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Predictors of Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement With the SAPIEN 3

Victor Mauri, MD,[a] Andreas Reimann,[a] Daniel Stern, MD,[a] Maximilian Scherner, MD,[b] Elmar Kuhn, MD,[b] Volker Rudolph, MD,[a] Stephan Rosenkranz, MD,[a] Kaveh Eghbalzadeh, MD,[b] Kai Friedrichs, MD,[a] Thorsten Wahlers, MD,[b] Stephan Baldus, MD,[a] Navid Madershahian, MD,[b] Tanja K. Rudolph, MD[a]

ABSTRACT

OBJECTIVES The aim of this study was to identify predictors of permanent pacemaker implantation (PPMI) following transcatheter aortic valve replacement (TAVR) with a balloon-expandable transcatheter valve (Edwards SAPIEN 3).

BACKGROUND New-onset conduction disturbances requiring PPMI remain a major concern following TAVR. Predictors are not yet well defined.

METHODS The influence of angiographic implantation depth, device landing zone calcium volume, oversizing, pre- and post-dilation, and baseline conduction disturbances on PPMI rate was analyzed in 229 patients undergoing TAVR with the SAPIEN 3 device.

RESULTS PPMI was performed in 14.4% of patients. Patients requiring PPMI had higher left ventricular outflow tract (LVOT) calcium volume in the area below the left coronary cusp ($LVOT_{LC}$) and the area below right coronary cusp ($LVOT_{RC}$) ($LVOT_{LC}$ median calcium 23.7 mm^3 vs. 3.0 mm^3; $p < 0.001$; $LVOT_{RC}$ median calcium 6.6 mm^3 vs. 0.3 mm^3; $p = 0.014$), a higher prevalence of pre-existing right bundle branch block (15% vs. 2%, $p = 0.004$), and lower implantation depth (ventricular portion of the stent frame 29 ± 12% vs. 21 ± 5%; $p < 0.001$). On multivariate regression analysis, $LVOT_{LC}$ calcium volume >13.7 mm^3, $LVOT_{RC}$ calcium volume >4.8 mm^3, pre-existing right bundle branch block, and implantation depth >25.5% emerged as independent predictors of PPMI. Upon modification of the implantation technique, aiming at a high final valve position, implantation depth decreased from 24% ventricular portion to 21% ($p = 0.012$), accompanied by a decrease in PPMI rate (19.2% vs. 9.2%; $p = 0.038$).

CONCLUSIONS $LVOT_{LC}$ and $LVOT_{RC}$ calcium load, baseline right bundle branch block, and implantation depth were identified as independent predictors of the need for PPMI post-TAVR. Patient groups with different PPMI risk could be stratified using these 4 predictors. A slightly higher valve implantation site may prevent excessive PPMI rates.
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Over the past decade, transcatheter aortic valve replacement (TAVR) has become the standard of care in inoperable patients and those considered at high surgical risk, with excellent results (1). Although several limitations of first-generation transcatheter heart valves such as paravalvular regurgitation (PVR) and vascular complications are reduced by the current generation of TAVR prostheses, new-onset conduction disturbances requiring permanent pacemaker implantation (PPMI) remain among the most frequent complications (2). Clinical effects associated with PPMI after TAVR are currently the subject of controversy. Although PPMI was associated with prolonged

From the [a]Department of Cardiology, Heart Center, University of Cologne, Cologne, Germany; and the [b]Department of Cardiothoracic Surgery, Heart Center, University of Cologne, Cologne, Germany. Drs. Wahlers, Baldus, Madershahian, and Rudolph are proctors for Edwards Lifesciences. Dr. Baldus also received a research grant from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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hospital stay, higher rates of rehospitalization, and increased mortality in a recent analysis of the PARTNER (Placement of Aortic Transcatheter Valves) trial, long-term outcomes were found to be unaffected by PPMI in other studies (3–6). Although the clinical impact of PPMI after TAVR remains controversial, the effects of long-term right ventricular pacing leading to worsened cardiac output due to interventricular dyssynchrony are well studied (3,7,8).

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The recently introduced Edwards SAPIEN 3 balloon-expandable transcatheter heart valve (Edwards Lifesciences, Irvine, California) showed a significant reduction of PVR, but rates of PPMI ranging from 12.4% to 25.5% were reported, which are substantially higher than those reported for previous generations of balloon-expandable valves (9–14). Understanding the factors contributing to PPMI is a major concern in order to avoid PPMI, especially in the context of the currently ongoing discussion of extending TAVR indications to younger and lower-risk patients (15,16). The aim of our study was to identify risk factors associated with the need for PPMI after TAVR with a SAPIEN 3 prosthesis, thereby focusing on the particular role of implantation depth and calcium distribution patterns of the device landing zone (DLZ).

METHODS

PATIENT POPULATION. Two hundred seventy-nine consecutive patients undergoing TAVR with SAPIEN 3 prostheses between August 2013 and January 2016 were included in the analysis. Patients had symptomatic severe aortic stenosis and were considered not suitable for conventional aortic valve replacement by the heart team. Procedural outcomes were reported according to the Valve Academic Research Consortium 2 consensus (17).

