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Minimizing Permanent Pacemaker Following Repositionable Self-Expanding Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to minimize the risk of permanent pacemaker implantation (PPMI) with contemporary repositionable self-expanding transcatheter aortic valve replacement (TAVR).

BACKGROUND Self-expanding TAVR traditionally carries a high risk of PPMI. Limited data exist on the use of the repositionable devices to minimize this risk.

METHODS At NYU Langone Health, 248 consecutive patients with severe aortic stenosis underwent TAVR under conscious sedation with repositionable self-expanding TAVR with a standard approach to device implantation. A detailed analysis of multiple factors contributing to PPMI was performed; this was used to generate an anatomically guided MInimizing Depth According to the membranous Septum (MIDAS) approach to device implantation, aiming for pre-release depth in relation to the noncoronary cusp of less than the length of the membranous septum (MS).

RESULTS Right bundle branch block, MS length, largest device size (Evolut 34 XL; Medtronic, Minneapolis, Minnesota), and implant depth > MS length predicted PPMI. On multivariate analysis, only implant depth > MS length (odds ratio: 8.04; 95% confidence interval: 2.58 to 25.04; $p < 0.001$) and Evolut 34 XL (odds ratio: 4.96; 95% confidence interval: 1.68 to 14.63; $p = 0.004$) were independent predictors of PPMI. The MIDAS approach was applied prospectively to a consecutive series of 100 patients, with operators aiming to position the device at a depth of < MS length whenever possible; this reduced the new PPMI rate from 9.7% (24 of 248) in the standard cohort to 3.0% ($p = 0.035$), and the rate of new left bundle branch block from 25.8% to 9% ($p < 0.001$).

CONCLUSIONS Using a patient-specific MIDAS approach to device implantation, repositionable self-expanding TAVR achieved very low and predictable rates of PPMI which are significantly lower than previously reported with self-expanding TAVR. (J Am Coll Cardiol Intv 2019;12:1796–807) © 2019 by the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) is an established alternative to surgical aortic valve replacement (SAVR) but has carried a higher risk of permanent pacemaker (PPM) implantation (PPMI) (1–3). This risk has historically been higher with self-expanding rather than balloon-expandable TAVR (4). In recent studies of TAVR in low surgical risk patients, the outcomes of

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TAVR were favorable in relation to SAVR, but the excess of pacemaker implantation with self-expanding TAVR was noted (5); the rate of new PPM was 17.4% with self-expanding TAVR, 6.6% with balloon-expandable TAVR (6), and 4.1% to 6.1% with SAVR (5,6). However, device positioning has emerged as an important determinant of PPMI, with higher device implantation resulting in lower rates of PPMI (7–9). Recent iterations of self-expandable TAVR devices are repositionable (10,11), which provides a further opportunity to reduce the risk of PPMI by intraprocedural optimization of device positioning. We sought to first retrospectively study patients undergoing a standard approach to self-expandable repositionable TAVR implantation and performed a detailed analysis of anatomic, electrophysiological, and procedural factors contributing to PPMI in this context. We then used information from this analysis to modify practice and prospectively evaluated the impact of this new patient-specific precision-medicine based approach on new PPMI.

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METHODS

STUDY POPULATION AND PROCEDURE. Between November 2016 and March 2018, 456 patients were treated with TAVR at NYU Langone Health. After excluding patients with balloon-expandable TAVR and other valve designs, previous PPMI, previous bioprosthesis, and poor computed tomography (CT) imaging quality, a total of 248 patients with severe native aortic stenosis were treated with contemporary repositionable self-expanding TAVR and included in the final analysis (**Figure 1**). The devices employed included the Evolut R, Evolut Pro, and Evolut 34 XL (Medtronic, Minneapolis, Minnesota). TAVR sizing was based on contrast CT, with all measurements over-read by an expert CT imager (H.J.).

All cases were performed with transfemoral access, conscious sedation and local anesthesia. All procedures were performed in a Siemens Zeego or Pheno hybrid operating room (Siemens Medical Solutions USA, Malvern, Pennsylvania), which incorporates fluoroscopy with autocalibration. When the devices were deployed to 80%, a pre-release coaxial root angiogram was performed to determine suitability for immediate device release or device repositioning. Device positioning was assessed as a modifiable parameter on final pre-release angiogram, measured retrospectively using Siemens syngo software, Syngo Via, version VA20F, as depth in mm from the base of the noncoronary cusp (NCC) to the prosthesis stent inflow on the corresponding side (**Central Illustration**). A final post-release angiogram was not routinely performed, rather the fully deployed valve function was assessed with expert intraprocedural echocardiography, conserving the use of contrast. In our "standard" approach, we implanted the repositionable prosthesis in line with instructions for use of the device (3 to 5 mm), aiming for the higher range of the instructions for use (3 to 4 mm) in relation to the NCC and recapturing and repositioning the device when the device initially landed considerably lower than this target.

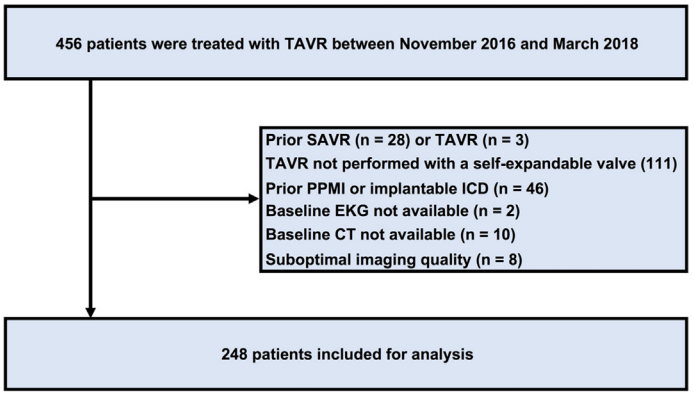
Following the procedure, patients had several electrocardiograms (ECGs) to document serial changes in conduction and were routinely discharged the following day in the absence of significant changes in cardiac conduction. In the event of persistent high-grade atrioventricular heart block, PPMI was performed. Follow-up was complete in all patients to 30 days, capturing potentially procedure-related PPMI. The study complies with the Declaration of Helsinki and a locally appointed ethics committee confirmed its appropriateness as a clinical quality improvement initiative.

