openheart

Modifiable risk factors for permanent pacemaker after transcatheter aortic valve implantation: CONDUCT registry

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To cite: Rudolph T, Droppa M, Baan J, *et al*. Modifiable risk factors for permanent pacemaker after transcatheter aortic valve implantation: CONDUCT registry. *Open Heart* 2023;**10**:e002191. doi:10.1136/openhrt-2022-002191

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Received 31 October 2022
Accepted 14 December 2022

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ABSTRACT

Objective The onset of new conduction abnormalities requiring permanent pacemaker implantation (PPI) after transcatheter aortic valve implantation (TAVI) is still a relevant adverse event. The main objective of this registry was to identify modifiable procedural risk factors for an improved outcome (lower rate of PPI) after TAVI in patients at high risk of PPI.

Methods Patients from four European centres receiving a balloon-expandable TAVI (Edwards SAPIEN 3/3 Ultra) and considered at high risk of PPI (pre-existing conduction disturbance, heavily calcified left ventricular outflow tract or short membranous septum) were prospectively enrolled into registry.

Results A total of 300 patients were included: 42 (14.0%) required PPI after TAVI and 258 (86.0%) did not. Patients with PPI had a longer intensive care unit plus intermediate care stay (65.7 vs 16.3 hours, p<0.001), general ward care stay (6.9 vs 5.3 days, p=0.004) and later discharge (8.6 vs 5.0 days, p<0.001). Of the baseline variables, only pre-existing right bundle branch block at baseline (OR 6.8, 95% CI 2.5 to 18.1) was significantly associated with PPI in the multivariable analysis. Among procedure-related variables, oversizing had the highest impact on the rate of PPI: higher than manufacturer-recommended sizing, mean area oversizing as well as the use of the 29 mm valve (OR 3.4, 95% CI 1.4 to 8.5, p=0.008) all were significantly associated with PPI. Rates were higher with the SAPIEN 3 (16.1%) vs SAPIEN 3 Ultra (8.5%), although not statistically significant but potentially associated with valve sizing. Implantation depth and postdelivery balloon dilatation also tended to affect PPI rates but without a statistical significance.

Conclusion Valve oversizing is a strong procedure-related risk factor for PPI following TAVI. The clinical impact of the valve type (SAPIEN 3), implantation depth, and postdelivery balloon dilatation did not reach significance and may reflect already refined procedures in the participating centres, giving attention to these avoidable risk factors.

Trial registration number NCT03497611.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While a number of registries have documented the rates of permanent pacemaker implantation (PPI) with different valves, much less evidence has been provided for the procedural variables associated with the need for PPI after transcatheter aortic valve implantation (TAVI).

WHAT THIS STUDY ADDS

⇒ Valve oversizing has been found to be strongly associated with PPI following TAVI. The clinical impact of the valve type (SAPIEN 3), implantation depth, and postdelivery balloon dilatation did not reach significance and may indicate improvements in the procedures performed at the participating centres considering these avoidable risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Determining factors associated with an increased likelihood of PPI allows the optimisation of preprocedural and intraprocedural care, potentially decreasing the incidence rates of postoperative PPI.

INTRODUCTION

Within the last decade, transcatheter aortic valve implantation (TAVI) has established itself to be a standard therapy in moderate-risk and high-risk patients with symptomatic aortic stenosis (AS) and recently even non-inferior to surgical aortic valve replacement in low-risk patients.[1–6] A new generation of balloon-expandable transcatheter heart valves (THVs), such as Edwards SAPIEN 3/3 Ultra, has been shown to reduce periprocedural complications (reduced moderate or severe paravalvular regurgitation and major vascular complications) and improve 30-day and 12-month outcomes.[7] However, despite technological advances, permanent pacemaker implantation (PPI) remains a potential postprocedural complication after TAVI, leading to reduced survival, increased costs, and prolonged hospital stay.[8]

To date, several reports on PPI rates and predictors associated with the use of the Edwards SAPIEN 3 THV have been published.[9–17] Pre-existing conduction

disturbance, aortic valve calcification, greater implantation depth/oversizing, and several other anatomical and procedural factors, including heavily calcified left ventricular outflow tract (LVOT), complete right bundle branch block (RBBB), prolonged QRS duration, and short membranous septum, have been associated with the need for PPI after SAPIEN 3 THV TAVI. Maeno *et al* used these data to develop a scoring algorithm to predict PPI post TAVI, including non-coronary cusp (NCC) device-landing zone calcium volume, RBBB, short membranous septum length and ventricular implantation depth as predictive factors.[16] In a recent study examining PPI rates of balloon-expandable and self-expanding THV in a large cohort of patients with AS, both RBBB and left bundle branch block were identified as predictors for PPI after TAVI, in addition to age, sex, history of hypertension, obesity, diabetes mellitus, and myocardial infarction, among others.[17]