MEASUREMENTS OF VALVE IMPLANTATION DEPTH. Assessment of valve implantation depth was based on off-line evaluation of post-deployment aortic angiograms. If necessary, the projection angle was adjusted during the procedure to obtain an orthogonal view of the valve frame, thus avoiding inaccuracy in depth measurements. The overall length of the stent frame as well as the distance from the native aortic annulus to the inflow end of the stent frame was measured at the septal side. Implantation depth was expressed as the percentage of the ventricular part of the stent frame in relation to the overall stent frame length. The native aortic annulus was identified by tracing a line linking the sinuses of Valsalva. Angiograms were evaluated before all statistical analyses by 2 experienced investigators who were unaware of outcome measures (interobserver variability 2.47 ± 1.28%; intraclass correlation coefficient = 0.97). Measurements were performed with OsiriX version 5.9 (Pixmeo SARL, Geneva, Switzerland).

COMPUTED TOMOGRAPHIC DATA ANALYSIS. Analysis (performed by 2 experienced investigators; interobserver variability for total calcium volume 47.8 ± 123.6 mm^3; intraclass correlation coefficient = 0.98) was based on pre-operative multislice computed tomographic images routinely acquired for procedure planning on a dual-source computed tomographic scanner (Siemens Healthcare, Erlangen, Germany) with a slice thickness of 1 mm and 40 ml of intravenously administered contrast agent (Accupaque, GE Healthcare, Braunschweig, Germany). For calcium quantification, 6 zones of interest were defined: above the aortic annulus, calcium load was assessed for each of the 3 aortic valve cusps separately in an area reaching from the basal plane to the lower coronary artery. The left ventricular outflow tract (LVOT) area of interest was defined by measuring 10 mm from the basal plane into the left ventricle, and also the LVOT area was subdivided into 3 zones analogous to the aortic valve cusps and assessed separately. Voxels exceeding a pre-defined limit of 500 Hounsfield units were considered to represent calcium. If necessary, the threshold was adjusted manually.

Percentage of oversizing was calculated using the formula (nominal prosthesis area/multislice computed tomographic area − 1) × 100. Patients were categorized as undersized, within sizing range, or oversized according to the manufacturer's sizing recommendations. Selection of prosthesis size was at the discretion of the operating physicians, who were aware of the sizing guidelines.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or as median with interquartile range, and categorical variables are reported as frequencies and percentages. The Kolmogorov-Smirnov test was used to test for normal distribution. Accordingly, the Student *t* test or Mann-Whitney *U* test was used to test for statistically significant differences. The Fisher exact test was used for statistical distribution analysis of categorical variables. Differences in baseline variables were analyzed by calculating standardized mean differences. On the basis of receiver-operating characteristic curve

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
CI = confidence interval
DLZ = device landing zone
LVOT = left ventricular outflow tract
$LVOT_{LC}$ = left ventricular outflow tract area below the left coronary cusp
$LVOT_{NC}$ = left ventricular outflow tract area below the noncoronary cusp
$LVOT_{RC}$ = left ventricular outflow tract area below the right coronary cusp
OR = odds ratio
PPMI = permanent pacemaker implantation
PVR = paravalvular regurgitation
RBBB = right bundle branch block
TAVR = transcatheter aortic valve replacement

TABLE 1 Baseline Patient Demographics, Electrocardiographic Findings, and Calcium Volume

	All (N = 229)	No PPMI (n = 196)	PPMI (n = 33)	d Value
Demographics				
Age (yrs)	80.2 ± 6.4	79.9 ± 6.2	81.9 ± 7.2	0.30
Female	101 (44.1)	82.00 (41.8)	19.00 (57.6)	0.32
COPD	53 (23.1)	47.0 (24.0)	6.00 (18.2)	0.14
PAD	53 (23.1)	49.0 (25.0)	4.00 (12.1)	0.34
Previous cardiac surgery	62 (27.1)	57.0 (29.1)	5.00 (15.2)	0.34
Diabetes mellitus	67 (29.3)	55.0 (28.1)	12.00 (36.4)	0.18
Arterial hypertension	192 (83.8)	164.0 (83.7)	28.00 (84.8)	0.03
Prior MI	47 (20.5)	40.0 (20.4)	7.00 (21.2)	0.02
CAD	134 (58.5)	116.0 (59.2)	18.00 (54.5)	0.09
LVEF (%)	56 ± 12.0	56 ± 12.0	57 ± 9.0	0.10
Logistic EuroSCORE I (%)	15.6 ± 11.5	15.7 ± 11.8	14.7 ± 9.7	0.10
Baseline ECG findings				
Atrial fibrillation	82 (35.8)	71 (36.2)	11 (33.3)	0.06
AVB grade I	16 (7.4)	14 (7.1)	2 (6.1)	0.05
LBBB	11 (4.8)	10 (5.1)	1 (3.0)	0.11
RBBB	9 (3.9)	4 (2.0)	5 (15.2)	0.49
LAHB	14 (6.1)	14 (7.1)	0	0.41
Incomplete RBBB	8 (3.5)	6 (3.1)	2 (6.1)	0.14
MSCT measurements				
Minimal diameter (mm)	22.0 ± 2.7	22.1 ± 2.7	21.7 ± 2.8	0.14
Maximal diameter (mm)	28.6 ± 3.0	28.7 ± 3.0	28.4 ± 3.2	0.08
Perimeter (mm)	80.8 ± 8.3	80.9 ± 8.2	80.2 ± 9.0	0.08
Area (mm^2)	499.0 ± 104	501.0 ± 104	491.0 ± 108	0.09
Distance to RCA (mm)	16.4 ± 3.0	16.5 ± 2.9	15.8 ± 3.2	0.24
Distance to LCA (mm)	12.7 ± 2.9	12.7 ± 2.8	12.7 ± 3.7	0.01
Calcium volume				
NCC (mm^3)	275.0 (156–484)	279.0 (158–482)	265.0 (140–520)	0.11
RCC (mm^3)	202.0 (114–340)	208.0 (117–345)	187.0 (98–327)	0.15
LCC (mm^3)	173.0 (102–338)	170.0 (97–332)	229.0 (124–426)	0.31
$LVOT_{NC}$ (mm^3)	8.4 (0.0–40)	7.0 (0.0–36)	16.0 (4.4–79)	0.32
$LVOT_{RC}$ (mm^3)	0.3 (0.0–11)	0.3 (0.0–9.2)	6.6 (0.0–26)	0.40
$LVOT_{LC}$ (mm^3)	4.7 (0.0–34)	3.0 (0.0–28)	23.7 (4.0–101)	0.66
Total DLZ (mm^3)	740.0 (470–1,252)	737.0 (468–1,190)	768.0 (528–1,497)	0.26