MULTIDETECTOR COMPUTED TOMOGRAPHY IMAGE ACQUISITION AND ANALYSIS. An ECG-gated multidetector CT study was performed pre-TAVR, as a standard-of-care investigation. Patients were evaluated using a Siemens Somatom Force scanner (Siemens Medical Solutions USA) using collimation of

ABBREVIATIONS AND ACRONYMS

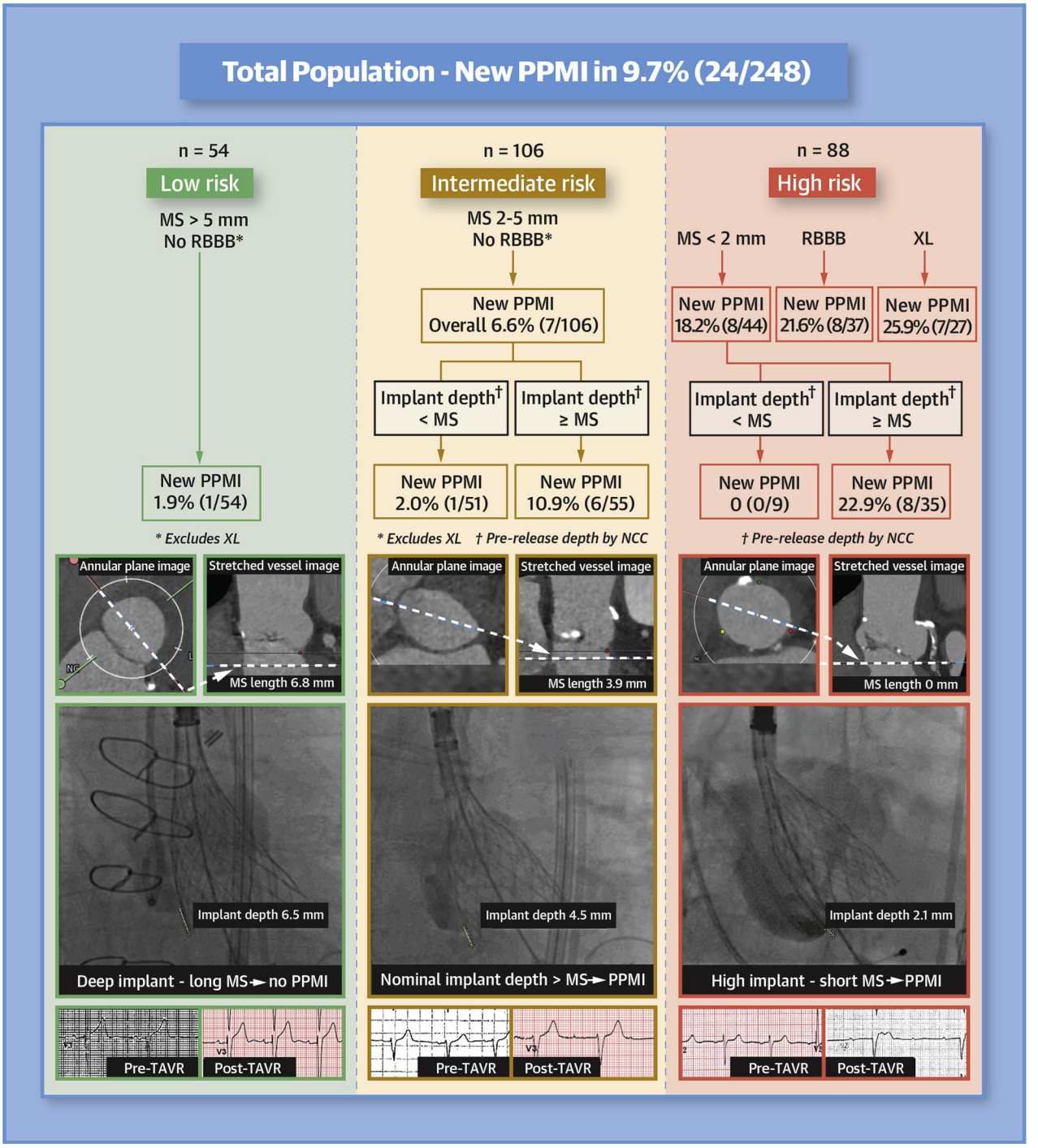
AV = atrioventricular
CI = confidence interval
CT = computed tomography
ECG = electrocardiogram
LBBB = left bundle branch block
MIDAS = MInimizing Depth According to the membranous Septum
MS = membranous septum
NCC = noncoronary cusp
PPM = permanent pacemaker
PPMI = permanent pacemaker implantation
RBBB = right bundle branch block
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement

FIGURE 1 Study Workflow



The source of the retrospective cohort studied is described. CT = computed tomography; EKG = electrocardiogram; ICD = implantable cardioverter-defibrillator; PPMI = permanent pacemaker implantation; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

CENTRAL ILLUSTRATION **The Impact on PPMI of TAVR Device Positioning in Relation to MS Length**



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Data from the retrospective cohort are shown. Identified risk factors for new PPMI included MS length <2 mm, RBBB, and larger prosthesis (XL). The frequencies of new PPMI in each stratum of risk are shown as specified along with corresponding case examples. MS = membranous septum; PPMI = permanent pacemaker implantation; RBBB = right bundle branch block; TAVR = transcatheter aortic valve replacement.

