International Journal of Cardiology 333 (2021) 152–158

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Impact of Interventricular membranous septum length on pacemaker need with different Transcatheter aortic valve implantation systems

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ARTICLE INFO

*Article history:*
Received 11 December 2020
Received in revised form 2 February 2021
Accepted 26 February 2021
Available online 3 March 2021

*Keywords:*
TAVI
Pacemaker implantation
Membranous septum

ABSTRACT

Background
The need for new permanent pacemaker implantation (PPI) after Transcatheter Aortic Valve Implantation (TAVI) remains a critical issue. Membranous Septum (MS) length is associated with PPI after TAVI. The aim of this study was to identify different MS thresholds for the contemporary THV-platforms.

Methods
This retrospective, case-control study enrolled all patients who underwent a successful TAVI procedure with contemporary THV-platforms in the Erasmus University Medical Center between January 2016 and March 2020. The follow-up period for new PPI was 30 days. MS-length was determined by Computed Tomography.

Results
The study consisted 653 TAVI patients with median age 80.6 years (IQR 74.7–84.8). New PPI occurred in 120 patients (18.4%). Patients with new PPI had a shorter MS-length (2.9 mm (IQR 2.3–4.3) vs. 4.2 mm (IQR 2.9–5.7), $p < 0.001$). MS-length < 3 mm identified a high-risk phenotype with 30.3% PPI-rate (OR 6.5 [95%CI 2.9–14.9]), MS-length 3–6 mm an intermediate-risk phenotype with 15.4% PPI-rate (OR 2.7 [95%CI 1.2–6.2]) and MS > 6 mm a low-risk phenotype with a 6.3% PPI-rate (reference). For the Lotus valve, there was no significant difference in PPI-rates between the high-risk (45.8%, OR 3.5 [95%CI 0.8–15.1]) and low-risk group (20%).
By multivariate analysis MS-length, Agatston-score, use of Lotus valve, and ECG with first-degree AV block, RBBB or bifascular block were independent predictors for new PPI.

Conclusion
MS-length was an independent predictor for new PPI post-TAVI. Three phenotypes were found based on MS-length. MS < 3 mm was universally associated with a high risk for new PPI (>30%). MS > 6 mm represented a low-risk phenotype with PPI-rate < 10%. PPI-rate varied per THV type in the intermediate phenotype. PPI-rate with Lotus was high regardless of MS-length.



## 1. Introduction

Transcatheter Aortic-Valve Implantation (TAVI) is an alternative to surgical aortic valve replacement (SAVR) but conduction disorders and need for new permanent pacemaker implantation (PPI) remain a vexing issue [1–3]. The risk for new PPI varies per Transcatheter Heart Valve platform (THV) from <10% to 35% [4,5]. New PPI after TAVI is associated with adverse clinical outcomes, including mortality, reduced left ventricular ejection fraction and re-hospitalizations [6–8].

Established risk factors for conduction disturbances post-TAVI include male gender, aortic root calcifications, small left ventricular outflow tract (LVOT) and pre-existing conduction disturbances, especially first-degree atrioventricular block (AVB) and right bundle branch block (RBBB). Procedural risk factors are THV oversizing, post-dilatation and implantation depth (ID) [4,9]. The ID is linked to the length of the membranous part of the interventricular septum (MS) [10,11]. The MS corresponds to the location where the atrioventricular bundle of His surfaces the LVOT and thus becomes vulnerable for pressure trauma imposed by the THV. Conceivably, a short MS increases the likelihood of interaction between the AV bundle and the THV upon implantation. A longer MS may preclude contact between AV bundle and THV, unless the THV is implanted deeply into the LVOT [12,13].

A recent study revealed the association of MS-length with the risk of new PPI with the self-expanding Evolut THV [12]. The aim of the present

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https://doi.org/10.1016/j.ijcard.2021.02.080

study was to correlate MS-length with risk for new PPI and to identify different MS thresholds for the contemporary TAVI platforms.

## 2. Methods

### 2.1. Study population

For this retrospective, case-control study we included all consecutive patients who underwent a successful TAVI procedure with contemporary THV platforms, i.e. Sapien3 (Edwards Lifesciences, Irvine, CA, United States), Evolut R and Pro (Medtronic, Minneapolis, MN, United States), Lotus (Boston Scientific, Marlborough, MA, United States) or ACURATE (Boston Scientific, Marlborough, MA, United States), in the Erasmus University Medical Center between January 2016 and March 2020. Pre-procedure work up included geriatric assessment, ECG, transthoracic echocardiography (TTE) and multislice computed tomography (MSCT). Standard in hospital care post TAVI implied daily ECG and predischarge TTE. Outpatient clinical follow up was planned at 30 days. Valve selection was performed based on the pre-procedural MSCT and all valves were implanted according to the manufactures guidelines. Data were collected in a dedicated prospective TAVI database. A successful TAVI procedure was defined as a procedure with the patient alive for hospital discharge without conversion to SAVR. We excluded patients with a pacemaker prior to TAVI or a failing surgical bioprosthesis or suboptimal CT imaging quality precluding MS-length measurement. The primary clinical endpoint was the need for a new PPI within 30 days after TAVI and the main purpose of this study was to reveal the correlation of MS-length with PPI for various contemporary THV platforms. All patients consented for the TAVI procedure and data collection for research purposes. The Medical Ethics Committee of the Erasmus University Medical Center waived the need for additional informed consent (MEC-2019-0771). The investigation conforms to the principles outlined in the Declaration of Helsinki.