Values are mean ± SD, n (%), or median (interquartile range).

AVB = atrioventricular block; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DLZ = device landing zone; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LCA = left coronary artery; LCC = left coronary cusp; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; $LVOT_{LC}$ = left ventricular outflow tract area below the left coronary cusp; $LVOT_{NC}$ = left ventricular outflow tract area below the noncoronary cusp; $LVOT_{RC}$ = left ventricular outflow tract area below the right coronary cusp; MI = myocardial infarction; MSCT = multislice computed tomographic; NCC = noncoronary cusp; PAD = peripheral artery disease; PPMI = permanent pacemaker implantation; RBBB = right bundle branch block; RCA = right coronary artery; RCC = right coronary cusp.

analysis, best discriminatory thresholds were calculated by determination of the Youden index for implantation depth, as well as separately for each area of interest in the calcification analysis. Two-sided p values <0.05 were considered statistically significant.

A multivariate logistic regression analysis was performed to investigate the independent influence of possible variables on PPMI. After initial univariate regression analysis, variables with p values <0.05 were included in the multivariate regression model to test for independence. All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM, Armonk, New York).

RESULTS

Two hundred seventy-nine patients underwent TAVR with SAPIEN 3 devices during the study period. After exclusion of patients with pre-existing pacemakers (n = 47) and patients converted to open surgery (n = 3), 229 patients remained for further analysis. Patient characteristics, including baseline conduction disturbances, are presented in Table 1. The mean age was 80 ± 6 years, the mean logistic European System for Cardiac Operative Risk Evaluation score was 15.6 ± 11.5%, and 44% of patients were women. The baseline characteristics of patients with and without new-onset conduction disturbances requiring PPMI were similar regarding sex, logistic European System for Cardiac Operative Risk Evaluation score, comorbidities, and annular dimensions (Table 1). Also the frequency of baseline atrioventricular (AV) conduction disturbances did not differ between patients with or without PPMI after TAVR except for right bundle branch block (RBBB), which was significantly more frequent in patients requiring PPMI post-TAVR (15.2% vs. 2.0%; p = 0.004). Procedural characteristics and outcomes are shown in Tables 2 and 3, respectively. PPMI was performed in 14.4% of patients, mainly because of complete AV block (88%). Other indications included bradyarrhythmia, grade II AV block and grade I AV block with left bundle branch block. Time to first occurrence of new-onset conduction disturbance, time to PPMI, and adverse events associated with PPMI are shown in Table 4.

The post-procedural PPMI rate was related to implantation depth. Implantation depth was significantly greater in patients requiring PPMI than in those without need for PPMI (ventricular part of the stent frame, 29 ± 11% vs. 21 ± 5%; p < 0.001). PPMI rate was significantly higher in the upper quartile of implantation depth (range 24% to 50% ventricular part of the stent frame) compared with the lower quartiles (PPMI rate 34.5% vs. 7.6%; p < 0.001). Receiver-operating characteristic curve analysis revealed a ventricular part of the stent frame of 25.5% as the best threshold to discriminate between patients with high and low risk for PPMI. PPMI rate was 44.2% in patients with a ventricular part of the stent frame of >25.5% compared with 7.5% in patients implanted with a ventricular part lower than this threshold (p < 0.001) (Table 5).

Quantification of calcium volume of the 3 aortic valve cusps, as well as calcium volume of the LVOT, subdivided into 3 regions analogous to the aortic valve cusps, and its association with PPMI is presented in Table 5. The total calcium volume of the DLZ as well as the calcification of the 3 cusps did not differ significantly between patients with and those without need for PPMI. However, patients requiring PPMI exhibited significantly higher median calcium volumes in all 3 defined LVOT regions (area below the left coronary cusp [$LVOT_{LC}$] 23.7 mm^3 vs. 3.0 mm^3; $p < 0.001$; area below the right coronary cusp [$LVOT_{RC}$] 6.6 mm^3 vs. 0.3 mm^3; $p = 0.014$; area below the noncoronary cusp [$LVOT_{NC}$] 16.1 mm^3 vs. 7.0 mm^3; $p = 0.035$) (Figure 1). Further analysis using receiver-operating characteristic statistics revealed $LVOT_{LC}$ calcium of 13.7 mm^3, $LVOT_{RC}$ calcium of 4.8 mm^3, and $LVOT_{NC}$ calcium of 3.2 mm^3 as the best discriminatory cutoffs to distinguish between patients with high and low risk for PPMI following TAVR (PPMI rates above and below the threshold: $LVOT_{LC}$, 26.5% vs. 7.5% [$p < 0.001$]; $LVOT_{RC}$, 25.9% vs. 8.1% [$p = 0.001$]; $LVOT_{NC}$, 19.1% vs. 7.5% [$p = 0.020$]).