0.6 mm at a fixed pitch of 0.2 with an injection of 50 to 70 ml of iopamidol (Isovue-370; Bracco Diagnostics, Monroe Township, New Jersey). A dedicated protocol was formulated, with 100 to 120 kV and tube current modified according to the patient's size. Image acquisition was, for the most part, performed with retrospective ECG gating. CT Digital Imaging and Communications in Medicine (DICOM) data were analyzed by a dedicated advanced imaging core laboratory, using 3mensio Valves software version 8.0, 9.0, or 9.1 (Pie Medical Imaging, Maastricht, the Netherlands). Annular and left ventricular outflow tract sizing were made in mid-systole. Calcium quantification of leaflet calcification was made using the J-score from contrast scans (850-Hounsfield Unit threshold of detection) (12). The membranous septum (MS) was measured by determining the thinnest part of the interventricular septum on the perpendicular annular plane (axial) image (usually in line with the tricuspid annulus), using the perpendicular crosshairs to find the corresponding stretched vessel image and using the latter to measure the perpendicular vertical distance from the annular plane to the vertex of the muscular septum (**Central Illustration**).

PROSPECTIVE SERIES. Data from the retrospective analysis was used to optimize depth of implantation according to patient anatomy and, following a period of standardization of image analysis and procedural technique, operators followed an anatomically guided approach to device positioning based on the CT-determined MS length. Specifically, rather than simply following our standard approach, operators attempted to position the prosthesis at a pre-release depth in relation to the NCC of smaller than the length of the MS. The frequency of new PPMI following this prospective, anatomically guided MInimizing Depth According to the membranous Septum (MIDAS) approach was compared with the standard approach.

STATISTICAL ANALYSIS. Continuous variables were tested for a normality of distribution by using the Shapiro-Wilk test and were reported and analyzed appropriately thereafter. Categorical variables were compared by chi-square statistics or the Fisher exact test. Mann-Whitney *U*-test were used in case of abnormal distribution. Receiver-operating characteristic curves were generated using new PPMI as the endpoint. Multivariate analysis was also performed using a forward-logistic regression stepwise method and generated a predictive model for PPMI that was further evaluated using c-statistics of the receiver-operating characteristic curve. All parameters significant for prediction of pre-procedural or post-procedural new PPMI ($p < 0.05$) were entered into a multivariate regression model. Sensitivity, specificity, negative predictive value, and positive predictive value were calculated using specific cut-offs by using the Youden index generated from the receiver-operating characteristic curve on the basis of the predictive probability for PPMI. All the analyses were considered significant at a 2-tailed p value <0.05. SPSS statistics software version 25.0 (SPSS, Chicago, Illinois) were used to perform all statistical evaluations.

RESULTS

PATIENTS AND RELEVANT OUTCOMES. All but 1 patient was treated by the transfemoral approach under conscious sedation (99.6%). In-hospital mortality was 0.4% and in-hospital stroke 2.4%; mortality at 30 days was 1.2%. There was 1 device embolization/"pop-out" (0.4%) and paravalvular leak ≥ moderate in 0.4%. The overall rate of PPMI was 9.7% (24 of 248 cases). The majority of pacemakers were implanted within 72 h of the procedure with only 3 patients undergoing new pacemaker implantation beyond that time (at days 6, 11, and 73, respectively). The indication for PPMI was complete heart block in 22 of 24 patients, and in 1 patient there was high-grade second-degree heart block. In a further patient, there was Mobitz type 1 heart block, left bundle branch block (LBBB), occasional dizzy spells, and heart rate of 50 beats/min with a reduced ejection fraction of 25%; a cardiac resynchronization therapy defibrillator was implanted.

MS LENGTH: REPRODUCIBILITY. In paired sample comparisons of repeated measures of 20 randomly selected consecutive cases at independent sittings, interobserver measurements revealed a paired samples correlation coefficient of 0.83; $p < 0.001$ and paired difference of 0.23 mm (95% confidence interval [CI]: −0.27 to 0.73; $p = 0.35$); intraobserver measurements revealed a paired samples correlation coefficient of 0.82; $p < 0.001$ and paired difference of 0.07 mm (95% CI: −0.58 to 0.44; $p = 0.78$).

BASELINE PREDICTORS OF PPMI. Baseline clinical, electrocardiographic, echocardiographic, and CT variables and procedural variables are shown (**Tables 1 and 2**). Notable baseline predictors of PPMI were right bundle branch block (RBBB) (**Table 1**) and larger aortic annular and root dimensions on CT (**Table 2**), but not degree of device oversizing by annular CT angiography perimeter (**Table 3**). Shorter MS length was a predictor of PPMI. Indeed, 23 of the 24 patients undergoing new PPMI had MS <5 mm. Patients with a MS ≥5 mm had a PPMI rate of 1.4%, whereas if MS