### 2.2. MSCT analysis

MSCT was performed in all patients as part of the pre-procedural planning. 3mensio Structural Heart software program (Pie Medical Imaging, Maastricht, the Netherlands) was used to derive reconstructions of the ECG-guided contrast scan in end-systole. Apart from standard assessment of aortic root calcification, dimensions and arterial access, MS-length was measured retrospectively using the following algorithm with 3mensio Structural Heart software program. MS-length measurement was performed by imagers who were blinded for the outcomes post-TAVI. For a standardized analysis, the cursor in the perpendicular co-planar view was placed on the intersect of the non-coronary and right coronary cusp. MS was defined on this perpendicular co-planar view as the thinnest part of the interventricular septum between LVOT and right atrium from the nadir of the non-coronary cusp to the tip of the muscular interventricular septum, frequently demarcated by the hinge point of the septal leaflet of the tricuspid valve. Supplementary Fig. S1 demonstrates the method of MS-length determination.

### 2.3. Measurement of implantation depth

The ID was determined on the final angiogram in a projection with the 3 cusps aligned using dedicated software offline (CAAS Workstation 8.1; Pie Medical Imaging, Maastricht, the Netherlands). The depth was measured from the edge of the frame up to the nadir of the non-coronary cusp (NCC) and left-coronary cusp (LCC).

### 2.4. Statistical analysis

Distribution of continuous variables were tested for normality with the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation or median (interquartile range) and analyzed with a student's *t*-test, Mann Whitney U- or Kruskal-Wallis-test as appropriate. Categorical variables were reported as percentage and compared with Chi-Square or Fishers Exact test. A 2-sided $p < 0.05$ was considered statistically significant. The Intraclass Correlation Coefficient was used to check for intraobserver variability. Threshold determination of the MS-length was defined based on the distribution of new PPI percentages. Univariate logistic regression was used to calculate the Odds Ratio between the groups, with the low-risk group as reference. Additional analysis of all PPI predictors were assessed by multivariate analysis, using backward-stepwise logistic regression. The following parameters were included in the model: MS-length, Agatston score, baseline ECG with first-degree AV block, RBBB or bifascular block, Gender, LBBB, ID, postdilatation, percentage oversizing and aortic valve area. A *p*-value <0.05 was predefined as the cut-off for inclusion of the univariate parameters into the multivariate logistic regression model. This model was further evaluated using c-statistics of the receiver-operating characteristic curve. All statistics were performed with SPSS software version 25.0 (SPSS, Chicago IL, United States).

## 3. Results

The patient flow is depicted in supplementary Fig. S2. A total of 653 TAVI patients were enrolled. Overall, median age was 80.6 years (IQR 74.7–84.8), 51.9% were male and the median Society of Thoracic Surgeons (STS)-score was 3.0% (IQR 1.9–4.8) (Table 1). The following THVs were used: Sapien3 in 226, Evolut in 291, Lotus in 92 and ACURATE in 44 patients respectively. Notably, aortic valve calcium defined by Agatston score was significantly lower with ACURATE ($p = 0.036$) and the ID, measured by angiography, was significantly deeper for Evolut. A total of 120 patients (18.4%) received a PPI within 30 days after TAVI and 77% of these within 1 week. New PPI-rates varied per THV platform from 6.8% to 30.4% ($p = 0.002$) (Table 2). Indications for PPI were complete 3rd degree heart block (80.7%), Mobitz type 2 heart block (4.2%), AF with bradycardia (11.8%) or first-degree AV block with LBBB and prolonged conduction times (3.4%). Patients with new PPI were more often male (60% vs. 50%, $p = 0.05$) with higher rates of first-degree AV block (29.2% vs. 17.3%, $p = 0.003$) or a RBBB (25% vs. 3.2%, $p \leq 0.001$) at baseline. CT-analysis showed a larger annulus area (477.3 (IQR 416.0–536.1) vs. 454.7 (IQR 403.0–514.4), $p = 0.034$) and higher calcification levels (Agatston score 3456 (IQR 2342–4829) vs. 2621 (IQR 1840–3758), $p \leq 0.001$)) in patients with new PPI. After correction for gender, the Agatston score remained higher in patients with new PPI.