Mean area oversizing was 6.9 ± 11.8% in patients with need for PPMI compared with 5.1 ± 13.7% in those without need for PPMI ($p = 0.472$). According to the manufacturer's sizing recommendations, prosthesis size was within sizing range in 82% and 65%, undersized in 12% and 21%, and oversized in 6% and 14% comparing patients with and those without need for PPMI, respectively, with no significant difference between groups ($p = 0.196$). Oversizing >20% was similar in both groups (9% vs. 14%; $p = 0.585$) and had no influence on PPMI rate (Table 2).

Both pre- and post-dilation rates were numerically higher in patients eventually requiring PPMI, but without reaching statistical significance (pre-dilation, 64% vs. 48% [$p = 0.131$]; post-dilation, 9% vs. 4% [$p = 0.162$]).

Univariate logistic regression analysis revealed $LVOT_{LC}$ calcium volume >13.7 mm^3 (odds ratio [OR]: 4.4; 95% confidence interval [CI]: 2.0 to 9.7; $p < 0.001$), $LVOT_{RC}$ calcium >4.8 mm^3 (OR: 4.0; 95% CI: 1.8 to 8.6; $p < 0.001$), $LVOT_{NC}$ calcium >3.2 mm^3 (OR: 2.9; 95% CI: 1.2 to 7.0; $p = 0.018$), deep valve implantation with a ventricular part of the stent frame >25.5% (OR: 9.7; 95% CI: 4.3 to 21.9; $p < 0.001$), and pre-existing RBBB (OR: 8.3; 95% CI: 2.1 to 33.0; $p = 0.003$) as predictors of PPMI after TAVR. After the inclusion of these parameters in multivariate analysis, elevated calcium volume of $LVOT_{LC}$ (OR: 3.7; 95% CI: 1.3 to 10.6; $p = 0.016$) and $LVOT_{RC}$ (OR: 4.7; 95% CI: 1.6 to 14.1; $p = 0.005$), deep valve implantation (OR: 15.7; 95% CI: 5.7 to 43.5; $p < 0.001$), and pre-existing RBBB (OR: 16.9; 95% CI: 3.0 to 95.5; $p = 0.001$) emerged as independent predictors of need for PPMI after TAVR, whereas elevated $LVOT_{NC}$ calcium did not (OR: 0.8; 95% CI: 0.2 to 2.9; $p = 0.736$). Out-of-range oversizing ($p = 0.210$), oversizing >20% ($p = 0.424$), pre-dilation ($p = 0.094$), and post-dilation ($p = 0.169$) were not predictive, nor was any other variable (Table 6).

Several groups with differing risk for PPMI emerged by combination of the 4 independent risk factors identified by multivariate analysis (Figure 2). The PPMI rates were 12.7%, 19.6%, and 86.7% in patients with 1 (10 of 79 patients), 2 (9 of 46 patients),

TABLE 2 Procedural Characteristics

	All (N = 229)	No PPMI (n = 196)	PPMI (n = 33)	d Value
Access site				
Transfemoral	195 (85.2)	164 (83.7)	31 (93.9)	0.21
Transapical	30 (13.1)	29 (14.8)	1 (3.0)	
Transaortic	4 (1.7)	3 (1.5)	1 (3.0)	
Valve size (mm)				
23	74 (32.3)	62 (31.6)	12 (36.4)	0.01
26	93 (40.6)	82 (41.8)	11 (33.3)	
29	62 (27.1)	52 (26.5)	10 (30.3)	
Pre-dilation	114 (49.8)	93 (47.7)	21 (63.6)	0.33
Post-dilation	10 (4.4)	7 (3.6)	3 (9.1)	0.23
Mean area oversizing (%)	5.4 ± 13.4	5.1 ± 13.7	6.9 ± 11.8	0.14
Sizing range				
Undersized	45 (19.7)	41 (20.9)	4 (12.1)	0.01
Within sizing range	154 (67.2)	127 (64.8)	27 (81.8)	
Oversized	30 (13.1)	28 (14.3)	2 (6.1)	
Oversized >20%	31 (13.5)	28 (14.3)	3 (9.1)	0.16
Mean implantation depth (% ventricular part of the stent frame)	22.4 ± 6.9	21.3 ± 5.0	29.3 ± 11.5	0.91
Implantation depth				
<20%	85 (37.1)	79 (40.3)	6 (18.2)	0.84
20%-30%	126 (55.0)	109 (55.6)	17 (51.5)	
>30%	18 (7.9)	8 (4.1)	10 (30.3)	

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

TABLE 3 Procedural Outcomes

In-hospital mortality	8 (3.5)
Vascular complications	20 (8.7)
Bleeding	14 (6.1)
Stroke	4 (1.7)
Coronary obstruction	0 (0.0)
PVR 2+ at discharge	1 (0.5)
Permanent pacemaker implantation	33 (14.4)

Values are n (%).
PVR = paravalvular regurgitation.