TABLE 1 Baseline Characteristics and PPMI

	Total (N = 248)	PPMI (n = 24)	No PPMI (n = 224)	p Value
Baseline clinical variables				
Age, yrs	83.2 ± 6.9	84.4 ± 5.3	83.1 ± 7.1	0.271
Male	142 (57.3)	10 (41.7)	132 (58.9)	0.104
Height, m	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.070
Weight, kg	73.1 ± 17.8	76.8 ± 12.9	72.7 ± 18.2	0.290
Body surface area, m^2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.109
Body mass index, kg/m^2	27.5 ± 6.0	27.9 ± 5.4	27.5 ± 6.1	0.785
STS score, %	6.0 ± 2.9	5.9 ± 2.6	6.0 ± 3.0	0.569
Frailty	184 (74.2)	20 (83.3)	164 (73.2)	0.326
Congestive heart failure	140 (56.5)	14 (58.3)	126 (56.3)	0.901
Diabetes	76 (30.7)	7 (29.2)	69 (30.8)	0.836
Chronic kidney disease	60 (24.2)	7 (29.2)	53 (23.7)	0.575
Chronic lung disease	65 (26.2)	6 (25.0)	59 (26.3)	0.858
Chronic liver disease	6 (2.4)	0 (0.0)	6 (2.7)	0.414
Baseline electrocardiographic variables				
Persistent atrial fibrillation	43 (17.3)	4 (16.7)	39 (17.4)	0.927
Presence of first-degree AVB	29 (11.7)	4 (16.7)	25 (11.2)	0.425
Presence of left anterior fascicular block	12 (4.8)	1 (4.2)	11 (4.9)	0.872
Presence of left posterior fascicular block	4 (1.6)	1 (4.2)	3 (1.3)	0.296
Presence of LBBB	14 (5.7)	0 (0.0)	14 (6.3)	0.206
Presence of RBBB	37 (14.9)	8 (33.3)	29 (13.0)	**0.008**
Presence of bifascicular block	8 (3.2)	2 (8.3)	6 (2.7)	0.240
Baseline heart rate, beats/min	71.3 ± 14.4	68.4 ± 12.3	71.6 ± 14.6	0.305
Heart rate <40 beats/min	0	0	0	
Heart rate <50 beats/min	4 (1.6)	0	4 (1.8)	0.509
PR interval, ms	177.5 ± 39.6	184.8 ± 46.4	176.7 ± 38.9	0.371
PR interval ≥250 ms	7 (2.8)	2 (8.3)	7 (3.1)	0.178
PR interval ≥300 ms	4 (1.6)	1 (4.2)	3 (1.3)	0.281
QRS duration, ms	101.2 ± 27.9	111.8 ± 27.4	100.0 ± 27.8	0.058
P axis, degree	47.1 ± 23.4	48.4 ± 16.5	47.0 ± 24.0	0.712
R axis, degree	8.9 ± 45.5	4.7 ± 58.2	9.3 ± 44.1	0.679
QTc, ms	447.0 ± 40.1	454.1 ± 26.7	446.2 ± 41.3	0.399
Baseline echocardiographic variables				
Baseline LVEF, %	64.5 ± 11.6	65.4 ± 12.8	64.4 ± 11.5	0.669
Peak jet velocity, m/s	4.1 ± 0.6	4.1 ± 0.6	4.1 ± 0.6	0.716
Mean pressure gradient, mm Hg	41.2 ± 13.4	41.4 ± 13.6	41.2 ± 13.4	0.938
Aortic valve area, cm^2	0.7 ± 0.2	0.8 ± 0.3	0.7 ± 0.2	0.331
Left ventricular end-diastolic diameter, mm	41.4 ± 7.3	41.9 ± 5.5	41.4 ± 7.5	0.771

Values are mean ± SD or n (%). p Values in **bold** are statistically significant.

AVB = atrioventricular block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PPMI = permanent pacemaker implantation; STS = Society of Thoracic Surgeons.

was <5 mm, it was 12.9% (23 of 178); if MS was <2 mm, the rate of PPMI was 18.2% (8 of 44).

PROCEDURAL PREDICTORS OF PPMI. Procedural variables are shown in Table 3. Procedural predictors of PPMI included larger device size, pre-release implant depth, and pre-release implant depth > MS length. There was no difference in PPMI between Evolut R and Evolut Pro (Table 3, Figure 2), but there was a clear correlation between increasing device size and PPMI (Table 3, Figure 2).

MULTIVARIATE PREDICTORS OF PPMI. A multivariate model including presence of RBBB, MS length, device size, and implant depth relative to MS length showed only device size (34 XL) and implant depth in relation to MS length to remain significant predictors of new PPMI (Table 4). Predicted probabilities

TABLE 2 CT Characteristics and PPMI

	Total (N = 248)	PPMI (n = 24)	No PPMI (n = 224)	p Value
Annulus perimeter, mm	75.5 ± 16.4	78.0 ± 7.5	75.2 ± 17.0	0.442
Annulus area, mm^2	429.4 ± 82.3	470.8 ± 86.2	424.9 ± 80.8	**0.009**
Mean annulus diameter, mm	23.9 ± 2.4	25.2 ± 2.6	23.7 ± 2.4	**0.005**
LVOT perimeter, mm	73.3 ± 8.2	77.1 ± 8.8	72.9 ± 8.1	**0.016**
LVOT area, mm^2	408.3 ± 96.3	450.7 ± 102.6	403.7 ± 94.7	**0.023**
LVOT perimeter > annulus perimeter	88 (35.5)	12 (50.0)	76 (33.9)	0.118
LVOT/annulus perimeter ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.572
LVOT/annulus area ratio	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	0.885
LVOT/annulus mean diameter ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.963
SOV mean diameter, mm	31.4 ± 3.5	33.4 ± 3.7	31.2 ± 3.5	**0.003**
STJ diameter, mm	27.4 ± 3.4	28.8 ± 3.6	27.2 ± 3.4	**0.031**
Ascending aorta diameter at 40 mm, mm	32.5 ± 3.4	33.7 ± 3.2	32.4 ± 3.4	0.077
Aortic root angulation, degrees	47.3 ± 9.3	50.2 ± 10.5	47.0 ± 9.1	0.109
LCA height, mm	13.6 ± 3.1	14.7 ± 3.1	13.5 ± 3.1	0.068
RCA height, mm	16.5 ± 3.0	17.9 ± 3.6	16.3 ± 2.9	**0.015**
Bicuspid aortic valve	14 (5.7)	1 (4.2)	13 (5.8)	0.741
Moderate or severe LVOT calcium	59 (23.8)	9 (37.5)	50 (22.3)	0.097
Severe valve calcium	69 (27.8)	8 (33.3)	61 (27.2)	0.276
HU-850 valve calcium volume, mm^3	162.1 (63.2–323.9)	220.0 (108.6–369.5)	156.1 (58.9–322.2)	0.146
HU-850 valve calcium volume ≥250 mm^3	88 (35.5)	11 (45.8)	77 (34.4)	0.265
HU-850 valve calcium volume ≥500 mm^3	28 (11.3)	4 (16.7)	24 (10.7)	0.381
MS length, mm	3.9 ± 2.3	2.9 ± 1.9	4.0 ± 2.3	**0.026**
MS length <2 mm	44 (17.1)	8 (33.3)	36 (16.1)	**0.035**
MS length <5 mm	178 (71.8)	23 (95.8)	155 (69.2)	**0.006**

Values are mean ± SD, n (%), or mean (interquartile range), unless otherwise indicated. p Values in **bold** are statistically significant.

