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Research paper

Impact of membranous septum length on pacemaker need with different transcatheter aortic valve replacement systems: The INTERSECT registry

Thijmen W. Hokken [a], Mohammed Muhemin [b], Taishi Okuno [c], Verena Veulemans [d], Bernardo B. Lopes [e], Alessandro Beneduce [f], Romano Vittorio [f], Joris F. Ooms [a], Rik Adrichem [a], Tara Neleman [a], Isabella Kardys [a], Joost Daemen [a], Alaide Chieffo [f], Matteo Montorfano [f], Joao Cavalcante [e], Tobias Zeus [d], Thomas Pilgrim [c], Stefan Toggweiler [b], Nicolas M. Van Mieghem [a,*]

[a] Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Heart Center Lucerne, Lucerner Kantonsspital, Lucerne, Switzerland
[c] Department of Cardiology, Inselspital Bern, University Hospital, University of Bern, Bern, Switzerland
[d] Department of Cardiology, Pulmonology and Vascular Diseases, University Hospital Düsseldorf, Düsseldorf, Germany
[e] Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN, USA
[f] Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy

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ABSTRACT

Background: New permanent pacemaker implantation (new-PPI) remains a compelling issue after Transcatheter Aortic Valve Replacement (TAVR). Previous studies reported the relationship between a short MS length and the new-PPI post-TAVR with a self-expanding THV. However, this relationship has not been investigated in different currently available THV. Therefore, the aim of this study was to investigate the association between membranous septum (MS)-length and new-PPI after TAVR with different Transcatheter Heart Valve (THV)-platforms.

Methods: We included patients with a successful TAVR-procedure and an analyzable pre-procedural multi-slice computed tomography. MS-length was measured using a standardized methodology. The primary endpoint was the need for new-PPI within 30 days after TAVR.

Results: In total, 1811 patients were enrolled (median age 81.9 years [IQR 77.2–85.4], 54% male). PPI was required in 275 patients (15.2%) and included respectively 14.2%, 20.7% and 6.3% for Sapien3, Evolut and ACURATE-THV($p < 0.01$). Median MS-length was significantly shorter in patients with a new-PPI (3.7 mm [IQR 2.2–5.1] vs. 4.1 mm [IQR 2.8–6.0], $p = <0.01$). Shorter MS-length was a predictor for PPI in patients receiving a Sapien3 (OR 0.87 [95% CI 0.79–0.96], $p = <0.01$) and an Evolut-THV (OR 0.91 [95% CI 0.84–0.98], $p = 0.03$), but not for an ACURATE-THV (OR 0.99 [95% CI 0.79–1.21], $p = 0.91$). By multivariable analysis, first-degree atrioventricular-block (OR 2.01 [95% CI 1.35–3.00], $p = <0.01$), right bundle branch block (OR 8.33 [95% CI 5.21–13.33], $p = <0.01$), short MS-length (OR 0.89 [95% CI 0.83–0.97], $p < 0.01$), annulus area (OR 1.003 [95% CI 1.001–1.005], $p = 0.04$), NCC implantation depth (OR 1.13 [95% CI 1.07–1.19] and use of Evolut-THV(OR 1.54 [95% CI 1.03–2.27], $p = 0.04$) were associated with new-PPI.

Conclusion: MS length was an independent predictor for PPI across different THV platforms, except for the ACURATE-THV. Based on our study observations within the total cohort, we identified 3 risk groups by MS length: MS length ≤3 mm defined a high-risk group for PPI (>20%), MS length 3–7 mm intermediate risk for PPI (10–20%) and MS length > 7 mm defined a low risk for PPI (<10%). Anatomy-tailored-THV-selection may mitigate the need for new-PPI in patients undergoing TAVR.

Abbreviations: AVB, Atrioventricular Block; ECG, Electrocardiogram; ICC, Intraclass correlation coefficient; ID, Implantation Depth; LVOT, Left Ventricular Outflow Tract; MS, Membranous Septum; MSCT, Multislice Computed Tomography; NCC, Non-Coronary Cusp; PPI, Permanent Pacemaker Implantation; RBBB, Right Bundle Branch Block; STS-PROM, Society of Thoracic Surgeon's Predicted Risk of Mortality; TAVR, Transcatheter Aortic Valve Replacement; THV, Transcatheter Heart Valve; TTE, Transthoracic Echocardiography.

* Corresponding author. Department of Interventional Cardiology, Thoraxcenter, ErasmusMC, Office Nt 645, Dr Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: n.vanmieghem@erasmusmc.nl (N.M. Van Mieghem).
@drnvanmieghem (N.M. Van Mieghem)

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1. Introduction

The need for new permanent pacemaker implantation (PPI) remains a compelling issue after transcatheter aortic valve Replacement (TAVR). PPI rate post-TAVR varies between 2 and 35% based on established patient-inherent risk factors, including age, male gender, conduction disturbances at baseline (especially first-degree Atrioventricular block (1st degree AVB) and right bundle branch block (RBBB)), as well as anatomical factors like the (membranous septum (MS)-length, left ventricular outflow tract (LVOT) and aortic valve calcifications) and procedural factors (transcatheter heart valve (THV) design, oversizing, postdilatation and implantation depth (ID)).[1–3] Of these factors, THV selection and ID can be controlled by the operator.

The His bundle pierces the membranous septum and surfaces in the LVOT at the interleaflet triangle demarcated by the right and non-coronary cusp and the transition of the membranous to the muscular part of the interventricular septum. As such it is subject to pressure trauma by the THV frame that is expanded in the LVOT with TAVR.[4] A short MS length is associated with a high likelihood of interaction between a THV and the conduction system. Previous studies reported the relationship between a shorter MS-length, ID and the need for PPI post-TAVR with a self-expanding supra-annular functioning THV.[5,6] The aim of this multi-center study was to evaluate the correlation between MS length and need for new PPI for different contemporary THV platforms.

