is controversial. Since the aortic annulus is the device landing zone, the radial force of the TAVR device mainly affects the area of the LVOT containing the aortic annulus and thereby the conduction system located within the membranous septum. A study using older TAVR devices observed an independent correlation between annular calcification and the need for PPM implantation [31]. In our study, solely including third-generation TAVR devices (Edwards SAPIEN 3 and Medtronic Evolut R), we did not find an impact of total LVOT calcification on the conduction system. Two further studies investigating either the Edwards SAPIEN 3 or the self-expandable Accurate Neo...
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valve (former Symetis SA, Ecublens, Switzerland) confirmed this finding. However, both studies identified calcification of the LVOT below the left or right coronary cusp as an independent predictor of the need for a new PPM [29, 30]. In the present study, we focused on the shape and orientation of annular calcifications. While the shape of the calcifications at the level of the annulus had no influence on the conduction system, orientation was more important: calcifications which crossed the annulus increased the risk for AV block and tended to increase the need for a new PPM. Those AV blocks occurred within the first 2 days after TAVR. We observed the strongest effect if the orientation of the annular calcification axis was orthogonal to the annulus; the QRS time increased by 26 ms, indicating that the membranous septum was mainly affected by orthogonal calcifications. The risk for new PPM implantation was 5 times higher in patients with orthogonal annular calcifications. In line with the results of Mauri et al. [30], most of the orthogonal annular calcifications were located below the left coronary cusp. In order to elucidate this effect, we analyzed the postprocedural MSCT scans. Intriguingly, the orthogonal plaques did not – as expected – spare the annular ring after TAVR but remained more or less at their pre-TAVR location. This may explain the impact of annular calcifications below the left cusp on the conduction system:

**Fig. 4.** Impact of calcification orientation on new bundle branch block (nBBB) and the need for a new permanent pacemaker (PPM). Logistic regression was performed to determine the risk associated with different orientations of annular calcification. Representative pictures are shown at the left.
since calcifications stay in place after TAVR, the TAVR valves move – in particular due to orthogonal, left-located annular calcifications – inferoseptally towards the membranous septum, thereby injuring the His bundle and/or the predestined fibers of the left bundle branch.

Relevant orthogonal annular calcifications occurred in only 6.5% of the patients undergoing TAVR in our study. However, if orthogonal calcification is present, the risk for new PPM implantation is high. We divided the patients with orthogonal calcifications into those receiving an Edwards SAPIEN 3 valve and those receiving a Medtronic Evolut R valve. Considering the low total number of procedures on patients with orthogonal annular calcifications, the QRS time difference and risk for new PPM implantation were more pronounced among the patients receiving the Edwards SAPIEN 3 valve. One could speculate that the sudden radial force due to balloon expansion may lead to an inferoseptally directed shift of the valve towards the membranous septum, thereby exerting pressure on the His bundle area. Hence, the data suggest that balloon expansion should be performed with caution, with careful sizing. Strategies for avoiding extensive radial force should, if anatomically possible, be implemented.

**Limitations**

This study has the limitation of a retrospective single-center study. Furthermore, we cannot answer the question as to whether a self-expandable valve is superior in case of orthogonal annular calcification, since the number of Medtronic Evolut R valves in patients with orthogonal plaques is too low in the present study. Moreover, in 5 patients we found a decrease in QRS time of > 10 ms. Some had underlying right BBB and isolated fusion beats due to right ventricular pacing, which was not detected by the automatic ECG analysis software and led to an apparent decrease in QRS time after TAVR.
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Conclusions

This study describes a novel mechanism causing the development of new AV conduction disturbances following TAVR: orthogonal annular calcifications. These may cause new conduction disturbances after TAVR via a shift of the TAVR valve inferoseptally towards the membranous septum, thereby injuring the His bundle and/or the predestined fibers of the left bundle branch. Consequently, orthogonal plaques are risk factors for the need of a new PPM, in particular after treatment with an Edwards SAPIEN 3 valve (Fig. 5). The total calcification volume and the location of the calcification did not influence the conduction system using either the Edwards SAPIEN 3 or the Medtronic Evolut R valve.

Acknowledgments

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Statement of Ethics

The Ethics Committee of the University of Freiburg approved the study design (EK No. 29/11), and the study complies with the Declaration of Helsinki.

References


Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions


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