### 3.1. Membranous septum

Patients with new PPI presented with a shorter MS-length (2.9 (IQR 2.3–4.3) vs. 4.2 (IQR 2.9–5.7), $p < 0.001$) and similar ID. More patients with new PPI had an ID length beyond the MS (85 vs. 73%, $p = 0.009$). Only in the SAPIEN3 (3.9 [IQR 2.8–5.3) vs. 2.7 [IQR 1.7–3.2], $p \leq 0.001$) and Evolut cohorts (4.1 [IQR 2.9–5.8] VS 3.3 [IQR 2.6–4.4], $p \leq 0.003$) was MS-length different for patients with and without new PPI. MS-length was similar for patients with vs. without new PPI in Lotus (4.7 [IQR 3.3–5.7] vs. 4.0 [IQR 2.7–5.1], $p = 0.077$) and ACURATE (4.3 [IQR 2.8–5.8] vs. 2.5 [IQR 2.1vs. 4.2], $p = 0.45$) cohorts. The ACURATE sample was deemed too small for meaningful analysis given the low PPI-rate (6.8%, n = 3).

The Evolut valve was implanted deeper than the other THV and was the only valve that had a significant lower implantation depth for patients with new PPI, compared to those without a new PPI (7.8 [IQR6.4–11.7] vs. 7.3 [IQR5.0–9.7], $p = 0.048$).

To find useful cut-off points for different risk categories based on the MS-length, we looked at new PPI per millimeter increase in MS-length. Three phenotypes based on MS-lengths (high-risk <3 mm, intermediate-risk 3-6 mm and low-risk>6 mm) were determined, based on a linear correlation between the MS-length and the PPI

**Table 1**
Baseline characteristics.

| | Total | No PPI | PPI | *p*-Value |
|---|---|---|---|---|
| | 653 | 533 (81.6) | 120 (18.4) | |
| Age | 80.6 (74.7–84.8) | 80.5 (74.1–84.7) | 80.9 (76.1–85.9) | 0.076 |
| Male | 339 (51.9) | 267 (50.1) | 72 (60.0) | **0.05** |
| BMI | 26.4 (23.7–29.9) | 26.3 (23.7–29.9) | 27.0 (23.8–30.2) | 0.66 |
| STS score | 3.0 (1.9–4.8) | 3.1 (2.1–4.8) | 3.6 (2.2–5.8) | **0.042** |
| EuroII score | 2.9 (1.8–5.2) | 2.8 (1.8–5.2) | 3.3 (1.9–5.3) | 0.12 |
| NYHA 3–4 | 334 (56.0) | 270 (55.0) | 64 (61.0) | 0.26 |
| frailty | 270 (41.5) | 216 (40.6) | 54 (45.4) | 0.34 |
| Diabetes | 199 (30.5) | 159 (29.8) | 40 (33.3) | 0.28 |
| renal disease | 212 (32.6) | 169 (31.8) | 43 (35.8) | 0.40 |
| hypertension | 482 (73.8) | 394 (73.9) | 88 (73.3) | 0.90 |
| hyperlipemia | 381 (58.3) | 314 (58.9) | 67 (55.8) | 0.54 |
| COPD | 95 (14.5) | 79 (14.8) | 16 (13.3) | 0.67 |
| indication TAVI | | | | |
| aortic valve stenosis | 635 (97.2) | 515 (96.6) | 120 (100) | 0.14 |
| aortic valve regurgitation | 3 (0.5) | 3 (0.6) | 0 | |
| mixed | 15 (2.3) | 15 (2.8) | 0 | |
| Baseline ECG | | | | |
| history of AF | 191 (29.2) | 150 (28.1) | 41 (34.2) | 0.19 |
| first-degree AVB | 127 (19.4) | 92 (17.3) | 35 (29.2) | **0.003** |
| LAHB | 10 (1.5) | 7 (1.3) | 3 (2.5) | 0.34 |
| LPHB | 2 (0.3) | 1 (0.2) | 1 (0.8) | 0.25 |
| LBBB | 61 (9.3) | 53 (9.9) | 8 (6.7) | 0.27 |
| RBBB | 47 (7.2) | 17 (3.2) | 30 (25) | **<0.001** |
| bifascicular block | 11 (1.7) | 6 (1.1) | 5 (4.2) | **0.019** |
| heart rate | 68 (61–77) | 69 (62–79) | 69 (60–76) | 0.37 |
| PR interval, ms | 180 (160–200) | 178 (160–198) | 184 (158–215) | 0.063 |
| QRS, ms | 100 (91–116) | 100 (91–113) | 109 (96–139) | **<0.001** |
| R axis, degree | 17 (−20–50) | 19 (−21–51) | 19 (−18–55) | 0.89 |
| Echocardiography | | | | |
| LVEF, % | 58 (50–65) | 57 (50–65) | 56 (49–63) | 0.42 |
| peak jet velocity, m/s | 4.0 (3.6–4.5) | 4.0 (3.6–4.5) | 4.1 (3.6–4.7) | 0.14 |
| mean pressure gradient, mmHg | 39 (30–47) | 39 (30–48) | 38 (32–51) | 0.73 |
| AVA, cm2 | 0.80 (0.60–0.90) | 0.80 (0.60–0.90) | 0.77 (0.60–0.90) | 0.13 |
| LVEDD, mm | 50 (45–56) | 50 (45–56) | 52 (47–57) | 0.22 |
| CT-scan | | | | |
| mean diameter (mm) | 24.2 (22.7–25.7) | 24.1 (22.7–25.6) | 24.7 (23.0–26.1) | **0.038** |
| Annulus area (mm2) | 460.3 (403.5–517.1) | 454.7 (403.0–514.4) | 477.3 (416.0–536.1) | **0.034** |
| Agatston score | 2740 (1917–3952) | 2621 (1840–3758) | 3456 (2342–4829) | **<0.001** |
| Male | 3313 (2407–4547) | 3171 (2222–4375) | 3861 (2543–5242) | **0.008** |
| Female | 2181 (1517–3028) | 2133 (1526–2950) | 2763 (1430–4093) | **0.045** |
| MS | 3.9 (2.8–5.4) | 4.2 (2.9–5.7) | 2.9 (2.3–4.3) | **<0.001** |
| Procedure | | | | |
| predilatation | 130 (19.9) | 109 (20.5) | 21 (17.5) | 0.47 |
| postdilatation | 188 (28.8) | 145 (27.2) | 43 (35.8) | 0.059 |
| ID NCC | 6.0 (4.4–8.3) | 6.0 (4.4–8.2) | 6.4 (4.6–8.7) | 0.28 |
| ID LCC | 5.9 (4.2–8.0) | 5.9 (4.2–7.7) | 6.2 (3.9–11.9) | 0.41 |
| MS - ID | −2.2 (−4.6–0.06) | −1.9 (−4.2–0.2) | −3.3 (−5.4–1.2) | **<0.001** |
| MS - ID <0 | 437 (75.2) | 349 (73.0) | 88 (86.3) | **0.005** |