Nevertheless, most of the current evidence is derived from single-centre series with a lack of a consistent definition of potentially associated variables and the unexplained differences in the number and type of identified variables. In the previously published retrospective analysis by our group, several baseline characteristics, including older age, pulmonary hypertension, prolonged QRS duration, bradycardia, first-degree atrioventricular (AV) block, left anterior hemiblock (LAHB), RBBB as well as higher calcium volume in LVOT were significantly associated with PPI following TAVI.[18]

In the present prospective, multicentre analysis of patients at high risk of PPI based on their disease characteristics, we aimed to identify potentially modifiable procedural variables that can reduce the risk of PPI in high-risk patients.

METHODS/DESIGN

CONDUCT is a prospective, multicentre, observational registry of patients undergoing balloon-expandable TAVI at four European institutions: (1) Heart and Diabetes Centre Nordrhein-Westfalen, Germany; (2) Academic Medical Center (AMC), Amsterdam University, The Netherlands; (3) University Hospital Tübingen, Germany; and (4) Linköping University Hospital, Sweden. Site selection was based on the site's prior experience with TAVI and the recommendations of the steering committee.

Objectives

The primary objective was to identify procedural variables that can be adjusted to result in an improved outcome (lower rate of PPI) of TAVI in patients with a high risk of procedure-related PPI. The secondary objectives were to verify the results for increased risk of PPI developed in the retrospective phase and to determine PPI-related and overall clinical outcomes in the high-risk cohort of patients.

Patient population

A high-risk cohort of patients was formed based on the results from the retrospective analysis of patients undergoing TAVI at our institutions.[18] Patients undergoing transfemoral TAVI with a balloon-expandable device due to AS and having at least one of the previously identified risk factors for PPI, including pre-existing conduction disturbance (RBBB, LAHB, atrioventricular (AV) block, prolonged QRS duration and bradycardia), heavily calcified LVOT or short membranous septum, were prospectively included in our registry. Patients with a prior pacemaker, indication for PPI prior to TAVI, and valve-in-valve implantation were excluded from the registry. The decision to perform TAVI was made by the local heart team and conducted according to the local protocol.

Documentation and endpoints

Patient demographics, medical history, symptoms, surgical risk scores (EuroScore II and Society of Thoracic Surgeons risk score), and echocardiographic and ECG parameters were recorded at baseline. Periprocedural details and postprocedural outcomes, including device success and complications, were also reported. In addition, data on the time until pacemaker implantation, underlying rhythm disturbances, and in-hospital outcomes were collected. All data were subject to automatic checks for plausibility and completeness.

A routine multislice CT scan performed prior to TAVI was obtained for each patient. The type of scanner, transverse slice thickness, acquisition time, electrographic R–R interval threshold for scanning initiation, and tube current/voltage were specific to each site. Contrast agent was used at all centres and calcium quantification was performed by a single designated, experienced core lab in Tübingen (Germany) as described previously.[18]

Implantation depth was assessed relative to the annular plane. Data were classified as the percentage of valve being below the annulus.[14 15] Sizing classifications were determined by the physiological aortic annulus area in relation to the nominal area range of the implanted valve declared by the manufacturer. Oversizing was defined as physiological annulus area smaller than minimum area range of the valve size. Undersizing was defined as the physiological annulus area bigger than the maximum area range of the implanted valve size.

Statistics

Pseudonymised data and CT scans were sent to the Institute for Pharmacology and Preventive Medicine (Cloppenburg, Germany). Missing data were requested but were not imputed in case of no provision. The analysis was based on available data only.

For the analysis, patients were stratified into those receiving PPI versus those not receiving PPI after TAVI. Data were analysed using descriptive statistics, with categorical variables presented as absolute values and frequencies (%) and the continuous variables presented as means±SD and/or median (IQR). Group comparisons

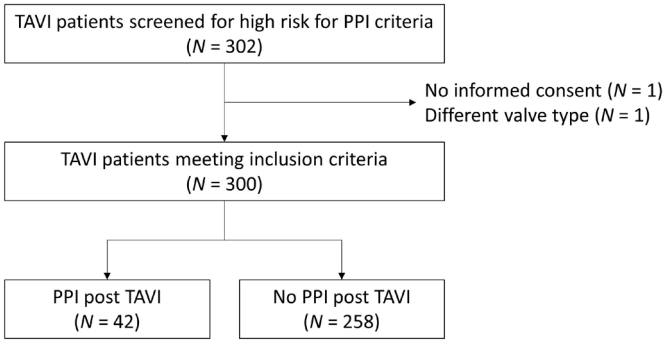

Figure 1 Flowchart of study patients. PPI, permanent pacemaker implantation; TAVI transcatheter aortic valve implantation.

were carried out using t-test or Mann-Whitney U test for continuous variables as appropriate, depending on distribution, and Fisher exact or χ^2 test for categorical variables. Test for normal distribution was carried using Kolmogorov-Smirnov test.