2. Methods

2.1. Study population

The "International Registry to investigate the INTerventricular MEmbRanous SEptum length to Predict Abnormal Conduction after TAVR" (INTERSECT)-registry is a retrospective, observational multicenter collaboration including all consecutive who underwent a successful TAVR between February 2014 and May 2021. Patient selection for TAVR was performed per local standard practice. Permanent pacemaker prior to TAVR, failing surgical bio-prosthesis or suboptimal Multislice Computed Tomography (MSCT) imaging quality precluding MS-length measurement were formal exclusion criteria. This analysis included only those contemporary THV platforms of which >100 were implanted within the inclusion period of this registry. The study was conducted in accordance with the declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects Act per Institutional Review Boards' review (MEC-2020-0807). Additional informed consent for this study was waived by the Ethics Committee of the Erasmus University Medical Center because of the retrospective and anonymous nature of the research.

2.2. Study procedures

A dedicated database captured relevant patient demographics, medical history and comorbidities, Electrocardiogram (ECG), Transthoracic Echocardiography (TTE), MSCT, procedural and clinical follow up data. Final THV ID was measured on the final angiogram from the nadir of the non-coronary cusp (NCC) to the edge of the THV frame in the LVOT. Need for PPI was assessed at 30 days of follow up.

2.3. Membranous septum measurement

MS length was measured on the pre-procedural MSCT in end-systole using dedicated software packages (3mensio Structural Heart software program (Pie Medical Imaging, Maastricht, the Netherlands in 5 centers and Merlin Diagnostic Workcenter, Phönix-PACS, Freiburg, Germany) in 1 center). The MS length was defined by the distance from the basal aortic annulus at the level of the intersect of the right and non-coronary cusp and the transition of the membranous to the muscular part of the interventricular septum which often coincides with the hinge point of the septal leaflet of the tricuspid valve (Fig. 1). Investigators from each center were trained to perform the MS-length measurement according to a standardized protocol. To check for inter-observer variability, 10 randomly selected CT-scans were analyzed by all imagers. The two-way mixed Intraclass Correlation Coefficient (ICC) for absolute agreement was 0.81 ([95% CI 0.30–0.96], p = <0.01) between all centers using 3mensio and 0.76 ([95% CI 0.21–0.93], p < 0.01) between 3mensio and Merlin diagnostic workcenter.

2.4. Outcomes and definitions

The primary clinical endpoint was the need for a new PPI within 30 days after TAVR. We also evaluated the correlation of new PPI with MS length for the different THV platforms. High risk for new PPI post-TAVR was defined as a PPI-rate of >20%, intermediate risk 10–20% and low risk as <10%.

2.5. Statistical analysis

Distribution of continuous variables were tested for normality with a Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation or median (25th–75th percentile) and analyzed with a student's T-test, ANOVA, Mann Whitney U- or Kruskal-Wallis-test as appropriate. Categorical variables were reported as number and percentages and compared with Chi-Square.

The relation between MS-length and new PPI post-TAVR was investigated using a generalized linear mixed effect models (dependent variable: new PPI post-TAVR, independent variable: MS-length) with random intercepts per center, to adjust for clustering of patients within centers. First, a univariable model was applied. Subsequently, the model was adjusted for potential confounders. To identify potential confounders, we applied univariable generalized linear mixed effect models to identify other variables associated with new PPI. The following variables were assessed in our model: gender, age, BMI, STS, baseline ECG with first-degree AVB or RBBB, annulus area, aortic valve calcification, MS-length, ID and THV platform. A *P*-value <0.10 defined the cut-off for inclusion of these variables into the multivariable model. Missing values for covariates were present in less than 4% of the cases, except for aortic valve calcification (36.5% missing values), final ID at the NCC site (21.4% missing values), baseline ECG with first-degree AVB (13.9% missing values) and pre RBBB (13.4%). Missing data were imputed using

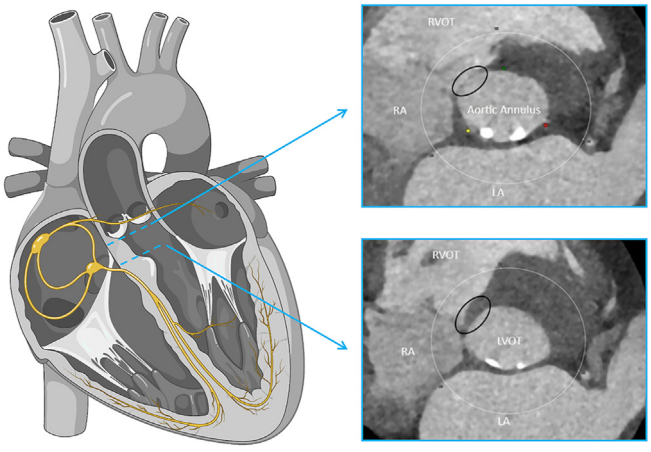


Fig. 1. Membranous Septum measurement. Illustration of MS-length measurement (created with BioRender.com). AV-node = Atrioventricular node, MS = membranous septum, RBB = right bundle branch, LBB = left bundle branch, RA = right atrium, RVOT = right ventricular outflow tract, LA = left atrium, LVOT = left ventricular outflow tract.

multiple imputation in the multivariable model by chained equations using 30 iterations. Results from 20 imputed data sets were then pooled using Rubin's Rules. Finally, we applied a univariable generalized linear mixed effect model in a subgroup analysis to find the relation between MS-length and new PPI per THV.

A 2-sided P < 0.05 was considered statistically significant. All statistics were performed with SPSS software version 25.0 (IBM, Chicago IL, United States) or R statistical software version 4.1.0 (Foundation for Statistical Computing, Vienna, Austria, packages: mice, lme4).