Values are median (interquartile range) or number (percentage). STS = Society of Thoracic Surgeons, NYHA = New York Heart Association, AF = atrial fibrillation, AVB = atrioventricular block, LAHB, left anterior hemiblock, LPHB = left posterior hemiblock, LBBB = left bundle branch block, RBBB = right bundle branch block, LVEF = left ventricular ejection fraction, AVA = aortic valve area, LVEDD = left ventricular end diastolic dimensions. MS = membranous septum, ID = Implantation Depth, NCC = Non Coronary cusp, LCC = Left Coronary cusp. The p-values in bold are p-values <0.05, which displays a significant difference between the groups.

percentages. Fig. 1 shows the different PPI-rate per phenotype for the overall cohort and for each THV. The Odds Ratio (OR) is calculated with the low-risk phenotype as reference per THV. For the overall cohort, the high-risk phenotype had a PPI-rate of 30.3% (OR 6.5 [95%CI 2.9–14.9]), the intermediate-risk phenotype 15.4% (OR 2.7 [95%CI 1.2–6.2]) and the low-risk phenotype 6.3%. The Evolut valve had a PPI-rate of 28.6% with the high-risk phenotype (OR 6.5 [95%CI 1.9–23.0]), 18.7% with the intermediate-risk phenotype (OR 3.8 [95%CI 1.1–12.9]) and 5.8% in the low-risk phenotype. The Sapien3 valve had a PPI-rate of 30.4% (OR 15.3 [95%CI 2.0–118.0]) in the high-risk phenotype. However, there was no significant difference between the intermediate-risk and low-risk phenotypes (7.2% vs. 2.8%, OR 2.7 [95%CI 0.3–22.5]). The PPI-rate for the Sapien3 valve was 3% when the MS-length was >4 mm. The Lotus valve demonstrated PPI-rates of >20% across the different phenotypes without significant differences between the different thresholds (high-risk phenotype PPI-rate 45.8%, OR 3.4 [95%CI 0.8–15.1]) and low-risk phenotype 20% PPI-rate).

### 3.2. MS-length and ID measurement variability

All measurements of the MS-length were determined by an experienced imager. To check for intra-observer variability 32 patients (5%) were randomly selected and the MS-length was reassessed with a time-interval of 6 months between the two measurements. The Intraclass Correlation Coefficient (ICC) showed an excellent correlation of 0.98 ([95%CI 0.96–0.99], $p \leq 0.001$). Two imagers determined the