ORs were calculated by logistic regression. Multivariable logistic regression analysis was performed to identify baseline and procedural parameters being associated with the outcome (PPI after TAVI). In the multivariable analysis, all other baseline variables of potential interest (p<0.05; diabetes, chronic obstructive pulmonary disease (COPD), QRS ≥110 ms, AF, RBBB complete, distance to left coronary artery (LCA) <median, aortic annulus calcification NCC >median) were included. Despite a p-value lower than 0.05, pulmonary artery pressure (PAP) was not included due to several missing data. For the multivariable model for the procedural parameters, all baseline variables plus as procedural variable of interest with p<0.05, valve type SAPIEN 3, were included.

All statistical analyses were performed using SPSS V.26.0. A p-value of <0.05 was considered significant.

RESULTS

Between January 2019 and November 2021, a total of 300 patients (171 in Germany, 80 in The Netherlands and 49 in Sweden) were documented: 42 (14.0%) of patients required PPI after TAVI and 258 (86.0%) patients did not (figure 1). In a total of 42 patients who had PPI, 36 (85.7%) had it before discharge and 6 (14.3%) after discharge with a median of 5 (IQR 1.8–7.0) days after TAVI. The major reason for PPI was AV block grade III (n=34, 80.9%), followed by AV block grade II (type Mobitz) (n=2, 4.8%) and sinoatrial block (n=2, 4.8%) (table 1).

Identification of patient baseline characteristics associated with PPI

Patients had a mean age of 79.9±6.3 years and 75.0% were female. In comparison to patients without PPI after TAVI, patients undergoing PPI had higher rates of diabetes (42.9% vs 26.0%, p=0.024) and COPD (16.7% vs 6.2%, p=0.028) (table 2). Further, patients with PPI had lower left ventricular ejection fraction (47.5% vs 51.2%, p=0.014) and higher systolic PAP (48.8 vs 39.5 mm Hg, p=0.010).

Table 1 Indication for PPI (n=42)

	n (%) or median (IQR)
Time point of PPI	
Before discharge	36 (85.7)
After discharge	6 (14.3)
Days after TAVI	5 (1.8–7.0)
Reason for PPI	
AV block III	34 (80.9)
AV block II, type Mobitz	2 (4.8)
SA block	2 (4.8)
Trifascicular block	1 (2.4)
Asystole	1 (2.4)

AV, atrioventricular; PPI, permanent pacemaker implantation; SA, sinoatrial; TAVI, transcatheter aortic valve implantation.

Differences in ECG-based characteristics included higher rates of atrial fibrillation (33.3 vs 19.5%, p=0.042), longer QRS duration (141.1 vs 116.8 ms, p<0.001) and presence of a complete RBBB (64.3 vs 17.5%, p<0.001) (table 3). In addition, results from CT data showed that pacemaker-dependent patients had a significantly shorter distance from the aortic annulus plane to the LCA (12.6 vs 14.0 mm, p=0.035) and a lower calcium volume of the NCC (289 vs 433 mm^3, p=0.044) than patients without a pacemaker (table 4).

In the univariable regression analysis, diabetes (OR 2.1, 95% CI 1.1 to 4.2, p=0.027), COPD (OR 3.0, 95% CI 1.2 to 7.9, p=0.023), atrial fibrillation (OR 2.1, 95% CI 1.0 to 4.2, p=0.045), QRS duration ≥110 ms (OR 5.2, 95% CI 2.1 to 12.7, p<0.001), complete RBBB (OR 8.4, 95% CI 4.1 to 17.1, p<0.001) and aortic calcium volume of NCC >median (OR 0.4, 95% CI 0.2 to 0.9, p=0.030) were independently associated with PPI after TAVI (table 5). However, after including these parameters in the multivariable analysis, only complete RBBB (OR 6.8, 95% CI 2.5 to 18.1, p<0.001) emerged as an independent baseline predictor of PPI (table 5).