CT = computed tomography; HU = Hounsfield unit; LCA = left circumflex coronary artery; LVOT = left ventricular outflow tract; MS = membranous septum; PPMI = permanent pacemaker implantation; RCA = right coronary artery; SOV = sinus of Valsalva; STJ = sinotubular junction.

generated from a multivariate analysis including baseline RBBB, device size, and implant depth in relation to MS length had a good predictive value for new PPMI, with c-statistic = 0.81 (95% CI: 0.72 to 0.90; p < 0.001). Simplification of this model to include simply device size 34 mm versus <34 mm yielded a slightly lower, but similar, c-statistic (0.79, 95% CI: 0.70 to 0.88, sensitivity 91.3%, specificity 59.5%, positive predictive value 19.4%, negative predictive value 98.5%).

PROSPECTIVE SERIES. Application of the information from the retrospective analysis was used to implement a prospective, anatomically guided MIDAS approach to perioperative pacer management and device positioning. This was implemented following completion of the retrospective analysis and a period of standardization of image interpretation by imagers and technique by proceduralists. Specifically, operators attempted to position the prosthesis at a pre-release depth according to the NCC smaller than MS length determined on the pre-procedural CT but not generally aiming for higher than 1-mm depth to minimize the potential risk of device pop-out.

Patients were studied prospectively from July 9, 2018, to November 19, 2018, and compared with the retrospective cohort (Figure 3). A total of 100 consecutive patients were followed after discharge for at least 30 days, and need for new PPM was documented. There were no cases of valve embolization or a second valve needed for valve malpositioning. The prospective MIDAS group (in comparison with the retrospective standard group) had similar rates of PPMI risk factors: MS length <2 mm (23.0% vs. 17.7%; p = 0.26), RBBB (12.0% vs. 14.9%; p = 0.48), and use of XL prosthesis (8.0% vs. 11.3%; p = 0.36). Although there were similar MS lengths in the MIDAS and standard groups (MIDAS 3.6 ± 1.9 mm vs. standard 3.9 ± 2.3 mm; p = 0.28), there was a small, but significant, difference in device depth (MIDAS device depth 2.3 ± 1.2 vs. standard device depth 3.3 ± 1.8 mm; p < 0.001). This translated to a dramatic difference in device

TABLE 3 Procedural Characteristics and PPMI

	Total (N = 248)	PPMI (n = 24)	No PPMI (n = 224)	p Value
Valve type				0.002
Evolut R	71 (28.6)	6 (25.0)	65 (29.0)	
Evolut Pro	149 (60.1)	11 (45.9)	138 (61.6)	
Evolut XL	28 (11.3)	7 (29.2)	21 (9.4)	
THV size				0.002
23 mm	8 (3.2)	1 (4.2)	7 (3.1)	
26 mm	104 (41.9)	4 (16.7)	100 (44.6)	
29 mm	108 (43.5)	12 (50.0)	96 (42.9)	
34 mm (Evolut XL)	28 (11.3)	7 (29.2)	21 (9.4)	
Oversizing by annulus perimeter, %	18.3 ± 7.8	19.8 ± 7.0	18.1 ± 7.9	0.308
Oversizing by annulus area, %	48.7 ± 45.1	49.2 ± 17.4	48.6 ± 47.1	0.954
Oversizing by LVOT perimeter, %	21.0 ± 7.4	21.4 ± 8.7	20.9 ± 7.2	0.685
Oversizing by LVOT area, %	56.1 ± 20.2	58.6 ± 26.1	55.8 ± 19.5	0.476
Pre-dilatation	61 (24.6)	6 (25.0)	55 (24.6)	0.962
Post-dilatation	102 (41.1)	11 (45.8)	91 (40.6)	0.622
Pre-release implant depth, mm	3.4 ± 1.8	4.5 ± 1.9	3.2 ± 1.8	**0.002**
MS length minus implant depth, mm	0.6 ± 3.1	−1.6 ± 2.4	0.9 ± 3.0	**<0.001**
Implant depth > MS length	113 (45.6)	20 (83.3)	93 (41.5)	**<0.001**

Values are n (%) or mean ± SD. p Values in **bold** are statistically significant. Evolut devices are manufactured by Medtronic (Minneapolis, Minnesota).
THV = transcatheter heart valve; other abbreviations as in Table 2.