**Table 2**
Valve characteristics.

| | Sapien3 | Evolut | Lotus | ACURATE | p-Value |
|---|---|---|---|---|---|
| total | 226 | 291 | 92 | 44 | |
| new PPI | 33 (14.6) | 56 (19.2) | 28 (30.4) | 3 (6.8) | 0.002 |
| Age | 81.3 (76.0–84.7) | 80.3 (73.8–85.1) | 80.1 (73.9–84.3) | 81.9 (77.7–84.1) | 0.50 |
| Male | 145 (64.2) | 134 (46.0) | 47 (51.1) | 13 (29.5) | <0.001 |
| BMI | 26.7 (24.1–30.0) | 26.0 (23.1–29.4) | 26.7 (23.9–33.9) | 27.4 (24.8–30.8) | 0.031 |
| STS score | 2.9 (1.8–4.5) | 3.4 (2.4–5.5) | 2.9 (2.0–4.9) | 3.2 (1.8–5.4) | 0.10 |
| EuroII score | 2.8 (1.7–4.8) | 3.1 (1.9–5.8) | 2.2 (1.6–4.9) | 3.2 (1.9–5.8) | 0.13 |
| NYHA 3–4 | 106 (51.0) | 159 (59.8) | 49 (59.8) | 20 (50) | 0.19 |
| frailty | 80 (35.4) | 129 (44.5) | 45 (49.5) | 16 (36.4) | 0.061 |
| Diabetes | 64 (28.3) | 89 (30.6) | 27 (29.3) | 19 (43.2) | 0.072 |
| renal disease | 73 (32.4) | 92 (31.7) | 26 (28.3) | 21 (47.7) | 0.14 |
| hypertension | 156 (69.0) | 221 (75.9) | 72 (78.3) | 33 (75.0) | 0.23 |
| hyperlipemia | 122 (54.0) | 181 (62.2) | 53 (57.6) | 25 (56.8) | 0.31 |
| COPD | 28 (12.4) | 51 (17.5) | 12 (13.0) | 4 (9.1) | 0.25 |
| Indication TAVI | | | | | |
| aortic valve stenosis | 219 (96.9) | 283 (97.3) | 89 (96.7) | 44 (100.0) | 0.68 |
| aortic valve regurgitation | 0 | 2 (0.7) | 1 (1.1) | 0 | |
| mixed | 7 (3.1) | 6 (2.1) | 2 (2.2) | 0 | |
| Implanted valve size | | | | | |
| Extra Small (20) | 2 (0.9) | 0 | 0 | 0 | <0.001 |
| Small (23) | 52 (23.0) | 8 (2.7) | 35 (38.0) | 11 (25.0) | |
| Medium (25/26) | 96 (42.5) | 89 (30.6) | 32 (34.8) | 30 (68.2) | |
| Large (27/29) | 76 (33.6) | 162 (55.7) | 25 (27.2) | 3 (6.8) | |
| Extra-large (34) | 0 | 32 (11.0) | 0 | 0 | |
| Baseline ECG | | | | | |
| history of AF | 72 (31.9) | 87 (29.9) | 21 (22.8) | 11 (25.0) | 0.39 |
| first-degree AVB | 43 (19.0) | 54 (18.6) | 24 (26.1) | 6 (13.6) | 0.29 |
| LAHB | 2 (0.9) | 4 (1.4) | 4 (4.3) | 0 | 0.10 |
| LPHB | 1 (0.4) | 1 90.3) | 0 | 0 | 0.90 |
| LBBB | 28 (12.4) | 20 (6.9) | 11 (12.0) | 2 (4.5) | 0.089 |
| RBBB | 17 (7.5) | 23 (7.9) | 3 (3.3) | 4 (9.1) | 0.45 |
| bifascicular block | 3 (1.3) | 4 (1.4) | 2 (2.2) | 2 (4.5) | 0.45 |
| heart rate | 67 (60–75) | 69 (62–79) | 68 (61–75) | 66 (59–80) | 0.78 |
| PR interval, ms | 182 (163–200) | 174 (155–198) | 184 (160–203) | 176 (157–191) | 0.25 |
| QRS, ms | 105 (94–119) | 98 (89–110) | 100 (90–119) | 104 (96–117) | 0.003 |
| R axis, degree | 12 (−20–44) | 21 (−20–54) | 20 (−21–46) | 19 (−10–58) | 0.24 |
| Echocardiography | | | | | |
| LVEF, % | 55 (50–60) | 59 (53–65) | 60 (55–65) | 57 (52–66) | **0.013** |
| peak jet velocity, m/s | 4.0 (3.5–4.4) | 4.1 (3.6–4.5) | 4.2 (3.7–4.6) | 4.2 (3.7–4.6) | 0.085 |
| mean pressure gradient, mmHg | 36 (28–45) | 40 (30–48) | 40 (33–48) | 43 (31–51) | 0.22 |
| AVA, cm2 | 0.80 (0.70–1.00) | 0.70 (0.60–0.90) | 0.80 (0.60–0.90) | 0.80 (0.70–0.93) | **0.004** |
| LVEDD, mm | 52 (48–58) | 49 (44–55) | 51 (46–55) | 48 (42–54) | **0.001** |
| CT-scan | | | | | |
| mean diameter (mm) | 25.4 (23.4–27.0) | 23.7 (22.3–25.0) | 23.7 (22.6–25.0) | 23.4 (22.4–24.2) | **<0.001** |
| Annulus area (mm2) | 506.9 (428.3–571.0) | 441.8 (392.0–491.1) | 440.9 (400.0–547.6) | 428.7 (395.6–459.4) | **<0.001** |
| % oversizing | 3.4 (1.3–6.6) | 19.8 (16.0–23.9) | 3.2 (1.2–6.0) | 5.3 (3.2–7.7) | **<0.001** |
| Agatston score | 2924 (2029–4300) | 2544 (1910–3760) | 2988 (1821–4150) | 2175 (1655–3440) | **0.036** |
| Male | 3348 (2418–4543) | 3181 (2250–4529) | 3633 (2493–4630) | 2791 (1863–3844) | 0.47 |
| Female | 2008 (1341–2991) | 2181 (1609–2974) | 2430 (1445–3272) | 2074 (1364–3400) | 0.86 |
| MS | 3.8 (2.7–5.2) | 3.9 (2.8–5.4) | 4.6 (2.9–5.7) | 4.3 (2.6–5.8) | 0.15 |
| ID NCC | 5.3 (4.3–6.8) | 7.4 (5.5–9.8) | 5.5 (4.0–6.7) | 5.7 (3.6–7.4) | **<0.001** |
| ID LCC | 4.7 (3.7–5.9) | 7.3 (5.7–10.1) | 5.1 (3.0–7.0) | 5.2 (4.1–6.9) | **<0.001** |
| MS-ID NCC | −1.8 (−3.1–0.2) | −3.4 (−6.8 - -0.7) | −1.2 (−3.0–0.9) | −1.2 (−3.3–0.6) | **<0.001** |