Identification of procedural variables associated with PPI (adjusted for differences in patient characteristics)

Patients with PPI post-TAVI received larger sized valves (27.3%±2.2% vs 26.6%±2.1%, p=0.027) than patients without PPI with 14.3% vs 17.1% receiving 23 mm, 28.6% vs 47.3% receiving 26 mm, and 57.1% vs 35.7% receiving 29 mm, respectively (p=0.026) (table 6). Mean area oversizing was 4.0%±19.6% in patients with PPI compared with 0.0%±17.3% in those without PPI (p=0.255). Based on the manufacturer's (Edwards) sizing recommendations, the prosthesis was oversized in 17.6% vs 11.7%, within normal sizing range in 61.8% vs 47.7%, and undersized in 20.6% vs 40.5%

Table 2 Patient baseline characteristics and echocardiography

	Total (N=300)	PPI+ (n=42)	PPI– (n=258)	P-value PPI+ versus PPI–
Age (years)	79.9±6.3	79.1±6.6	80.0±6.3	0.229
Female gender	225 (75.0)	34 (81.0)	191 (74.0)	0.337
BMI (kg/m$^{2)}$	27.5±4.7	27.5±5.7	27.5±4.5	0.908
Current smoker	21 (7.1)	2 (4.8)	19 (7.4)	0.749
Comorbidities				
Hypertension	237 (79.0)	36 (85.7)	201 (77.9)	0.249
Diabetes	85 (28.3)	18 (42.9)	67 (26.0)	**0.024**
Coronary artery disease	159 (53.0)	25 (59.5)	134 (51.9)	0.361
Congestive heart failure	64 (21.3)	9 (21.4)	55 (21.3)	0.987
Porcelain aorta	3 (1.0)	0 (0)	3 (1.2)	1.000
Endocarditis	2 (0.7)	0 (0)	2 (0.8)	1.000
Prior TIA/stroke	39 (13.0)	7 (16.7)	32 (12.4)	0.446
COPD	23 (7.7)	7 (16.7)	16 (6.2)	**0.028**
Renal insufficiency*	51 (17.0)	10 (23.8)	41 (15.9)	0.206
Creatinine (mg/dL)	1.2±0.7	1.2±0.4	1.2±0.7	0.077
EuroScore II (%)	3.1±2.9	3.2±2.3	3.1±2.8	0.783
STS risk score (%)	3.1±2.7	2.7±2.0	3.2±2.8	0.405
Echocardiography				
Severe calcified AS	268 (89.3)	39 (92.9)	229 (88.8)	0.592
AR moderate/severe	30 (10.0)	5 (12.2)	25 (9.7)	0.580
MR moderate/severe	61 (20.4)	12 (29.3)	49 (19.0)	0.129
TR moderate/severe	40 (13.4)	9 (22.0)	31 (12.1)	0.085
LVEF (%)	50.6±9.8	47.5±9.3	51.2±9.8	**0.014**
AVA, (cm^2)	0.80±0.23	0.77±0.19	0.79±0.24	0.794
AVA indexed (cm^2/m^2)	0.41±0.13	0.39±0.09	0.41±0.14	0.690
AV mean pressure gradient, (mm Hg)	46.9±16.9	44.9±15.4	47.3±17.1	0.497
AV peak pressure gradient (mm Hg)	72.6±23.3	67.7±19.1	73.4±23.8	0.255
Vmax (m/s)†	4.24±0.84	3.94±0.94	4.28±0.81	0.222
PAP systolic (mm Hg)‡	40.6±15.0	48.8±15.7	39.5±14.6	**0.010**

Values are mean±SD or number of patients (%).
Statistically significant values (p<0.05) are marked in bold.
*The definition of renal insufficiency corresponds to the definition in the EuroScore.
†Data available for 180/300 patients (PPI+: n=23, PPI –: n=157).
‡Data available for 173/300 patients (PPI+: n=22, PPI–: n=151).
AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PAP, pulmonary artery pressure; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack; TR, tricuspid regurgitation.

patients with and without a need for PPI, respectively, with a significant difference between the three sizing groups (p=0.029) (table 6). Notably, only 8.5% (7/82) of patients receiving SAPIEN 3 Ultra THV needed PPI compared with 16.1% (35/218) of patients receiving SAPIEN 3. It is important to note, however, that the distribution of valve sizes was different; more patients with SAPIEN 3 received a 29 mm valve than those with SAPIEN 3 Ultra (47.8% vs 14.6%). The depth of implantation, which is known to be strongly associated with PPI, did not reach significance in our analysis (mean NCC, right coronary cusp, LCC >median; 63.9% vs 47.3%, p=0.068). Patients with PPI tended to have a longer duration of the procedure (62.3 vs 49.9 min, p=0.065), although the difference was not significant. The difference in postdelivery balloon dilatation rates