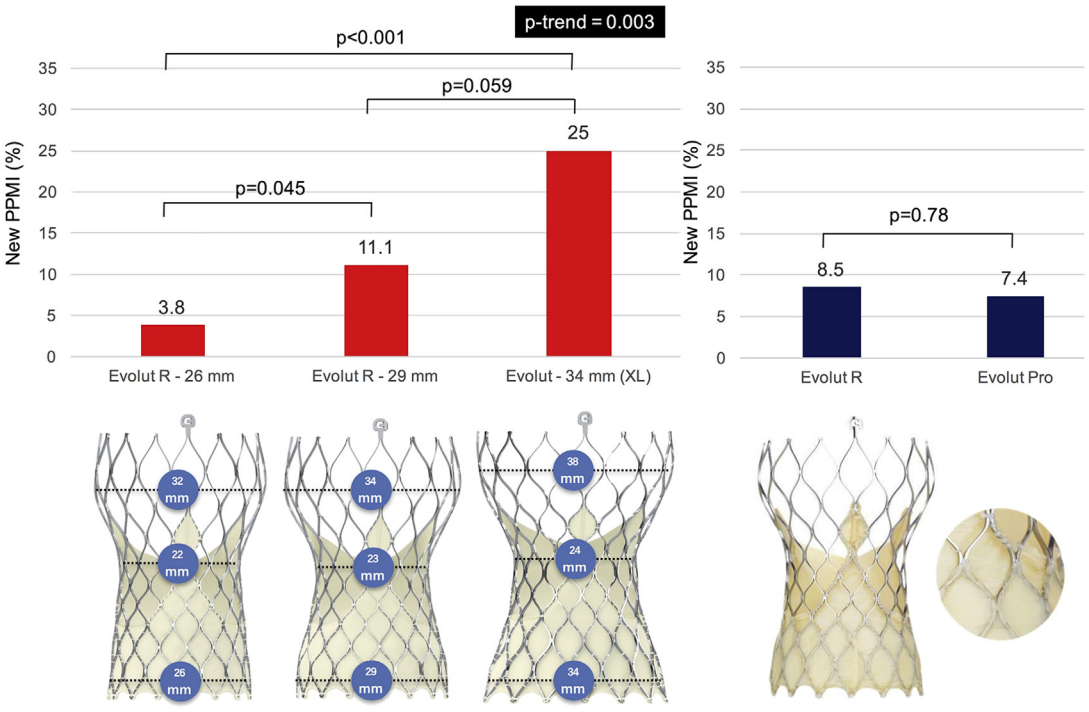
depth < MS length (MIDAS group 79.8% vs. standard group 54.8%; p < 0.001). In the MIDAS group, there were 3 cases of PPMI at 30 days with complete follow-up and no deaths. All 3 pacemakers were implanted periprocedurally with 2 implanted the day after the procedure, and the third, 3 days post-procedure. The new PPMI rate in the MIDAS group was 3.0% versus 9.7% in the standard group (p = 0.035). In line with this, the rate of new LBBB similarly declined significantly to 9% in the MIDAS group from 25.8% in the standard group (p < 0.001).

DISCUSSION

The data presented here have several clinically important implications for pre-procedural risk assessment and patient counselling, periprocedural planning, and device engineering to mitigate the risk of PPMI after repositionable self-expanding TAVR. Most importantly, the MIDAS-TAVR approach, which respected this individualized anatomy and delivered a precision-medicine ethos to procedural technique, resulted in a dramatic reduction in PPMI and LBBB, despite a minimally higher depth of implantation overall with no compromise to other potentially related clinical outcomes, such as valve embolization. This research translates the early small series observations of the importance of MS length by Hamdan et al. (13) published in 2015 into a well-validated busy clinical practice workflow that has an impact on an important clinical endpoint in this field. Indeed, the rate of new PPMI observed with self-expanding MIDAS-TAVR at 3.0% in our study, contrary to that reported from standard self-expanding TAVR (17.4%) (5), was at least as low as that reported from balloon-expandable TAVR (6.6%) (6) and comparable to that reported from SAVR (4.1%) (6) in a recent trial of balloon-expandable TAVR versus SAVR. However, the rate of new LBBB with self-expanding MIDAS-TAVR (9%) was considerably lower than that reported from balloon-expandable TAVR in the latter study (22%) and similar to that reported from SAVR (8%) (6).

PRE-PROCEDURAL RISK ASSESSMENT AND CASE SELECTION. The simple risk model presented separated patients at low, intermediate, and high risk of PPMI and afforded very high sensitivity and negative predictive values. From baseline data, risk strata of low, intermediate, and high risk had rates of PPMI of 1.9%, 6.6%, and 21.3%, respectively. With the expansion of TAVR to intermediate (2,3) and, likely soon, low surgical risk patients (14), it is reassuring that rates of PPMI equivalent to, or potentially even lower than surgery (**Figure 3**), may be achieved in the absence of nonmodifiable risk factors. Conversely, when there is higher risk of PPMI, patients may be appropriately counselled that their risk of PPMI could be considerably greater with contemporary self-expanding TAVR than surgery. Although

FIGURE 2 Device Comparisons



Larger prosthesis size was an independent predictor of new PPMI and there was an incremental frequency of new PPMI with increasing size **(left)**. The tissue skirt of the Evolut Pro (Medtronic, Minneapolis, Minnesota) did not influence new PPMI **(right)**. PPMI = permanent pacemaker implantation.

historically, balloon-expandable TAVR resulted in lower rates of PPMI than earlier-generation self-expanding TAVR (4), the overall PPMI rate of below 10% in the presented retrospective "standard" is at least as low as many contemporary series of balloon-expandable TAVR, and the rate in the prospective "MIDAS" series was significantly lower at 3%.

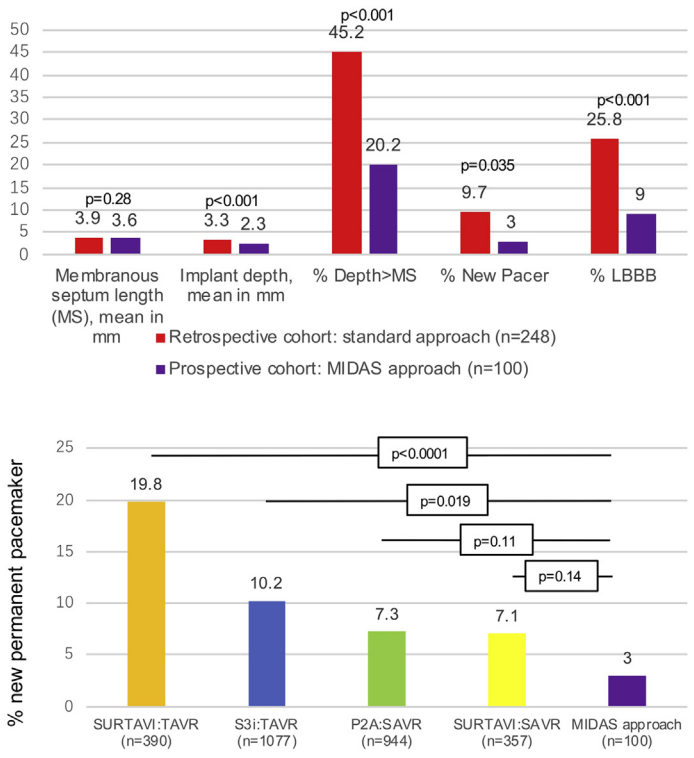
PERIPROCEDURAL PLANNING, THE MS, AND DEVICE POSITIONING. Higher (less ventricular) depth of deployment has several putative advantages: it minimizes the risk of paravalvular leak (15) and it may improve valve hemodynamics, reducing prosthesis-patient mismatch with self-expanding TAVR (16) and possibly the risk of leaflet thrombosis post TAVR (17). More relevant to this paper, depth of TAVR device implantation has long been known to be related to PPMI for several TAVR designs and has contributed significantly to best practice recommendations (7–9). The inception of repositionable self-expanding TAVR devices have led to an overall