Values are median (interquartile range) or number (percentage). % oversizing is defined as (Device size-mean diameter)/mean diameter x 100. STS = Society of Thoracic Surgeons, AF = atrial fibrillation, AVB = atrioventricular block, LAHB = left anterior hemiblock, LPHB = left posterior hemiblock, LBBB = left bundle branch block, RBBB = right bundle branch block, LVEF = left ventricular ejection fraction, AVA = aortic valve area, LVEDD = left ventricular end diastolic dimensions, MS = membranous septum, ID = implantation depth, NCC = non-coronary cusp, LCC left-coronary cusp. The p-values in bold are p-values <0.05, which displays a significant difference between the groups.

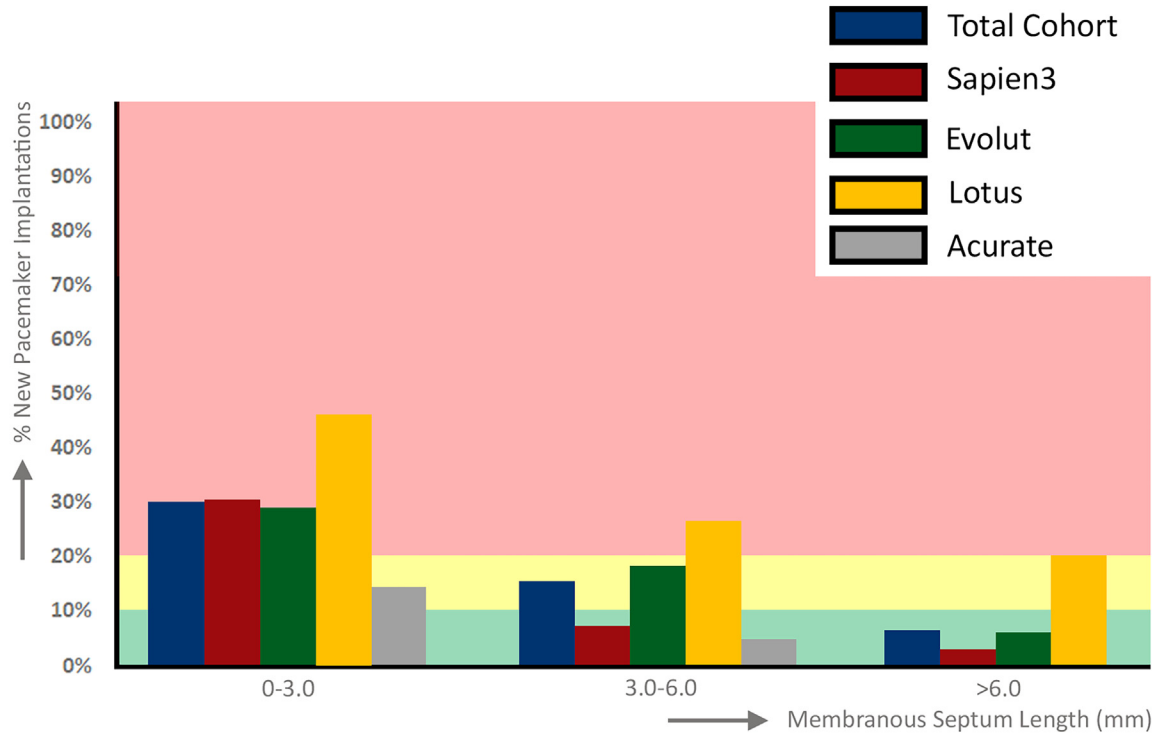
measurements using the same methodology. The ICC between the two imagers was 0.74 ([95%CI 0.20–0.91], $p = 0.005$).

### 3.3. Multivariate analysis

The results of the multivariable model, generated to predict the need for new PPI, are shown in Table 3. The variables included after backward selection were MS-length, Agatston score, and a baseline ECG with first-degree AV block, RBBB or bifascular block. Receiver operating characteristic curve analysis with the predicted probabilities of the logistic regression model revealed a c-statistic of 0.79 ([95%CI 0.74–0.84], $p \leq 0.001$).