TABLE 4 Indication, Timing, and Adverse Events of Pacemaker Implantation

Indication for PPMI	
AVB grade III	29 (87.9)
Bradyarrhythmia	2 (6.1)
AVB grade II (Mobitz type II)	1 (3.0)
AVB grade I + LBBB	1 (3.0)
Days to first occurrence of conduction disturbance	0.5 ± 1.5
First occurrence on same day as TAVR	29 (87.9)
First occurrence 1–3 days post-TAVR	2 (6.1)
First occurrence ≥4 days post-TAVR	2 (6.1)
Days post-TAVR to PPMI	3.5 ± 4.1
PPMI on same day as TAVR	8 (24.2)
PPMI 1–3 days post-TAVR	15 (45.5)
PPMI ≥4 days post-TAVR	10 (30.3)
PPMI-related adverse events	3 (9.1)
Cardiac tamponade	1 (3.0)
Pneumothorax	1 (3.0)
Bleeding	1 (3.0)

Values are n (%) or mean ± SD.
TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

and 3 (13 of 15) risk factors, respectively. The elevated PPMI rate in patients with 2 or more risk factors was driven largely by implantation depth (57.1% vs. 18.2%). Patients without any of the identified risk factors had a PPMI rate as low as 1.1% (1 of 89 patients). Using only the risk factors deep valve implantation and elevated $LVOT_{LC}$ calcium volume, the PPMI rate was 61.9% in patients with both elevated $LVOT_{LC}$ calcium load and deep valve implantation (13 of 21 patients), whereas patients without either of the 2 risk factors had a PPMI rate as low as 4.0% (5 of 124 patients). The PPMI rate was 27.3% (6 of 22 patients) in patients with deep valve implantation and 14.5% (9 of 62 patients) in patients with elevated $LVOT_{LC}$ calcium load.

After a preliminary analysis of our data revealing the strong influence of implantation depth on final PPMI rate, an implantation technique aiming at a high final prosthesis position was implemented at our hospital starting in February 2015 (Figure 3). The average ventricular portion of the stent frame decreased from 24 ± 8% in the 120 patients treated before February 2015 to 21 ± 5% in the following 109 patients ($p = 0.012$) (Figure 4). This was driven mainly by a significant reduction of patients with very low implantation with a ventricular part of the stent frame >30% (13% vs. 3%; $p = 0.006$). Accordingly, the PPMI rate decreased from 19.2% (23 of 120 patients) to 9.2% (10 of 109 patients) after the implementation of a high-implantation technique ($p = 0.038$).

DISCUSSION

The aim of the present study was to investigate predictors of the occurrence of new-onset conduction disturbances requiring PPMI after transcatheter aortic valve replacement using the balloon-expandable SAPIEN 3 aortic bioprosthesis. The main findings of the study are as follows: 1) deep valve implantation, elevated $LVOT_{LC}$ and $LVOT_{RC}$ calcification, and preexisting RBBB are independent predictors of PPMI after TAVR; 2) the combination of the 4 independent predictors identified several patient groups with differing PPMI risk; and 3) a minor modification of the implantation technique aimed at a slightly higher final valve position indeed reduced the PPMI rate after SAPIEN 3 implantation.

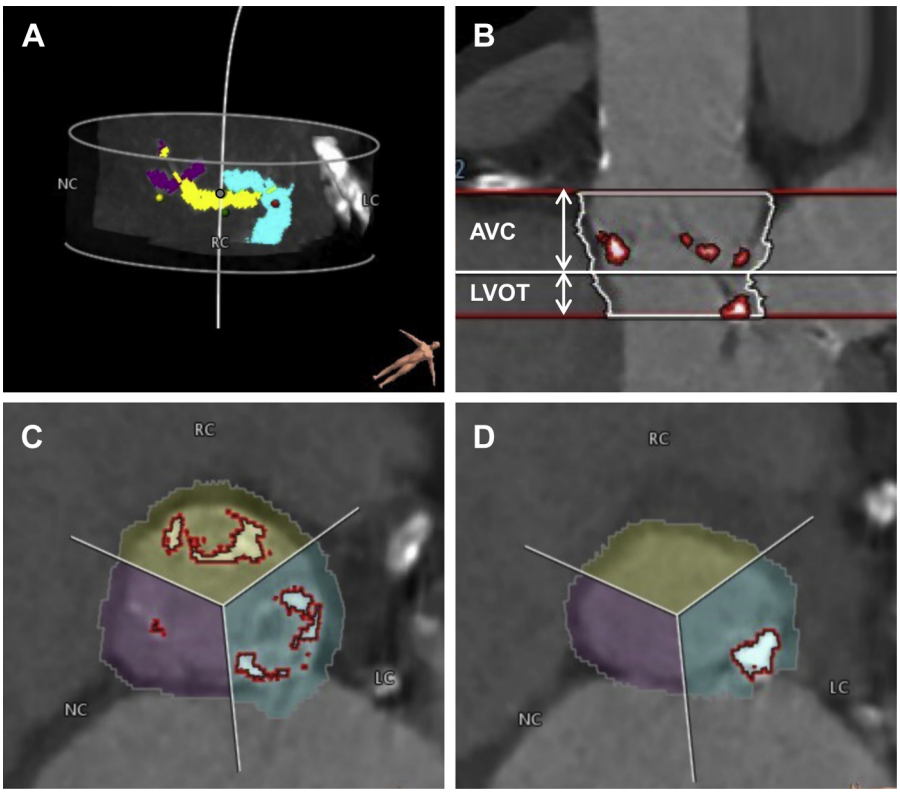
A number of risk factors have been associated with PPMI after TAVR, namely, baseline conductions disturbances and procedure-related factors such as oversizing, post-dilation, and implantation depth (18,19). On an anatomic level, the AV bundle penetrates the central fibrous body at the right fibrous