TABLE 4 Multivariate Logistic Regression Analysis of Predictors for PPMI

	Univariate		Multivariate			
			Pre-Procedural		Pre- and Post-Procedural	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
RBBB	3.36 (1.32–8.56)	0.008	2.84 (1.06–7.62)	0.038	–	–
MS length <5 mm	10.24 (1.36–77.35)	0.006	11.73 (1.50–92.02)	0.019	–	–
Evolut 34 XL	3.98 (1.48–10.69)	0.004	4.20 (1.45–12.15)	0.008	4.96 (1.68–14.63)	0.004
Implant depth > MS length	7.04 (2.33–21.28)	<0.001	–	–	8.04 (2.58–25.04)	<0.001

The Evolut device is manufactured by Medtronic (Minneapolis, Minnesota).
CI = confidence interval; OR = odds ratio; RBBB = right bundle branch block; other abbreviations as in Table 2.

FIGURE 3 The MIDAS Approach in Context



The prospectively employed the MInimizing Depth According to the membranous Septum (MIDAS) approach is compared with the retrospective standard approach for our center and MS length, implant depth, the percentage of cases where implant depth was deeper than MS length, and corresponding rates of new PPMI are shown **(top)**; importantly, a small difference in implant depth resulted in a large difference in the percentage of implant depth < MS length and a correspondingly large reduction in PPMI rates. This PPM rate is placed in the context of 30-day PPMI rates in the major trials for contemporary TAVR and SAVR (2,3) **(bottom)**. LBBB = left bundle branch block; MS = membranous septum; P2A = PARTNER (Placement of Aortic Transcatheter Valves) P2A trial; S3i = PARTNER (Placement of Aortic Transcatheter Valve) S3i trial; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation trial; other abbreviations as in Figure 1.

higher implant approach by many operators, including ourselves.

Beyond device positioning alone, it has been appreciated that the influence of depth of implantation on PPMI may vary according to individual patient anatomy, that this is related to the proximity of the atrioventricular (AV) bundle to the aortic annulus, and that there is anatomic heterogeneity in this proximity; moreover, the AV bundle has a surrogate anatomic parameter that may be identified on CT, the MS (13). The penetrating bundle of His itself is a heavily insulated structure with a sleeve of fibrous tissue continuous with the cardiac skeleton; in contrast, more caudally, the right and left bundle branches run on the crest of the interventricular septum where the insulation is significantly less. and hence here, the conduction system is more prone to damage.

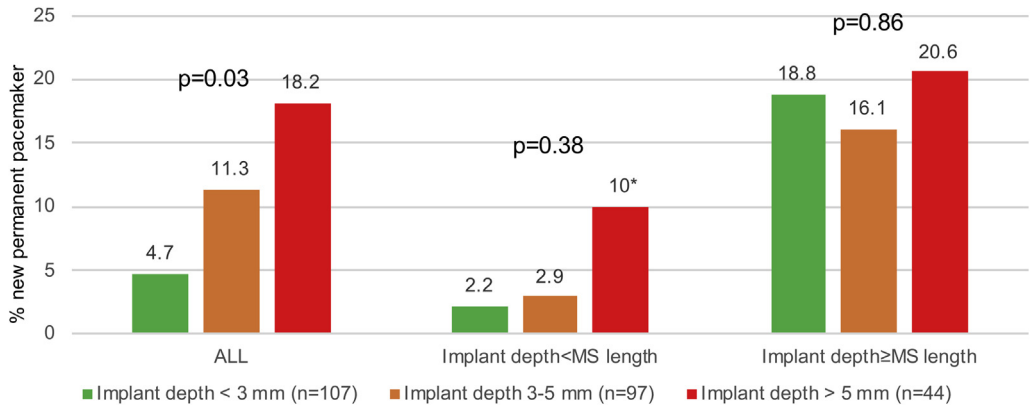
However, anatomic variation has been identified: Kawashima and Sasaki (18) reported in an anatomic study of 105 cadaveric specimens that, although the formerly mentioned typical path of the AV bundle (along the lower border of the MS) is the case in around 46.7% of cases, in 21.0%, the AV bundle passes within the MS (the so-called “naked bundle”), and in the remainder, it passes within the muscular part of the septum, although still in close proximity to the caudal aspect of the MS.

We recently demonstrated that MS length and the device depth in relation to this length was highly predictive of PPMI in contemporary balloon-expandable TAVR (8). However, measurement of the MS length was previously based on a coronal image, a method which was difficult to standardize numerically amongst even experienced structural heart imagers; it was also challenging to understand in relation to intraprocedural device positioning. This meant that clinically relevant cutoffs could not be recommended, despite considerable interest in doing so from the medical community (19). We have now developed a technique that is not only reproducible but is also easily learned and simply interpreted. The MS is demarcated cranially by the commissure between non- and right coronary cusps, and caudally by the vertex of the muscular interventricular septum. The MS length studied in the present study reflects not the actual MS length but rather the coaxial caudal length in relation to the basal annular plane, which is used intraprocedurally for TAVR device positioning.