3. Results

3.1. Study population

Our study included 1811 patients with a successful TAVR-procedure between February 2014 and May 2021. Baseline characteristics of the overall population are depicted in Table 1. Median age was 81.9 years [IQR 77.2–85.4], 54% were male and median Society of Thoracic Surgeon's Predicted Risk of Mortality (STS-PROM) was 3.2% [IQR 2.1–5.0]. TAVR was performed using either the balloon-expandable Sapien3 (Edwards Lifesciences, Irvine, CA) (N = 695), the self-expandable Evolut R and Pro(Medtronic, Minneapolis, MN) (N = 734) and ACURATE NEO(Boston Scientific, Marlborough, MA) (N = 382) THV. Baseline demographics of the different THV platforms are displayed in Table 2. Patients receiving a Sapien3 were more often male compared to those receiving an Evolut and ACURATE valve (64.6% vs. 50.0% vs. 42.1%, p = <0.01). Patients receiving a Sapien3 valve had a larger annulus area, compared to the Evolut and ACURATE valve (496 mm^2 [IQR 426–561] vs. 451 mm^2 [IQR 390–451] vs. 432 mm^2 [IQR 395–478], p = <0.01), had more frequently a bicuspid phenotype (8.6% vs. 6.3% vs. 3.4%, p = 0.02) and had more often a severely calcified aortic valve (54.5% vs. 50.3% vs. 31.3%, p = <0.01). Median MS-length varied from 4.0 mm [IQR 2.5–6.0] for the Sapien3 valve to 4.0 mm [IQR2.6–5.5] for the Evolut and 5.0 mm [IQR 3.8–7.0] for the ACURATE valve, p = <0.01. Predilatation was performed in 94.5% in the ACURATE group, compared to 35.9% in the Sapien3 group and 34.8% in the Evolut group (p = <0.01). Median ID at the NCC was 5.0 mm [IQR 3.7–6.8] in the Sapien3 group, 5.0 mm [IQR 3.0–8.0] in the Evolut group and 4.0 mm [3.0–5.0] in the ACURATE group (p < 0.01).

3.2. Need for new pacemaker implantation

Overall, 275 patients (15.2%) received a PPI post-TAVR. Indications for PPI included high-degree AV block (90.9%), sick sinus syndrome (7.3%) and new LBBB(1.8%). PPI-patients had a significantly higher rate of pre-existing 1st-degree AVB (29.5% vs. 17.9%, p < 0.01) and RBBB (32.5% vs. 6.7%, p < 0.01) as compared to those not receiving a new PPI. The incidence of a new PPI varied per THV design from 14.2% for the Sapien3, 20.7% for the Evolut and 6.3% for the ACURATE valve.

Patients with a new PPI had a larger annulus (475 mm^2 [IQR 409–551] vs. 457 mm^2 [IQR 401–520], p = <0.01) and a shorter MS-length (3.7 mm [IQR 2.2–5.1] vs. 4.1 mm [IQR 2.8–6.0], p = <0.01) and a deeper ID (6.0 mm [IQR 4.0–7.8] vs. 5.0 mm [IQR3.0–6.6], p = <0.01).

3.3. Multivariable analysis

Predictors for new PPI post-TAVR are found in Table 3. Baseline ECG with first-degree (OR 2.01 [95% CI 1.35–3.00], p = <0.01) or RBBB (OR 8.33 [95% CI 5.21–13.33], p = <0.01), short MS-length (OR 0.89 [95% CI 0.83–0.97], p < 0.01), annulus area (OR 1.003 [95% CI 1.001–1.005], p = 0.04), NCC Implantation depth (OR 1.13 [95% CI 1.07–1.19] and use of Evolut valve (1.54 [95% CI 1.03–2.27], p = 0.04) were associated with a higher need for PPI.

Table 1
Baseline characteristics of the overall study population.

	Total	non PPI	PPI	*P*-value
N	1811	1536 (84.8)	275 (15.2)	
Male	977/1811 (53.9)	815/1536 (53.1)	162/275 (41.1)	0.07
Age	81.9 [77.2–85.4]	81.7 [77.0–85.2]	82.6 [78.4–86.0]	0.03
BMI	26.5 [23.7–30.1]	26.3 [23.6–30.0]	27.3 [24.1–30.5]	0.03
Hypertension	1435/1811 (79.2)	1211/1536 (78.8)	224/275 (81.5)	0.33
Diabetes Mellitus	511/1811 (28.2)	426/1536 (27.7)	85/275 (30.9)	0.33
COPD	285/1811 (15.7)	235/1536 (15.3)	50/275 (18.2)	0.23
PVD	389/1811 (21.5)	317/1536 (20.6)	72/275 (26.2)	0.04
History of ACS	390/1811 (21.5)	319/1536 (20.8)	71/275 (25.8)	0.06
History of PCI	499/1811 (27.6)	422/1536 (27.5)	77/275 (28.0)	0.86
History of CABG	180/1811 (9.9)	147/1536 (9.6)	33/275 (12.0)	0.22
History of Stroke	261/1811 (14.4)	222/1536 (14.5)	39/275 (14.2)	0.91
NYHA 3/4	1095/1804 (60.7)	902/1529 (59.0)	193/275 (70.2)	<0.01
STS	3.2 [2.1–5.0]	3.2 [2.1–4.9]	3.4 [2.2–5.7]	0.045
Echocardiography				
LVEF (%)	59 [50–65]	58 [50–65]	60 [52–65]	0.2
LVEDD (mm)	49 [43–55]	49 [43–54]	49 [43–55]	0.08
AV mean (mmHg)	40 [31–48]	40 [31–48]	40 [32–48]	0.82
AV Velocity (m/s)	4.1 [3.6–4.4]	4.1 [3.6–4.5]	4.1 [3.6–4.4]	0.56
AVA (cm^2)	0.77 [0.60–0.90]	0.77 [0.60–0.90]	0.78 [0.60–0.88]	0.57
AR				0.1
None	519/1650 (31.5)	456/1397 (32.6)	63/253 (24.9)	
Trace	205/1650 (12.4)	168/1397 (12.0)	37/253 (14.6)	
Mild	697/1650 (42.2)	578/1397 (41.4)	119/253 (47.0)	
Moderate	206/1650 (12.5)	177/1397 (12.7)	29/253 (11.5)	
Severe	23/1650 (1.4)	18/1397 (1.3)	5/253 (2.0)	
MR				0.03
None	267/1668 (16.0)	237/1411 (16.8)	30/257 (11.7)	
Trace	270/1668 (16.2)	233/1411 (16.5)	37/257 (14.4)	
Mild	798/1668 (47.8)	667/1411 (47.3)	131/257 (51.0)	
Moderate	263/1668 (15.8)	222/1411 (15.7)	41/257 (16.0)	
Severe	70/1668 (4.2)	52/1411 (3.7)	18/257 (7.0)	
TR				<0.01
None	356/1637 (21.7)	319/1384 (23.0)	37/253 (14.6)	
Trace	357/1637 (21.8)	291/1384 (21.0)	66/253 (26.1)	
Mild	716/1637 (43.7)	611/1384 (44.1)	105/253 (41.5)	
Moderate	168/1637 (10.3)	132/1384 (9.5)	36/253 (14.2)	
Severe	40/1637 (2.4)	31/1384 (2.2)	9/253 (3.6)	
MSCT				
Bicuspid aortic valve	119/1811 (6.6)	102/1536 (6.6)	17/275 (6.2)	0.78
Annulus area (mm^2)	460 [403–522]	457 [401–520]	475 [409–551]	<0.01
Annulus perimeter (mm)	77.0 [72.0–82.0]	77.0 [72.0–82.0]	78.4 [73.0–84.7]	<0.01