TABLE 5 Permanent Pacemaker Implantation Rates Above and Below Median and Youden Index

		PPMI Rate (%)		p	Youden	PPMI Rate (%)		p
	Median	Below Median	Above Median	Value	Index	Below Youden Index	Above Youden Index	Value
Implantation depth	21.3%	7.0 (8/115)	21.9 (25/114)	0.001	25.5%	7.5 (14/186)	44.2 (19/43)	<0.001
NCC	275	15.7 (18/115)	13.2 (15/114)	0.707	791	13.1 (28/213)	31.3 (5/16)	0.062
RCC	202	17.4 (20/115)	11.4 (13/114)	0.259	204	17.4 (20/115)	11.4 (13/114)	0.259
LCC	173	12.2 (14/115)	16.7 (19/114)	0.353	131	9.1 (8/88)	17.7 (25/141)	0.083
$LVOT_{NC}$	8	11.3 (13/115)	17.5 (20/114)	0.193	3.2	7.5 (7/93)	19.1 (26/136)	0.020
$LVOT_{RC}$	0.3	9.6 (11/115)	19.3 (22/114)	0.038	4.8	8.1 (12/148)	25.9 (21/81)	0.001
$LVOT_{LC}$	5	7.9 (9/114)	20.9 (24/115)	0.008	13.7	7.5 (11/146)	26.5 (22/83)	<0.001
DLZ	740	13.9 (16/115)	14.9 (17/114)	0.853	1,778	12.6 (26/207)	31.8 (7/22)	0.024

The best discriminatory threshold between a low-risk and a high-risk group for PPMI was determined by calculation of Youden indices.
Abbreviations as in Table 1.

FIGURE 1 Device Landing Zone Calcium Quantification



(A) Three-dimensional reconstruction of total device landing zone calcium according to leaflet sector. The **red**, **green**, and **yellow dots** mark the nadirs of the coronary cusps and thus the basal plane. **(B)** The aortic valve complex (AVC) was defined from the basal plane **(white line)** to the lower coronary ostium **(long arrow)**. The left ventricular outflow tract (LVOT) was defined 10 mm below the basal plane **(short arrow)**. **(C)** Calcium load at AVC level (noncoronary cusp [NC] 118 mm^3, right coronary cusp [RC] 180 mm^3, left coronary cusp [LC] 230 mm^3). **(D)** Calcium at LVOT level ($LVOT_{NC}$ 0 mm^3, $LVOT_{RC}$ 0 mm^3, $LVOT_{LC}$ 301 mm^3). The elevated LVOT calcification was associated with permanent pacemaker implantation in this particular patient.

trigone and continues in the membranous part of the interventricular septum located in the area under the right and the noncoronary aortic cusps, giving rise to the left bundle branch (20). Damage through direct mechanical interaction of the valve stent frame with the AV conduction system in the LVOT may result in new-onset left bundle branch block or complete AV block after TAVR.

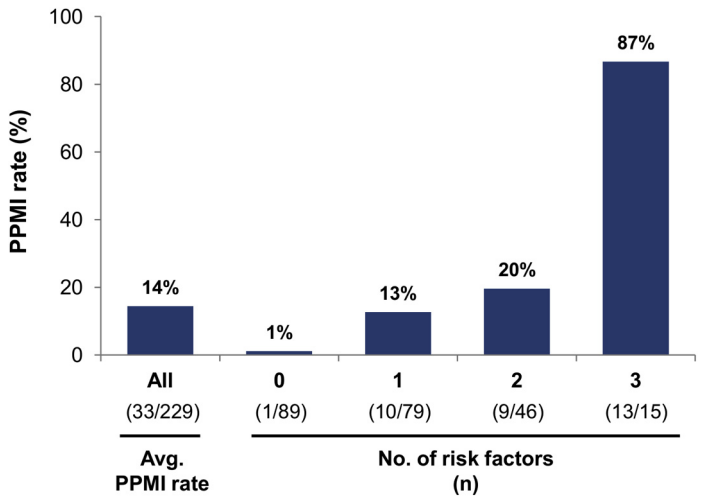
Although the PPMI rate was unaffected by sizing or by pre- and post-dilation in our study, implantation depth was found to be an independent predictor of PPMI. Valves in patients requiring PPMI because of new-onset AV conduction disturbances were implanted significantly deeper into the LVOT than in patients without need for PPMI. Implantation depth as a risk factor for PPMI has been described previously mainly in the context of TAVR with the self-expanding CoreValve device (Medtronic, Minneapolis, Minnesota), and the PPMI rate could be reduced by aiming at a higher final valve position (21,22). In a preliminary study of 29 patients, Tarantini et al. (23) described a relation between implantation depth and PPMI rate after SAPIEN 3 implantation and proposed an implantation technique aimed at a maximum LVOT extension of the stent frame of <8 mm to reduce PPMI rate, which would result in a ventricular portion of 36% to 44% depending on prosthesis size. A very recent study showed similar results and proposed an implantation technique aimed at a ventricular portion of <30% (12). In the present study, based on the currently largest SAPIEN 3 patient population, a ventricular implantation depth of <25.5% was found to be the best discriminatory threshold for reduced PPMI risk. From a clinical point of view, it is crucial to avoid very deep implantation, given the extremely high PPMI rate in the upper quartile of implantation depth. Therefore, the central marker was positioned markedly above the base-of-cusps line before inflation