Best practice recommendations for the repositionable self-expanding TAVR employed suggest a nominal implant depth of 3 to 5 mm; in the overall population studied retrospectively, our mean depth of implantation (pre-release frame inflow depth from the NCC) was 3.3 ± 1.8 mm. In the prospective (MIDAS) cohort, it was only minimally higher (2.3 ± 1.3 mm). More relevant than the implant depth is the implant depth in relation to MS length. Although depth of implantation predicts pacemaker implantation, it no longer predicts pacemaker implantation on correction for implant depth in relation to MS length. Indeed, although there was a trend to more PPMI in nominal (3 to 5 mm) versus higher (<3-mm implant depth), PPMI rates were uniformly high regardless of depth if implant depth was more than MS length and uniformly low regardless of depth if implant depth was less than MS length (Figure 4).

Thus, we propose a patient-specific best practice for device positioning, aiming for a pre-release device depth according to the NCC smaller than MS length

FIGURE 4 Depth of Implant and PPMI (in Isolation and in Relation to Patient-Specific Anatomy)



The rates of new PPMI are stratified according to implant depth above (aortic to) nominal **(green)**, nominal (3 to 5 mm below the basal annular plane, **orange**), and below (ventricular to) nominal **(red)** in the retrospective standard cohort. Although in regard to the data in totality, there is a significant increase in PPMI rate with progressively ventricular implantation depth **(left)**, when the implant depth was aortic to the MS length, PPMI rates were uniformly low **(center)**; conversely, when implant depth was ventricular to the MS length, PPMI rates were uniformly high **(right)**. *There was 1 new PPMI in 10 cases (a case with a 6.3-mm implant depth and a MS length of 7.5 mm). MS = membranous septum; PPMI = permanent pacemaker implantation.

determined on the pre-procedural CT, but not generally aiming for higher than 1-mm depth to minimize the potential risk of device embolization (also described as pop-out). Although this is straightforward in the intermediate MS risk range (MS length 2 to 5 mm), there may be challenges in avoiding pacemaker implantation in the high-risk (MS length <2 mm) group, where PPMI may occur despite even a very high implant (Central Illustration), and an overly aggressive anatomically based high implant approach may not be easily achievable without increasing the risk of device pop-out. We tested this proposed patient-specific best practice prospectively with our MIDAS approach and demonstrated a dramatic reduction in new PPMI to 3.0%.

DEVICE SIZE, CONTOURED SELF-EXPANDING FRAME DESIGN, AND IMPLICATIONS FOR DEVICE ENGINEERING. Although larger annular and root dimensions were associated with need for PPMI, the degree of oversizing was unrelated. Increasing device size was associated with significantly higher rates of PPMI (Figure 2), and the largest device, the Evolut 34 mm XL was an independent predictor of PPMI, even adjusting for pre-release implantation depth in relation to the MS (Table 4). The relationship to device size, but not degree of oversizing, to PPMI suggests a device-specific factor contributing to PPMI.

Importantly, the Evolut stent frame is contoured such that the inflow is larger than the more aortic aspect of the frame that makes contact with the annulus and leaflets. This contour is more exaggerated with progressively large device size (Figure 2), and because the devices are otherwise similar, this could be relevant. Indeed, the inflow of the Evolut R 26 mm is relatively cylindrical, whereas the Evolut 34 mm XL is almost conical (Figure 2); it is conceivable that the former may afford more stable device positioning. Moreover, the device expansion has an initial bias to the greater curve of the aorta (NCC side), and because the larger prostheses have further to expand, there is a greater potential for a mismatch in depth between opposing sides of the aortic annulus that may equalize unpredictably post-release. Potential engineering iterations to rectify this challenge include a steerable device to avoid greater curve bias and a device that may be retrieved and repositioned after the full length of the stent frame is expanded.

STUDY LIMITATIONS. MS length is an anatomic correlate of AV bundle location, and the exact location of the AV bundle may differ, as has been discussed (18). Although reproducibility of measurements of the MS were good, the MS length may approach the minimum resolution of CT, particularly with shorter MS length. Nevertheless, even with these imaging limitations, we were able to demonstrate enormous clinical utility in MS length that has become part of a standard workflow in one of the busiest self-expanding TAVR sites in the United States; this enabled a precision-medicine approach

that dramatically reduced the frequency of PPMI in our practice.

CONCLUSIONS

Importantly, device positioning in relation to a now easily assessed, patient-specific anatomic parameter, the MS length, presented an important and modifiable factor to further minimize the risk of PPM following TAVR. There is a physician-initiated multicenter collaboration using multiple repositionable devices planned for the United States, Europe, and China. Moreover, a prospective multicenter study sponsored by Medtronic designed to standardize practices using the Evolut Pro device is planned. Lastly, a retrospective case-control study will compare device depth in relation to MS length for the Lotus device (Boston Scientific, Marlborough, Massachusetts) in patients from the REPRISE (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System-Randomized Clinical Evaluation) trials that have had a PPM or not; this may lead to subsequent prospective studies with the Lotus Edge device.

Implementing this anatomically based, patient-specific MIDAS-TAVR approach may achieve extremely low and predictable rates of new pacemaker and new LBBB following repositionable self-expanding TAVR that could be at least as low as balloon-expandable TAVR and even as low as SAVR.

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PERSPECTIVES

WHAT IS KNOWN? Self-expanding TAVR traditionally carries a high risk of new PPMI. Limited data exist on the use of the repositionable devices to minimize this risk.

WHAT IS NEW? The MIDAS approach to self-expanding TAVR implantation was applied prospectively to a consecutive series of patients and reduced the total new PPMI rate from 9.7% to 3.0%.

WHAT IS NEXT? A small difference in device positioning can exert dramatic differences in the need for PPMI and this can be accounted for by differences in patient anatomy. The dramatic findings observed in this relatively small single center study require further validation in larger multicenter series and in other repositionable TAVR devices.

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