## 4. Discussion

The aim of this study was to analyze the impact of MS-length on the incidence of new PPI for different contemporary THV platforms. Main findings were: 1) overall new PPI-rate was 18,4% in an experience including 4 different THV designs. 2) MS-length was an independent predictor for new PPI. 3) Different phenotypes at risk for new PPI were




| | High Risk (<3mm) | | | Intermediate risk (3-6mm) | | | Low risk (>6mm) | |
|---|---|---|---|---|---|---|---|---|
| | n PPI (%) | OR [95%CI] | P-value | n PPI (%) | OR [95%CI] | P-value | n PPI (%) | OR [95%CI] |
| Total Cohort | 61/201 (30) | 6.5 [2.9-14.9] | **<0.001** | 52/340 (15) | 2.7 [1.2-6.2] | **0.017** | 7/112 (6) | 1.0 (ref) |
| Valve Platform | | | | | | | | |
| Sapien3 | 24/79 (30) | 15.3 [2.0-118.0] | **0.009** | 8/111 (7) | 2.7 [0.3-22.5] | 0.35 | 1/36 (3) | 1.0 (ref) |
| Evolut | 24/85 (29) | 6.5 [1.9-23.0] | **0.003** | 29/155 (19) | 3.8 [1.1-12.9] | **0.035** | 3/52 (6) | 1.0 (ref) |
| Lotus | 11/24 (46) | 3.4 [ 0.8-15.1] | 0.11 | 14/53 (26) | 1.4 [ 0.4-5.9] | 0.61 | 3/15 (20) | 1.0 (ref) |
| ACURATE | 2/14 (14) | 3.3 [0.3-40.8] | 0.35 | 1/21 (5) | 1.0 (ref) | - | 0 | - |

**Fig. 1.** PPI-rates per membranous septum length. Figure with the PPI-rates per length of the membranous septum for the total cohort and each valve platform. The green zone identified PPI-rates <10%, the yellow zone illustrates PPI-rates between 10 and 20% and the red zone showed a PPI-rate above 20%. The table shows the different risk groups, with thresholds based on equal MS-lengths for the total cohort. Values are presented as number (percentage). The OR is calculated with logistic regression, by comparing the high risk and the intermediate risk group with the low risk group (reference) per THV and are shown as OR (95% confidence interval), Except for the ACURATE group, due to no PPI-cases in the low-risk group. PPI = permanent pacemaker implantation, MS = membranous septum, OR = Odds Ratio, CI = Confidence interval.

identified based on MS-length: high-risk with MS < 3 mm, intermediate risk MS 3–6 mm and low-risk with MS > 6 mm. 4) Sapien3 had a single digit PPI-risk within the intermediate risk group, Evolut within the low-risk group 5) Lotus THV was associated with high PPI regardless of MS-length.

The need for PPI remains a vexing issue after TAVI, because of its association with increased comorbidities, including new hospitalizations. The impact of long-term right-ventricular pacing may thus not be trivial, especially in the context of expanding TAVI indications that target younger patients with longer life expectancy [9,14]. The pacemaker rates per valve platform in our study (including only pacemaker naïve subjects at baseline) varied from 6.8% for the ACURATE valve, to 14.6% for SAPIEN3, 19.2% for Evolut and 30.4% for the Lotus valve and were consistent with new PPI pacemaker rates in the respective post-market trials [1,2,15–17]. We found the classical PPI risk factors including root calcification, use of Lotus THV, and a baseline ECG with first-degree AV block, RBBB or bifascular block [4,9]. MS-length also emerged as an independent predictor for new PPI. MS-length and its spatial relationship to the bundle of His are patient-specific and highly variable. Typically, the His bundle exits the atrioventricular node and penetrates the inferior border of the MS before dividing into the left and right bundle branches. When the MS is small or absent, the His bundle moves even closer to the aortic root [18]. Anatomical studies located the His bundle in the right part of the MS in 50%, in the left part in 30% and immediately beneath the endocardium in 20% [19]. Patients with a His bundle located left-sided or beneath the endocardium appear particularly at risk for new conduction disturbances [20]. Our study highlighted that MS-length < 3 mm comprised a high PPI risk. Jilhaiawi et al. were the first to identify the importance of MS-length, in combination with the ID, for new PPI after TAVI with the self-expandable Evolut THV [12]. In