(*continued on next page*)

Table 1 (*continued*)

	Total	non PPI	PPI	*P*-value
Annulus mean dm (mm)	24.4 [22.9–26.0]	24.2 [22.9–25.9]	24.7 [23.0–26.6]	<0.01
LVOT mean dm (mm)	23.9 [22.0–25.7]	23.8 [22.0–25.6]	24.0 [22.0–26.0]	0.24
SOV mean dm (mm)	32.6 [30.0–35.1]	32.5 [30.0–35.0]	33.1 [30.5–35.8]	0.03
LCA height (mm)	14.0 [11.9–16.0]	14.0 [11.9–16.0]	14.0 [12.0–16.0]	0.12
RCA height (mm)	17.0 [15.0–19.3]	17.0 [14.9–19.3]	17.1 [15.0–19.4]	0.08
AV calcification				0.06
None	11/1149 (1.0)	11/954 (1.2)	0	
Mild	179/1149 (15.6)	158/954 (16.6)	21/195 (10.8)	
Moderate	383/1149 (33.3)	318/954 (33.3)	65/195 (33.3)	
Severe	576/1149 (50.1)	467/954 (49.0)	109/195 (55.9)	
Agatston score males	2943 [1381–4347]	2960 [2094–4225]	2805 [2054–4478]	0.75
Agatston score females	2032 [1281–2944]	2008 [1278–1894]	2286 [1234–3478]	0.23
MS Length (mm)	4.1 [2.7–6.0]	4.1 [2.8–6.0]	3.7 [2.2–5.1]	<0.01
ECG at baseline				
Rhythm				0.08
Sinus rhythm	1142/1448 (78.9)	948/1201 (78.9)	194/247 (78.5)	
Atrial fibrillation	301/1448 (20.8)	251/1201 (20.9)	50/247 (20.2)	
PR-time (ms)	180 [160–203]	180 [160–200]	188 [164–220]	<0.01
QRS-time (ms)	98 [88–114]	97 [88–110]	109 [92–135]	<0.01
Pre 1st degree AV block	307/1559 (19.7)	237/1322 (17.9)	70/237 (29.5)	<0.01
Pre BBB				<0.01
LBBB	173/1569 (11.0)	147/1323 (11.1)	26/246 (10.6)	
RBBB	169/1569 (10.8)	89/1323 (6.7)	80/246 (32.5)	
Procedure				
Predilatation	851/1769 (48.1)	742/1501 (49.4)	109/268 (40.7)	<0.01
Postdilatation	472/1800 (26.2)	394/1527 (25.8)	78/273 (28.6)	0.34
Final ID NCC (mm)	5.0 [3.1–6.9]	5.0 [3.0–6.6]	6.0 [4.0–7.8]	<0.01
Final ID LCC (mm)	5.0 [3.6–6.8]	5.0 [3.4–6.5]	6.0 [4.1–8.7]	<0.01

Baseline characteristics. BMI = Body Mass Index, COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease, ACS = Acute Coronary Syndrome, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Graft, NYHA = New York Heart Association, STS = Society of Thoracic Surgeons, LVEF = Left Ventricular Ejection Fraction, LVEDD = Left Ventricular End Diastolic Diameter, AV = Aortic Valve, AR = Aortic Regurgitation, MR = Mitral Regurgitation, TR = Tricuspid Regurgitation, MSCT = Multislice Computed Tomography, dm = diameter, LVOT = Left Ventricular Outflow Tract, SOV = Sinus of Valsalva, LCA = Left Coronary Artery, RCA = Right Coronary Artery, MS = Membranous Septum, LBBB = Left Bundle Branch Block, RBBB = Right Bundle Branch Block, ID = implantation depth, NCC = non-coronary cusp, LCC = left-coronary cusp.

Table 4 shows the predictors for new PPI per THV design. A RBBB at baseline ECG was the only consistent predictor across different THV designs. First-degree AVB, MS length and final ID at NCC site were not associated with new PPI after ACURATE THV implant.

3.4. Membranous septum

Fig. 2 shows the PPI-rate across the range of MS-lengths according to THV platform. A shorter MS-length was a significant predictor for PPI post-TAVR in patients receiving a Sapien3 (OR 0.87 [95% CI 0.79–0.99],

Table 2
Valve characteristics according to THV platform.