Table 3 Patient ECG parameters at baseline

	Total (N=300)	PPI+ (n=42)	PPI– (n=258)	P-value PPI+ versus PPI–
Heart rate (beats/min)	70.3±14.7	71.2±15.9	70.1±14.5	0.801
Bradycardia <60 beats/min	85 (28.4)	8 (19.0)	77 (30.0)	0.146
Atrial fibrillation	64 (21.4)	14 (33.3)	50 (19.5)	**0.042**
QRS duration (ms)	120.2±27.6 118.0 (98.0–140.0)	141.1±25.5 143.5 (127.0–160.3)	116.8±26.5 112.0 (96.0–138.0)	**<0.001**
≥110	174 (58.2)	36 (85.7)	138 (53.7)	**<0.001**
PQ duration (ms)	194.9±41.6 190.0 (166.0–219.0)	190.4±40.4 182.0 (151.0–231.0)	195.4±41.7 192.0 (168.0–216.0)	0.553
AV block				
None	203 (67.9)	31 (73.8)	172 (66.9)	0.376
First degree	96 (32.1)	11 (26.2)	85 (33.1)	
Second or third degree	0	0	0	
LBBB complete	34 (11.4)	3 (7.1)	31 (12.1)	0.441
RBBB complete	72 (24.2)	27 (64.3)	45 (17.5)	**<0.001**
LAHB	86 (28.8)	13 (31.0)	73 (28.4)	0.735
LPHB	3 (1.0)	0 (0)	3 (1.2)	1.000

Values are mean±SD or number of patients (%).
Statistically significant values (p<0.05) are marked in bold.
AV, atrioventricular; LAHB, left anterior hemiblock; LBBB, left bundle branch block; LPHB, left posterior hemiblock; PPI, permanent pacemaker implantation.

was also not significant between patients with and without PPI in our cohort (4.8% vs 2.0%, p=0.264).

The univariable analysis of procedure-related variables indicated only the valve size 29 mm (OR 2.4, 95% CI 1.2 to 4.7, p=0.009) to be an independent predictor of PPI after TAVI. In the multivariable analysis, valve size of 29 mm (OR 3.4, 95% CI 1.4 to 8.5, p=0.008) remained the only independent predictor of PPI.

Postprocedural outcomes and hospitalisation

Differences in postprocedural outcomes, such as device success or severe periprocedural complications, did not reach statistical significance (table 7). Patients undergoing PPI had a delayed discharge (7 days vs 5 days, p<0.001), longer intensive care unit plus intermediate care stay (46 hours vs 2 hours, p<0.001) and general ward care stay (7 days vs 5 days, p=0.004) than those who did not receive PPI (table 7).

DISCUSSION

In the current study, the major findings are as follows: (1) larger valve size is an independent procedural predictor of PPI after TAVI in high-risk patients with AS; (2) valve type (SAPIEN 3), higher implantation depth and postdelivery balloon dilatation may be potentially associated with PPI and should be carefully considered; (3) pre-existing RBBB is an independent patient-related variable associated with PPI after TAVI; and (4) patients undergoing PPI tend to have worse hospitalisation characteristics, including longer hospital stay and delayed discharge.

The association between the onset of new AV conduction disturbance requiring PPI after TAVI is well known, although the rates have decreased with new-generation balloon-expandable prostheses.[19] In the present population of 300 patients undergoing transfemoral TAVI due to AS and identified for being at a high risk of PPI, the incidence of PPI after TAVI was 14.0%, which is within the range reported for patients undergoing TAVI with the new-generation SAPIEN 3 device (4 to 20%).[19] However, since we included only TAVI patients who had at least one risk factor for PPI, we expected the incidence of PPI to be considerably higher. Such a low number of patients with PPI post TAVI may indicate the procedural and technical improvements in TAVI. Furthermore, fewer patients with SAPIEN 3 Ultra THV required PPI after TAVI, which could possibly indicate its superiority compared with the SAPIEN 3 THV.

Identified patient characteristics associated with PPI

Several studies have found pre-existing RBBB to be the strongest patient-related predictor for PPI after TAVI,[8 11 14 20] which was confirmed by the results of our study. In the retrospective analysis for the same group of centres, RBBB was also one of the patient-related variables significantly associated with PPI.[18] Patients with a high burden of PPI following TAVI in our study had a

Table 4 Patient annular dimensions and calcification at baseline.