TABLE 6 Univariate and Multivariate Regression Analysis to Identify Predictors of Permanent Pacemaker Implantation

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Age (yrs)	1.1	0.99–1.13	0.094			
Female	1.9	0.89–3.98	0.096			
LVEF	1.0	0.98–1.04	0.618			
Logistic EuroSCORE I	1.0	0.96–1.03	0.619			
Atrial fibrillation	0.9	0.40–1.92	0.749			
AVB grade I	0.8	0.18–3.74	0.787			
LBBB	1.8	0.22–14.42	0.588			
RBBB	8.3	2.11–32.98	0.003	16.9	3.0–95.5	0.001
Incomplete RBBB	2.0	0.38–10.26	0.417			
NCC calcification >790.8 mm^3	3.0	0.97–9.29	0.056			
RCC calcification >203.8 mm^3	0.6	0.29–1.30	0.200			
LCC calcification >131.4 mm^3	2.2	0.93–5.02	0.075			
$LVOT_{NC}$ calcification >3.2 mm^3	2.9	1.20–7.01	0.018	0.8	0.2–2.9	0.736
$LVOT_{RC}$ calcification >4.8 mm^3	4.0	1.83–8.58	<0.001	4.7	1.6–14.1	0.005
$LVOT_{LC}$ calcification >13.7 mm^3	4.4	2.02–9.70	<0.001	3.7	1.3–10.6	0.016
Pre-dilation	1.9	0.90–4.12	0.094			
Post-dilation	2.7	0.66–10.96	0.169			
Out-of-range oversizing	0.4	0.09–1.71	0.210			
Oversizing >20%	0.6	0.17–2.10	0.424			
Implantation depth >25.5% ventricular part of the stent frame	9.7	4.32–21.90	<0.001	15.7	5.7–43.5	<0.001

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

FIGURE 2 Permanent Pacemaker Implantation Rate Dependent on Presence of Risk Factors



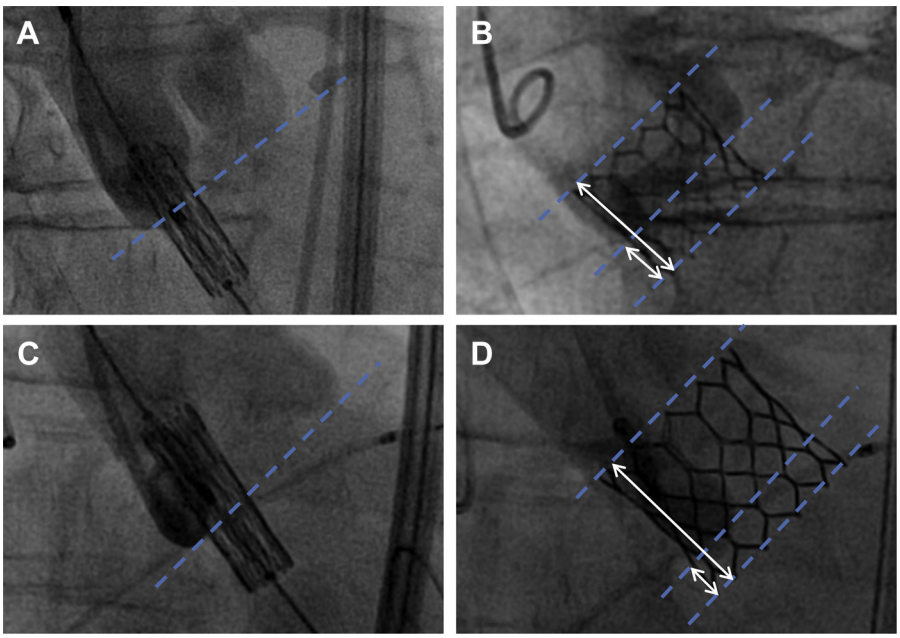
Several patient groups with differing rates of permanent pacemaker implantation (PPMI) emerged by combination of the 4 risk factors elevated left ventricular outflow tract (LVOT) calcification in the area below the left coronary cusp, elevated LVOT calcification in the area below the right coronary cusp, pre-existing right bundle branch block, and deep valve implantation.

and thus still higher than the current manufacturer's recommendation, which is to position the lower end of the central marker on the base-of-cusps line. Implementing the described high-implantation technique systematically in February 2015, after a preliminary analysis of our data, the PPMI rate was reduced from 19.2% to 9.2%. Of note, implantation with a ventricular portion of <23% did not increase the risk for relevant PVR in our cohort ($p = 0.851$), nor did we observe any case of valve embolization or coronary obstruction, which might have been due to the larger meshes in the upper segment of the stent frame.