	Sapien3	Evolut	ACURATE	*P*-value
N	695	734	382	
Male	449/695 (64.6)	361/734 (50.0)	161/382 (42.1)	<0.01
Age	81.5 [76.2–85.1]	82.0 [77.5–85.7]	82.0 [78.2–85.2]	0.1
BMI	26.9 [23.9–30.6]	26.0 [23.9–30.6]	26.6 [23.8–30.2]	0.003
Hypertension	537/695 (77.3)	593 (80.8)	305/382 (79.8)	0.25
Diabetes Mellitus	211/695 (30.4)	199/734 (27.1)	101/382 (26.4)	0.27
COPD	112/695 (16.1)	132/734 (18.0)	41/382 (10.7)	<0.01
PVD	145/695 (20.9)	198/734 (27.0)	46 (382 (12.0)	<0.01
History of ACS	141/695 (20.3)	205/734 (27.9)	44/382 (11.5)	<0.01
History of PCI	197/695 (28.3)	221/734 (30.1)	81/382 (21.2)	<0.01
History of CABG	81/695 (11.7)	76/695 (10.4)	23/382 (6.0)	0.01
History of Stroke	91/695 (13.1)	116/734 (15.8)	54/382 (14.1)	0.34
NYHA 3/4	425/693 (61.3)	464/732 (63.4)	206/379 (54.4)	0.013
STS-PROM	3.0 [2.1–4.6]	3.4 [2.2–5.4]	3.2 [2.1–4.9]	<0.01
Echocardiography				
LVEF (%)	58 [48–65]	60 [50–65]	60 [55–65]	<0.01
LVEDD (mm)	49 [43–55]	48 [42–53]	45 [41–50]	<0.01
AV mean (mmHg)	40 [31–48]	41 [32–50]	42 [33–51]	<0.01
AV Velocity (m/s)	4.0 [3.6–4.5]	4.1 [3.7–4.4]	4.2 [3.7–4.6]	0.14
AVA (cm^2)	0.8 [0.6–0.9]	0.7 [0.6–0.9]	0.8 [0.6–0.9]	
AR				<0.01
None	198/607 (32.6)	175/692 (25.3)	146/351 (41.6)	
Trace	81/607 (13.3)	101/692 (14.6)	23/351 (6.6)	
Mild	242.607 (39.9)	312/692 (45.1)	143/351 (40.7)	
Moderate	77/607 (12.7)	96/692 (13.9)	33/351 (9.4)	
Severe	9/607 (1.5)	8/692 (1.2)	6/351 (1.7)	
MR				<0.01
None	98/630 (15.6)	64/694 (9.2)	105/344 (30.5)	
Trace	121/630 (19.2)	130/694 (18.7)	19/344 (5.5)	
Mild	292/630 (46.3)	344/694 (49.6)	162/344 (47.1)	
Moderate	98/630 (15.6)	119/694 (17.1)	46/344 (13.4)	
Severe	21/630 (3.3)	37/694 (5.3)	12/344 (3.5)	
TR				<0.01
None	127/620 (20.5)	94/675 (13.9)	135/342 (39.5)	
Trace	157/620 (25.3)	167/675 (24.7)	33/342 (9.6)	
Mild	262/620 (42.3)	313/675 (46.4)	141/342 (41.2)	
Moderate	62/620 (10.0)	80/675 (11.9)	26/342 (7.6)	
Severe	12/620 (1.9)	21/675 (3.1)	7/342 (2.0)	
MSCT				
Bicuspid aortic valve	60/695 (8.6)	46/734 (6.3)	13/3.4 (3.4)	0.02
Annulus Area (mm^2)	496 [426–561]	451 [390–451]	432 [395–478]	<0.01
Annulus Perimeter (mm)	80.0 [74.6–85.0]	76.2 [71.0–81.0]	75.0 [71.7–79.0]	<0.01
Annulus mean dm (mm)	25.2 [23.4–26.8]	24.0 [22.4–25.6]	24.0 [22.7–25.0]	<0.01
LVOT mean dm (mm)	25.0 [23.0–26.5]	23.2 [21.5–24.9]	23.2 [22.0–24.7]	<0.01

(*continued on next page*)

Table 2 (*continued*)

	Sapien3	Evolut	ACURATE	*P*-value
SOV mean dm (mm)	33.5 [30.5–36.4]	32.0 [29.7–34.7]	32.0 [30.0–35.0]	<0.01
LCA height (mm)	14.5 [12.0–16.5]	13.2 [11.2–15.6]	13.9 [11.7–15.5]	<0.01
RCA height (mm)	17.8 [15.2–20.0]	17.0 [15.0–19.0]	16.0 [14.0–18.9]	<0.01
Severe AV calcification	253/464 (54.5)	288/573 (50.3)	35/112 (31.3)	<0.01
Agatston score males	3214 [2245–4549]	2676 [1864–3884]	3369 [2536–4083]	<0.01
Agatston score females	1986 [1210–2911]	2033 [1271–2906]	2175 [1378–3329]	0.51
MS length (mm)	4.0 [2.5–6.0]	4.0 [2.6–5.5]	5.0 [3.8–7.0]	
ECG at baseline				
Rhythm				0.54
Sinusrhythm	464/596 (77.9)	128/596 (21.5)	151/184 (82.1)	
Atrial fibrillation	527/668 (78.9)	140/668 (21.0)	33/184 (17.9)	
PR-time (ms)	181 [162–204]	178 [160–204]	182 [164–202]	0.27
QRS-time (ms)	102 [90–122]	98 [88–112]	94 [82–107]	<0.01
PRE 1st degree AVB	114/588 (19.4)	133/653 (20.4)	60/318 (18.9)	0.84
Pre BBB				<0.01
LBBB	82/597 (13.7)	65/651 (10.0)	26/319 (8.2)	
RBBB	76/597 (12.7)	64 (9.8)	29/319 (9.1)	
Procedure & Outcomes				
Predilatation	236/657 (35.9)	254/730 (34.8)	361/382 (94.5)	<0.01
Postdilatation	99/690 (14.3)	216/732 (29.5)	157/378 (41.5)	<0.01
Final ID NCC (mm)	5.0 [3.7–6.8]	5.0 [3.0–8.0]	4.0 [3.0–5.0]	<0.01
New PPI	99/695 (14.2)	152/734 (20.7)	24/382 (6.3)	<0.01

Baseline characteristics of the different transcatheter heart valves. BMI = Body Mass Index, COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease, ACS = Acute Coronary Syndrome, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Graft, NYHA = New York Heart Association, STS = Society of Thoracic Surgeons, LVEF = Left Ventricular Ejection Fraction, LVEDD = Left Ventricular End Diastolic Diameter, AV = Aortic Valve, AR = Aortic Regurgitation, MR = Mitral Regurgitation, TR = Tricuspid Regurgitation, MSCT = Multislice Computed Tomography, dm = diameter, LVOT = Left Ventricular Outflow Tract, SOV = Sinus of Valsalva, LCA = Left Coronary Artery, RCA = Right Coronary Artery, MS = Membranous Septum, LBBB = Left Bundle Branch Block, RBBB = Right Bundle Branch Block, ID = implantation depth, NCC = non-coronary cusp, LCC = left-coronary cusp.

p = <0.01) or an Evolut-valve (OR 0.91 [95% CI 0.84–0.98], p = 0.03), but not in those receiving an ACURATE-valve (OR 0.99 [95% CI 0.79–1.21], p = 0.91). When we added interaction terms to the model, we could not demonstrate statistically significant effect modification by THV of the association between MS-length and new PPI (Sapien3 vs. Evolut: p = 0.47 and Sapien3 vs. ACURATE: p = 0.75).