	Total (N=263)	PPI+ (n=39)	PPI– (n=224)	P-value PPI+ versus PPI–
Contrast agent volume (mL)	71.3±24.6	77.6±47.9	70.2±17.6	0.540
Aortic annulus measurement				
Minimal diameter (mm)	24.9±11.1	24.5±3.4	25.0±11.8	0.806
Maximal diameter (mm)	28.9±2.8	28.8±3.3	28.9±2.7	0.900
Perimeter (mm)	83.8±8.6	84.2±10.0	83.8±8.4	0.787
Area (mm^2)	554.0±114.8	562.9±133.0	552.6±112.1	0.629
Distance to RCA (mm)	17.6±3.3	17.7±3.3	17.6±3.3	0.863
Distance to LCA (mm)	13.8±3.4	12.6±3.2	14.0±3.4	**0.035**
Membranous septum (mm)	5.1±2.5	5.1±2.6	5.1±2.5	0.999
Calcium volume				
Annulus				
NCC (mm^3)	414 (221–767)	289 (189–520)	433 (238–802)	**0.044**
NCC >median (%)	128 (50.0)	11 (32.4)	117 (52.7)	**0.027**
RCC (mm^3)	330 (156–646)	331 (165–812)	330 (155–619)	0.806
RCC >median (%)	127 (49.6)	17 (50.0)	110 (49.5)	0.961
LCC (mm^3)	285 (154–521)	308 (170–625)	280 (153–518)	0.572
LCC> median (%)	128 (49.8)	20 (58.8)	108 (48.4)	0.259
NCC+RCC+LCC (mm^3)	1004 (627–1851)	963 (619–1765)	1007 (620–1904)	0.714
NCC+RCC+LCC >median (%)	127 (49.8)	16 (47.1)	111 (50.2)	0.731
LVOT				
NCC (mm^3)	1.4 (0–39.0)	3.7 (0–48.6)	1.1 (0–37.9)	0.830
NCC >median (%)	127 (49.6)	19 (55.9)	108 (48.6)	0.432
RCC (mm^3)	0.0 (0.0–15.5)	0.3 (0–10.3)	0 (0–17.0)	0.980
RCC >median (%)	122 (47.7)	17 (50.0)	105 (47.3)	0.769
LCC (mm^3)	2.0 (0.0–51.6)	1.9 (0–75.8)	2 (0–45.4)	0.827
LCC >median (%)	127 (49.4)	16 (47.1)	111 (49.8)	0.768
NCC+RCC+LCC (mm^3)	25.7 (0.5–108.7)	27.6 (0.5–132.7)	23.9 (0.4–108.6)	0.837
NCC+RCC+LCC >median (%)	127 (50.0)	18 (52.8)	109 (49.5)	0.712
Total device-landing zone (mm^3)	1071 (660–1901)	1003 (560–1847)	1077 (661–1974)	0.596

Values are mean±SD, median (IQR) or number of patients (%)
Statistically significant values (p<0.05) are marked in bold.
LCA, left coronary artery; LCC, left coronary cusp; LVOT, left ventricular outflow tract; NCC, non-coronary cusp; PPI, permanent pacemaker implantation; RCA, right coronary artery; RCC, right coronary cusp.

higher prevalence of several comorbidities before the procedure, including COPD. The prevalence of COPD at baseline in patients undergoing TAVI has been reported to be between 12.5% and 43.4%, and COPD has been associated with an increased risk of respiratory complications and pneumonia following the procedure.[21 22] However, there has been no association between COPD and cardiovascular postoperative complications, which may require PPI.[21] Although both study groups had a high baseline systolic PAP, the rate was higher in the PPI group and is classified as mild-to-moderate pulmonary hypertension (systolic PAP 40–59 mm Hg).[23] Since RBBB is commonly found in patients with pulmonary hypertension, which is a complication of COPD, this may explain the difference in COPD prevalence between PPI and non-PPI groups in our study.

Compared with the retrospective data from this centre group, pulmonary hypertension, QRS >110 ms, first-degree AV block and LAHB were not associated with PPI by multivariable analysis in the present study.[18] Based on the previous reports, calcification of the LVOT, especially in the NCC zone, is one of the anatomical factors that are related to the pacemaker dependency after TAVI.[16 24] The results of the retrospective analysis supported this finding.[18] However, the analysis in the current study demonstrated no difference in the calcification of the

Table 5 Univariable and multivariable analyses for baseline characteristics

	Univariable analysis			Multivariable analysis		
Patient characteristics	OR	95% CI	P-value	OR	95% CI	P-value
Diabetes	**2.138**	**1.092 to 4.185**	**0.027**	1.849	0.792 to 4.312	0.155
COPD	**3.025**	**1.163 to 7.871**	**0.023**	2.255	0.649 to 7.831	0.201
Atrial fibrillation	**2.070**	**1.016 to 4.219**	**0.045**	0.850	0.316 to 2.285	0.748
QRS ≥110 ms	**5.174**	**2.107 to 12.705**	**<0.001**	1.810	0.542 to 6.048	0.335
RBBB complete	**8.440**	**4.156 to 17.141**	**<0.001**	**6.775**	**2.531 to 18.140**	**<0.001**
Distance to LCA <median	2.098	0.990 to 4.445	0.053	2.237	0.949 to 5.273	0.066
Aortic annulus calcification NCC >median	**0.429**	**0.200 to 0.923**	**0.030**	0.570	0.242 to 1.342	0.198

Statistically significant values (p<0.05) are marked in bold.
CI, confidence interval ; COPD, chronic obstructive pulmonary disease; LCA, left coronary artery; NCC, non-coronary cusp; OR, odds ratio; RBBB, right bundle branch block.