Calcification of the DLZ as a risk factor for PPMI was investigated previously using the semi-quantitative Agatston score, but a convincing relationship could not be shown (24,25). In a recent study, applying a similar method as used in our study, elevated calcification burden of the left coronary cusp was associated with higher PPMI rates in the context of TAVR with the SAPIEN XT or CoreValve prosthesis, whereas total DLZ calcium was similar in both groups (26). Also in our study, total DLZ calcium did not differ between patients with and those without need for PPMI, but the distribution of calcium was significantly different. We found a strong correlation between elevated $LVOT_{LC}$ and $LVOT_{RC}$ calcification and PPMI. It may be speculated that the described asymmetry of calcium distribution may lead to a shift of the expanded prosthesis away from the central line in the direction of the area under the right and noncoronary aortic cusps. Thereby, the mechanical stress on the AV conduction system might be increased locally by the uneven distribution of radial forces. Moreover, different stent expansion patterns of the SAPIEN 3 compared with the SAPIEN XT have been described recently (27). Whereas in the SAPIEN XT, the expansion area increased from the inflow level, reaching its peak at the outflow level, the SAPIEN 3 by contrast has its largest expansion at the LVOT end of the stent frame (105% of the nominal area). These different expansion patterns may contribute to an elevated localized pressure in the LVOT and thus higher rates of AV conduction disturbances requiring PPMI in SAPIEN 3 patients.

Also, pre-existing RBBB emerged as a strong predictor of PPMI after TAVR, as described previously in numerous studies (18,19). It should be noted that in patients with pre-existing RBBB, new-onset LBBB is clinically indistinguishable from complete AV block and results in need for PPMI. Thus, the higher PPMI rate in patients with baseline RBBB might be less influenced by implantation technique.

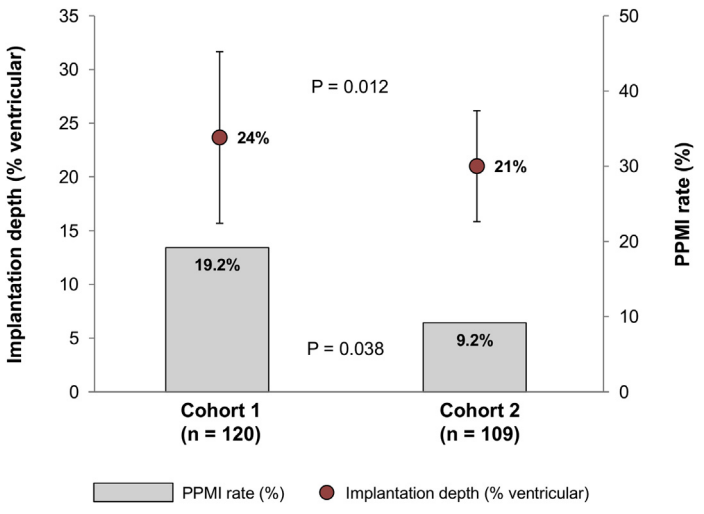
FIGURE 3 Assessment of Implantation Depth



Two clinical scenarios of low **(A,B)** and high **(C,D)** valve implantation illustrating the relationship between initial position of the central marker and final valve position. The native aortic annulus was marked by tracing a line linking the sinuses of Valsalva. The entire stent frame length **(long arrows)** and the ventricular portion below the aortic annulus **(short arrows)** were measured at the septal side. Implantation depth was expressed as a percentage of the ventricular part of the stent frame in relation to the complete stent frame length. **(A)** The central marker is located below the aortic annulus before deployment. **(B)** The initial low position of the central marker results in a low final valve position (ventricular part 38%), leading to pacemaker implantation in this particular case. **(C)** The central marker is located above the aortic annulus before deployment. **(D)** The initial high position of the central marker results in a high final valve frame position (ventricular part 22%).

STUDY LIMITATIONS. This study was a nonrandomized observational analysis with all inherent limitations. Besides implantation technique, growing experience of the operators and other, to date, unknown factors may have influenced the lower PPMI rate in the more recently treated patients. Moreover, implantation depth assessment was based on fluoroscopic images and could have been under- or overestimated in case of incongruity of the annulus and prosthesis plane. However, angiograms were optimized for valve frame orientation to address this issue in every patient. A rather new method for the determination of calcium volume was used, thereby using standard pre-operative contrast-enhanced multislice computed tomographic images as used previously (26). Finally, because of the relatively small number of patients, interactions of parameters influencing PPMI rate included in the multivariate analysis could not be analyzed. Moreover, it is not possible to draw any conclusive evidence whether PPMI influences mortality.

FIGURE 4 Implantation Depth and Permanent Pacemaker Implantation Rate Before and After Adoption of a High-Implantation Technique



After the implementation of a high-implantation technique, implantation height increased, while permanent pacemaker implantation (PPMI) rate decreased accordingly.

CONCLUSIONS

From our data, we conclude that the occurrence of new conduction disturbances requiring PPMI in most cases arises from a combination of patient-dependent features and low valve implantation. These findings emphasize the importance of high valve positioning to avoid excessive PPMI rates: although LVOT calcium burden and pre-existing RBBB as patient-related factors cannot be modified, a minor modification of the currently used implantation technique may effectively reduce the number of patients requiring PPMI without increasing the risk for PVR or coronary obstruction.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Tanja K. Rudolph, Department of Cardiology, Heart Center, University of Cologne, Kerpener Straße 62, Cologne 50937, Germany. E-mail: tanja.rudolph@uk-koeln.de.

PERSPECTIVES

WHAT IS KNOWN? New-onset conduction disturbances requiring PPMI occur in up to 26% of patients treated with the SAPIEN 3 transcatheter heart valve.

WHAT IS NEW? PPMI rate is strongly related to implantation depth and DLZ calcification pattern, and a patient's individual risk can be stratified on the basis of these risk factors. A slight modification of the implantation technique aimed at a higher final valve position significantly reduces PPMI rates.

WHAT IS NEXT? The impact of a modified implantation technique on long-term outcomes should be evaluated in future studies.

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