Based on our study observations within the total cohort, we identified 3 risk groups by MS length: MS length ≤3 mm defined a high-risk group for PPI (>20%), MS length 3–7 mm intermediate risk for PPI (10–20%) and MS length > 7 mm defined a low risk for PPI (<10%). Fig. 2 shows the odds ratio for a new PPI with each THV platform relative to the low risk MS reference of ≥7 mm. In the Sapien3 cohort, PPI-rate was 20% with the high-risk phenotype (OR 6.96 [95% CI 2.45–29.28], p = <0.01), 14% in the intermediate-risk phenotype (OR 4.88 [95% CI 1.75–20.37], p < 0.01) and 3.3% in the low risk phenotype. In the Evolut-cohort, PPI-rate was 25% with the high-risk phenotype (OR 3.14 [95% CI 1.45–7.87], p < 0.01), 20% with the intermediate-risk phenotype (OR 2.38 [95% CI 1.21–5.87], p = 0.04) and 9.6% with a low-risk phenotype. In the ACURATE cohort, PPI rate was <10% for all phenotypes (7.2% for the high risk phenotype, OR 1.36 [95% CI 0.26–10.49], p = 0.34, 6.8% for the intermediate risk phenotype, OR1.75 [0.45–11.59], p = 0.47 and 3.1% for the low risk phenotype).

Table 3
Multivariable analysis.

	Univariable		Multivariable	
	OR [95%CI]	p-value	OR [95%CI]	p-value
Male	0.79 [0.61–1.00]	0.08	1.34 [0.85–2.12]	0.21
Age	1.02 [1.00–1.04]	0.03	1.03 [0.99–1.05]	0.06
BMI	1.02 [0.99–1.05]	0.08	1.02 [0.99–1.06]	0.18
STS	1.03 [0.99–1.07]	0.19		
Pre 1AVB	1.99 [1.43–2.72]	<0.01	2.01 [1.35–3.00]	<0.01
Pre RBBB	6.42 [4.48–9.12]	<0.01	8.33 [5.21–13.33]	<0.01
Annulus Area	1.002 [1.001–1.004]	<0.01	1.003 [1.001–1.005]	0.04
AV calcification > severe	1.32 [0.97–1.80]	0.08	1.02 [0.70–1.46]	0.93
MS length	0.90 [0.84–0.95]	<0.01	0.89 [0.83–0.97]	<0.01
ID NCC	1.14 [1.08–1.20]	<0.01	1.13 [1.07–1.19]	<0.01
Valve platform				
Sapien3	ref		ref	
Evolut	1.63 [1.22–2.18]	<0.01	1.54 [1.03–2.27]	0.04
ACURATE	0.44 [0.27–0.71]	<0.01	0.94 [0.45–1.97]	0.87

Multivariable analysis. BMI = Body Mass Index, STS = Society of Thoracic Surgeons, 1AVB = First-degree atrioventricular block, RBBB = Right Bundle Branch Block, MS = membranous septum, ID = implantation depth, NCC = non-coronary cusp.

Excluding patients with bicuspid AS from the analysis did not change the overall findings (Supplemental Figure 1).

4. Discussion

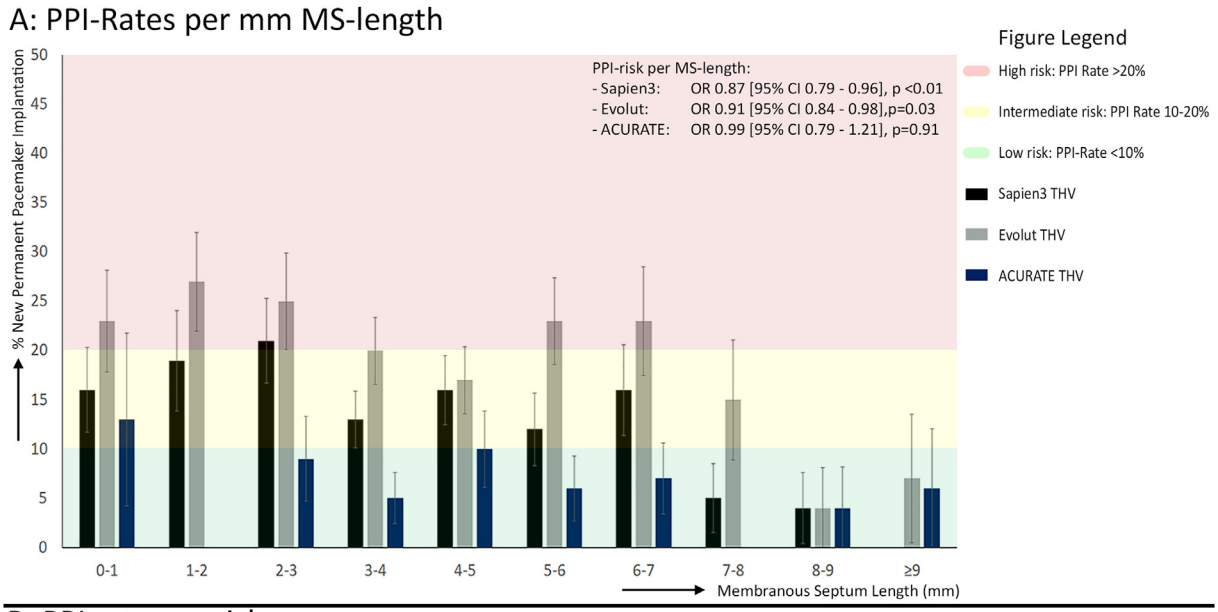
Our study is the largest registry to date evaluating the impact of MS-length on the need of new PPI post-TAVR and involving different THV concepts. Main findings are (1) MS length predicts new PPI post-TAVR. (2) MS length <3 mm denotes a high-risk phenotype and MS > 7 mm a low-risk phenotype for new PPI. (3) The need for a new PPI was consistently lower with the ACURATE THV as compared to both Evolut and Sapien3 and seemed not to be affected by MS length.