LVOT between patients receiving PPI following TAVI and those who did not. A possible explanation could be the overall low LVOT calcification grade in the present cohort (only 25 mm^3), which could impact statistical power. One can speculate that high LVOT calcification may be less common today due to the fact that TAVI has extended to low-risk and intermediate-risk patients, who typically present with a non-calcified or less calcified LVOT.

Identified procedure characteristics associated with PPI

Patients with PPI post TAVI in the present analysis had a larger implanted valve size, compared with patients without PPI. A large diameter valve has been previously found to be an independent risk factor for PPI in several other studies, including the retrospective study of this registry.[18 25 26] It is, however, unsurprising that patients requiring a larger valve size tend to have poorer outcomes post TAVI as they present with anatomical differences at baseline, such as more calcified annulus, which potentially impact the procedural factors, including larger balloon size and higher implantation depth. Furthermore, a higher number of patients with PPI in our study had an oversized prosthesis. Prosthesis oversizing to a certain degree is recommended for SAPIEN 3 to achieve device success and to avoid paravalvular leak, whereas excessive oversizing increases the risk of PPI due to added stress on the membranous septum, aortic annulus and LVOT.[27] Leber *et al* demonstrated that the rate of postprocedural PPI tended to be lower in patients with <15% oversizing compared with those with >25% oversizing for the Edwards SAPIEN XT.[28] Husser *et al* also showed that prosthesis oversizing was a predictor of PPI using the SAPIEN 3, suggesting avoidance of extreme oversizing.[11] On the other hand, Gonska *et al* concluded that oversizing had no significant effect on the PPI rate.[15] The rates of clinically relevant (moderate/severe) paravalvular regurgitation after TAVI were not significantly different between our study groups, despite the higher proportion of patients with PPI receiving the 29 mm valve. Moreover, the prevalence of paravalvular regurgitation after TAVI was low in the total patient population in our study, which may be due to the novel outer polyethylene terephthalate sealing cuff in SAPIEN 3 that provides a tighter seal and reduces the risk of leakage.[29]

We previously reported a valve implantation depth of >30% to be associated with an increased risk of PPI in the retrospective cohort of patients.[18] Although implantation depth did not reach statistical significance in the present analysis (p=0.068), the numerical difference in rates of NCC, RCC and LCC >median between patients with and without PPI was substantial (63.9 vs 47.3%), and a higher number of cases could potentially further prove this association. Schwerg *et al* compared the PPI rate in 'low implantation' with 'high implantation' independently from the patients' pre-existing conduction disturbances and suggested choosing a higher implantation technique with the central marker 2 mm or more over the annular plane to minimise the risk of PPI.[13] Furthermore, Mauri *et al* identified implantation depth as an independent predictor for PPI, proposing an implantation height of <25.5%.[14] Contrary to these findings, there was no impact of implantation depth of the prosthesis on the need of PPI post TAVI in our study. Furthermore, the valve was implanted higher in our cohort compared with the previous studies with a similar definition of implantation depth.[12 14] This may be explained by the fact that higher implantation depth has been established as a strong predictor of PPI, and many physicians tend to implement an implantation technique that results in a high final prosthesis position.

Similarly to the implantation depth, the difference in postdelivery balloon dilatation rates between patients with and without PPI was not statistically significant in our cohort (p=0.264), yet the numerical difference was present (4.8% vs 2.0%), indicating a distinct clinical association. In a recent meta-analysis on predictors of PPI after TAVR, postimplant balloon dilatation was among the 14 notable risk factors for PPI.[30] Therefore, the clinical role of postdelivery balloon dilatation in PPI rates after TAVI may be significant in larger cohorts.