**Table 3**
Logistic regression analysis.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR [95% CI] | significance | OR [95% CI] | significance |
| Gender | 1.49 [0.99–2.24] | 0.051 | | |
| Membranous Septum | 1.33 [1.18–1.49] | **<0.001** | 1.29 [1.12–1.48] | **<0.001** |
| ID | 1.03 [0.97–1.09] | 0.35 | | |
| Agatston score | 1.45 [1.17–1.53] | **<0.001** | 1.29 [1.12–1.49] | **<0.001** |
| First-degree AV block | 1.97 [1.25–3.11] | **0.003** | 1.90 [1.07–3.36] | **0.028** |
| RBBB | 10.12 [5.36–19.11] | **<0.001** | 13.16 [6.37–29.17] | **<0.001** |
| Bifascular block | 3.82 [1.15–12.73] | **0.021** | 5.06 [1.23–20.78] | **0.025** |
| LBBB | 0.65 [0.30–1.40] | 0.27 | | |
| Annulus Area | 1.00[0.99–1.00] | 0.47 | | |
| Postdilatation | 1.49 [0.98–2.27] | 0.060 | | |
| % Oversizing | 0.99 [0.97–1.0] | 0.53 | | |

OR = Odds Ratio. CI = confidence interval, AV Block = Atrioventricular block, RBBB = Right Bundle Branch Block, LBBB = Left Bundle Branch Block, ID = Implantation Depth. The p-values in bold are p-values <0.05, which displays a significant difference between the groups.

their study of 248 patients a MS cut-off <2 mm, 2–5 mm and > 5 mm defined high-risk, intermediate risk and low-risk for PPI respectively. Taken subtle differences to MS measurement into account, our study demonstrated similar MS thresholds for Evolut THV but extended the knowledge to other THV platforms that showed different thresholds. Addition of the MS-length measurement in the pre-procedural planning is therefore a valuable aid in patient tailored THV selection in order to reduce new PPI.

In our study, MS-length < 3 mm defined a high-risk phenotype and was universally associated with a high PPI-rate (>30%). Sapien3 or ACURATE THV were associated with single digit PPI-rates in the intermediate phenotype (MS 3–6 mm) vs. 18% with Evolut THV. MS >6 mm was a low-risk phenotype with PPI-rate < 10% for all THV platforms except for Lotus. Lotus was associated with a higher PPI of >20% regardless of MS-length. Our findings related to Lotus should be perceived with caution because of selection bias. Indeed aortic root calcification was an independent predictor for PPI and an important confounder because patients with Lotus TAVI had a higher calcium score as compared to the other THVs [15]. Still, the randomized REPRISE III trial demonstrated significantly higher PPI-rates with the Lotus valve (29%), compared to the CoreValve/Evolut valve (16%) [21]. Also, in the new-generation Lotus Edge valve, with incorporated Depth Guard™ technology to reduce the interaction between the valve frame and the LVOT, the PPI-rate remained high (Lotus 24% vs. Lotus Edge 42%, $p = 0.06$). The Lotus platform has recently been withdrawn from the market.

### *4.1. Study limitations*

Our study is a single center retrospective analysis with inherent limitations. THV selection was per operators discretion, so we acknowledge THV selection bias, which is illustrated by the higher aortic root calcium score with Lotus vs. other THV platforms. However, the consistent higher PPI-rates reported with Lotus TAVI cannot exclusively be explained by this selection bias. Both, the randomized REPRISE III study and post market registries with Lotus reported the highest in class PPI-rates [15,21].

There was an unbalanced THV distribution in our study sample and especially the ACURATE THV was underrepresented to allow in-depth analysis. We considered Evolut R and Evolut Pro as 1 THV platform and Lotus and Lotus Edge as 1 THV cohort for the analysis. Despite the fact that baseline characteristics and outcomes were similar within both THV families, there may be (subtle) differences in the need for new PPI for each of these devices individually. However, the FORWARD and FORWARD Pro post-market registries reported similar PPI-rates with Evolut R and Evolut Pro and we did not find differences between Evolut R and Evolut Pro or between Lotus and Lotus Edge in our study [22,23]. The ID-length was beyond the MS-length in the majority of patients and there was a significant difference in ID between the Evolut valve and the other THV and within the Evolut group, patients with a new PPI had a lower ID, compared to those without a new PPI. We acknowledge the importance of implantation depth despite the fact this was no independent predictor for new pacemakers in this analysis. Of note, ID was assessed by 2D angiography whereas MS length was determined by 3D MSCT. Arguably, MSCT after TAVI would have been more accurate and reproducible for the analysis of the relationship between the MS-length and the ID. Also, the difference in ID among patients with vs. without new pacemaker within the Evolut group was 0.5 mm. Evolut implantation with a 0.5 mm accuracy seems elusive.

All measurements were performed by one experienced imager but not in a corelab setting. Still, we believe the interaction of MS-length and new PPI with different THV platforms is valid but needs confirmation in larger study samples.

## 5. Conclusion

MS-length was an independent predictor for new PPI post-TAVI. Three phenotypes were found based on MS-length. MS <3 mm was universally associated with a high risk for new PPI (>30%). MS >6 mm represented a low-risk phenotype with PPI-rate < 10%. PPI-rate varied per THV type in the intermediate phenotype.

## Declaration of Competing Interest

None.

## Acknowledgement

The authors would like to thank Sanne Schipper and Tristan Slots of Pie Medical Imaging (Maastricht, the Netherlands) for their help to determine MS-length measurement with the 3MENSIO software.

## Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.02.080.

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