The MS is in conjunction with the right and non-coronary cusp of the aortic valve. There is considerable individual variability in MS length and its anatomical relationship with the AV node and the bundle of His.[7] Typically, the His bundle penetrates the distal borders of the MS near the transition to the muscular part of the interventricular septum and separates into a right and left bundle branch underneath the surface of the LVOT.[4] Not surprisingly prior studies have described the association of a short MS with need for new PPI after TAVR because the valve frame would more likely connect with the conduction system as opposed to a longer MS. Jilaihawi et al. reported for the first time a high need for new PPI after TAVR with the self-expanding Evolut THV in the presence of a short MS (<2 mm) but a low PPI rate with a MS > 5 mm.[5] A single-center experience extended these insights to other THV platforms and confirmed MS phenotypes at low, intermediate and high risk for PPI based on MS length.[8] The present multi-center study confirmed the association of these different MS phenotypes with new PPI except for the ACURATE THV. The new PPI rate with ACURATE THV remained low across the bandwidth of MS lengths. The lower PPI risk with ACURATE THV may be explained by a lower radial force than other THV platforms and its unique top-down deployment that minimizes interaction with the LVOT and the conduction system. Patient selection bias may have partly affected the difference in PPI among the different THV platforms. Indeed, by multivariable analysis, there was no difference between the Sapien3 and ACURATE THV. The Sapien3 group featured anatomies with a larger annulus, more severe aortic root calcium and a higher frequency of bicuspid aortic phenotypes, whereas the ACURATE group presented with longer MS and more shallow ID. Patient selection bias may at least partly

Table 4
Risk factors per transcatheter valve platform.

	Sapien3			Evolut			Acurate		
	no PPI	PPI	*P*-value	no PPI	PPI	*P*-value	no PPI	PPI	*P*-value
Pre 1AVB	92/504 (18.3)	22/84 (26.2)	0.88	90/519 (17.3)	43/134 (32.1)	<0.01	55/299 (18.4)	5/19 (26.3)	0.39
Pre RBBB	43/507 (8.5)	33/91 (36.3)	<0.01	26/517 (5.0)	38/135 (28.1)	<0.01	20/299 (6.7)	9/20 (45.0)	<0.01
Annulus Area (mm^2)	494 [424–555]	504 [448–575]	0.12	449 [390–507]	461 [394–536]	0.11	430 [395–477]	465 [399–517]	0.11
MS length (mm)	4.1 [2.5–6.0]	3.5 [2.2–5.0]	<0.01	4.0 [2.7–5.7]	3.7 [2.1–5.2]	0.04	5.0 [3.4–7.0]	4.2 [3.0–6.0]	0.26
Final ID NCC (mm)	5.0 [3.5–6.5]	5.7 [4.2–7.6]	<0.01	5.0 [3.0–8.0]	6.0 [4.0–8.7]	<0.01	4.0 [3.0–5.0]	4.3 [4.0–6.1]	0.2
MS > ID	209/223 (93.7)	14/223 (6.3)	<0.01	207/240 (86.3)	33/240 (13.8)	<0.01	186/195 (95.4)	9/195 (4.6)	0.42
MS < ID	245/300 (81.7)	55/300 (18.3)		283/365 (77.5)	82/365 (22.5)		92/99 (92.9)	7/99 (7.1)	

Risk factor per transcatheter valve platform. 1AVB = First-degree atrioventricular block, RBBB = Right Bundle Branch Block, MS = membranous septum, ID = implantation depth, NCC = non-coronary cusp.



B: PPI-rate per risk group

	Sapien3			Evolut			ACURATE		
	N (%)	OR [95% CI]	P-value	N (%)	OR [95% CI]	P-value	N (%)	OR [95% CI]	P-value
Low risk >7mm	3/92 (3.3)	ref		7/73 (9.6)	ref		2/65 (3.1)	ref	
Intermediate risk 3-7mm	54/382 (14.1)	4.88 [1.75 - 20.37]	**<0.01**	84/417 (20.1)	2.38 [1.21 - 5.87]	**0.04**	16/234 (6.8)	0.56 [-0.80 - 2.45]	0.47
High risk <3mm	42/221 (19.0)	6.96 [2.45 - 29.28]	**<0.01**	61/244 (25.0)	3.14 [1.45 - 7.87]	**<0.01**	6/83 (7.2)	0.31 [-1.34 - 2.35]	0.34

Fig. 2. Pacemaker rates per valve platform according to the MS length. A: PPI-rates as percentage with confidence interval per millimeter MS-length per transcatheter heart valve. B: cut-off points based on study observations per transcatheter heart valve. OR = Odds ratio, CI = confidence interval.

explain a higher PPI rate in the Sapien3 group as compared to other publications.[9–11] Consistent with existing literature our data upheld age, pre-existing conduction disorders, annular area and ID as risk factors for new PPI but also added MS length and THV design. Presence of RBBB at baseline was the sole risk factor applicable to all THV platforms. Prophylactic PPI in the context of pre-existing RBBB may reduce hospital stay and affect clinical outcome.[12]

Intuitively, ID and THV selection seem the only modifiable variables from a procedure point of view. An ID within the MS length was associated with a lower new PPI rate after TAVR with Sapien3 or Evolut THV. Jilaihawi et al. previously demonstrated that an ID < MS length reduced PPI-rate.[5] However, the relation between ID and MS length should be interpreted with caution because ID was measured by 2D angiography as opposed to MS length that was determined by 3D MSCT. Angiography also consistently underestimated ID measurements as compared to MSCT and it may be elusive to appreciate precise ID during TAVR.[13,14]

Anatomy tailored THV selection in the presence of a short MS may help mitigate need for PPI after TAVR but should also take into consideration risks for THV underexpansion, prosthesis patient mismatch and paravalvular leaks that may impact clinical outcome after TAVR.[15–17]

4.1. Study limitations

All data and imaging derived measurements were site reported without a central core laboratory. Still, local imagers were trained to perform MSCT analyses according to a standardized protocol resulting in reasonable correlations in MS length measurements across the different centers. THV selection was per physician's discretion and reflected local practices. By using generalized linear mixed models, we accounted for these center effects in the statistical analysis. Multiple imputations were used to account for missing data related to implantation depth, aortic valve calcifications and baseline ECG characteristics. We acknowledge the relative low event rate in the ACURATE cohort. Still, our series represent among the largest ACURATE data available. The Cusp Overlap implantation technique was not routinely applied in our series. The Cusp Overlap method may result in

higher THV implants and lower new PPI-rates. However, so far this promise of a lower rate of conduction disorders with Cusp Overlap has not been validated in large prospective studies with no clear selection bias, and therefore needs more robust research. Finally, local practices related to new pacemaker implantation may have varied, but we would not expect major differences because high degree AV block was the dominant indication for the implantation of a new pacemaker.

5. Conclusion

MS length was an independent predictor for PPI across different THV platforms, except for the ACURATE-THV. Based on our study observations within the total cohort, we identified 3 risk groups by MS length: MS length $\leq$3 mm defined a high-risk group for PPI (>20%), MS length 3–7 mm intermediate risk for PPI (10–20%) and MS length > 7 mm defined a low risk for PPI (<10%). Anatomy-tailored-THV-selection may mitigate the need for new-PPI in patients undergoing TAVR.

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Appendix A. Supplementary data

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References

1. Siontis GC, Juni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol*. Jul 15 2014;64(2):129–140. https://doi.org/10.1016/j.jacc.2014.04.033. S0735-1097(14)02436-X [pii].
2. Mahajan S, Gupta R, Malik AH, et al. Predictors of permanent pacemaker insertion after TAVR: a systematic review and updated meta-analysis. *J Cardiovasc Electrophysiol*. Mar 8 2021. https://doi.org/10.1111/jce.14986.
3. van Rosendael PJ, Delgado V, Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *Eur Heart J*. 06 01 2018;39(21):2003–2013. https://doi.org/10.1093/eurheartj/ehx785.
4. Saremi F, Hassani C, Sanchez-Quintana D. Septal atrioventricular junction region: comprehensive imaging in adults. *Radiographics*. Nov-Dec 2016;36(7):1966–1986. https://doi.org/10.1148/rg.2016160010.
5. Jilaihawi H, Zhao Z, Du R, et al. Minimizing permanent pacemaker following repositionable self-expanding transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. Sep 23 2019;12(18):1796–1807. https://doi.org/10.1016/j.jcin.2019.05.056. S1936-8798(19)31425-6 [pii].
6. Hamdan A, Guetta V, Klempfner R, et al. Inverse relationship between membranous septal length and the risk of atrioventricular block in patients undergoing transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. Aug 17 2015;8(9):1218–1228. https://doi.org/10.1016/j.jcin.2015.05.010. S1936-8798(15)00806-7 [pii].
7. Kawashima T, Sato F. Visualizing anatomical evidences on atrioventricular conduction system for TAVI. *Int J Cardiol*. Jun 1 2014;174(1):1–6. https://doi.org/10.1016/j.ijcard.2014.04.003. S0167-5273(14)00662-7 [pii].
8. Hokken TW, van Wiechen MP, Ooms JF, et al. Impact of Interventricular membranous septum length on pacemaker need with different transcatheter aortic valve implantation systems. *Int J Cardiol*. Jun 15 2021;333:152–158. https://doi.org/10.1016/j.ijcard.2021.02.080. S0167-5273(21)00391-0 [pii].
9. Li YM, Tsauo JY, Liao YB, Zhao ZG, Chen M. Comparison of third generation balloon-expandable Edwards Sapien 3 versus self-expandable Evolut R in transcatheter aortic valve implantation: a meta-analysis. *Ann Palliat Med*. Apr 20 2020. https://doi.org/10.21037/apm.2020.03.36. apm.2020.03.36 [pii].
10. Lanz J, Kim WK, Walther T, et al. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. *Lancet*. Nov 2 2019;394(10209):1619–1628. https://doi.org/10.1016/S0140-6736(19)32220-2. S0140-6736(19)32220-2 [pii].
11. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. May 2 2019;380(18):1695–1705. https://doi.org/10.1056/NEJMoa1814052.
12. Fukutomi M, Hokken T, Wong I, et al. Prophylactic permanent pacemaker strategy in patients with right bundle branch block undergoing transcatheter aortic valve replacement. *Cathet Cardiovasc Interv*. Aug 14 2021. https://doi.org/10.1002/ccd.29914.
13. Piayda K, Hellhammer K, Veulemans V, et al. Navigating the "optimal implantation depth" with a self-expandable TAVR device in daily clinical practice. *JACC Cardiovasc Interv*. Mar 23 2020;13(6):679–688. https://doi.org/10.1016/j.jcin.2019.07.048. S1936-8798(19)31656-5 [pii].
14. Vora AN, Tang GHL, Reardon MJ, et al. Transcatheter aortic valve implant depth measurements differ by aortography versus computed tomography. *JACC Cardiovasc Interv*. May 10 2021;14(9):1045–1047. https://doi.org/10.1016/j.jcin.2020.12.035. S1936-8798(20)32553-X [pii].
15. Sawaya F, Jorgensen TH, Sondergaard L, De Backer O. Transcatheter bioprosthetic aortic valve dysfunction: what we know so far. *Front Cardiovasc Med*. 2019;6:145. https://doi.org/10.3389/fcvm.2019.00145.
16. Genereux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. *J Am Coll Cardiol*. Mar 19 2013;61(11):1125–1136. https://doi.org/10.1016/j.jacc.2012.08.1039. S0735-1097(13)00036-3 [pii].
17. Hagar A, Li Y, Wei X, et al. Incidence, predictors, and outcome of paravalvular leak after transcatheter aortic valve implantation. *J Intervent Cardiol*. 2020;2020:8249497. https://doi.org/10.1155/2020/8249497.