Table 6 Procedural details

	Total (N=300)	PPI+ (n=42)	PPI– (n=258)	P-value PPI+ versus PPI–
Valve type				
SAPIEN 3	218 (72.7)	35 (83.3)	183 (70.9)	0.094
SAPIEN 3 Ultra	82 (27.3)	7 (16.7)	75 (29.1)	
Valve size (mm), mean	26.6±2.1	27.3±2.2	26.6±2.1	**0.027**
23	50 (16.7)	6 (14.3)	44 (17.1)	**0.026**
26	134 (44.7)	12 (28.6)	122 (47.3)	
29	116 (39.7)	24 (57.1)	92 (35.7)	
Mean area oversizing* (%)	0.5±17.6	4.0±19.6	0.0±17.3	0.255
Oversized	32 (12.5)	6 (17.6)	26 (11.7)	**0.029**†
Normal sized	127 (49.6)	21 (61.8)	106 (47.7)	
Undersized	97 (37.9)	7 (20.6)	90 (40.5)	
BAV completed	69 (23.0)	9 (21.4)	60 (23.3)	0.794
Balloon size	23.8±2.1	24.9±1.9	23.6±2.1	0.171
Balloon inflation during intervention	144 (48.0)	19 (45.2)	125 (48.4)	0.699
Implantation depth–ventricular part of frame under annulus (mm)				
NCC (mm)	4.8 (3.6–6.5)	5.0 (3.7–7.6)	4.8 (3.5–6.4)	0.557
NCC >median (%)	109 (49.5)	18 (50.0)	91 (49.5)	0.952
RCC (mm)	4.7 (3.8–6.1)	5.1 (4.1–6.8)	4.7 (3.7–5.9)	0.192
RCC >median (%)	108 (49.1)	22 (61.1)	86 (46.7)	0.115
LCC (mm)	4.8 (3.6–6.3)	5.1 (4.2–7.7)	4.7 (3.5–6.2)	0.282
LCC >median (%)	107 (48.6)	19 (52.8)	88 (47.8)	0.587
Mean of NCC, RCC, LCC (mm)	4.9 (3.8–6.0)	5.2 (4.0–6.8)	4.9 (3.8–5.9)	0.181
Mean NCC, RCC, LCC >median (%)	110 (50.0)	21 (58.3)	89 (48.4)	0.274
Implantation depth–ventricular part of frame under annulus (%)				
NCC (%)	21.4 (16.6–28.7)	21.5 (17.4–30.9)	21.4 (16.4–28.5)	0.371
NCC >median (%)	109 (49.5)	18 (50.0)	91 (48.5)	0.952
RCC (%)	21.8 (17.3–27.7)	23.7 (18.5–30.0)	21.5 (17.1–27.1)	0.113
RCC >median (%)	110 (50.0)	22 (61.1)	88 (47.8)	0.145
LCC (%)	22.1 (16.7–30.9)	23.7 (18.5–30.0)	21.9 (16.3–30.2)	0.172
RCC >median (%)	111 (50.5)	20 (55.6)	91 (49.5)	0.503
Mean of NCC, RCC, LCC (%)	22.3 (17.8–27.4)	24.3 (18.0–29.4)	22.1 (17.6–26.9)	0.126
Mean NCC, RCC, LCC >median (%)	110 (50.0)	23 (63.9)	87 (47.3)	0.068
Total procedure time (skin to skin) (min)	51.7±36.1	62.3±68.3	49.9±27.1	0.065
Fluoroscopy time (min)	11.8±5.7	12.1±7.5	11.7±5.4	0.680
Quantity contrast agent used (mL)	89.3±51.6	92.6±50.1	88.6±52.0	0.836
Postdelivery balloon dilatation	7 (2.4)	2 (4.8)	5 (2.0)	0.264
Postballoon size (mm)	24.8±1.7	24.5±2.1	25.0±1.8	0.777

Values are mean±SD deviation, median (IQR) or number of patients (%).
Statistically significant values (p<0.05) are marked in bold.
*Nominal area values for Edwards valves taken from Husser *et al*.[11] Oversizing was defined as measured area <min. Area declared by Edwards valve size. Undersized was defined as measured area >maximal area declared by Edwards valve size.
†P-value calculated by Mann-Whitney U test; Kruskal-Wallis test p=0.079.
BAV, balloon aortic valvuloplasty; LCC, left coronary cusp; NCC, non-coronary cusp; PPI, permanent pacemaker implantation; RCC, right coronary cusp.

Table 7 Postprocedural outcomes and hospitalisation characteristics

	Total (N=298)	PPI+ (n=42)	PPI– (n=256)	P-value PPI+ versus PPI–
Valve successfully delivered	287 (96.3)	40 (95.2)	247 (96.5)	0.658
Device success VARC-2				
Absence of immediate procedural mortality	297 (99.7)	42 (100)	255 (99.6)	1.000
Correct positioning of the valve	296 (99.3)	41 (97.6)	255 (99.6)	0.262
Intended performance of the valve	297 (99.7)	41 (97.6)	256 (100)	0.141
Paravalvular regurgitation				
None/trace	243 (81.8)	27 (64.3)	216 (84.7)	**0.004**
Mild	52 (17.5)	14 (33.3)	38 (14.9)	
Moderate	2 (0.7)	1 (2.4)	1 (0.4)	
Severe	0 (0)	0 (0)	0 (0)	
Moderate/severe paravalvular regurgitation	2 (0.7)	1 (2.4)	1 (0.4)	0.263
Procedure aborted	2 (0.7)	1 (2.4)	1 (0.4)	0.262
Complications				
Conversion to conventional surgery	4 (1.3)	1 (2.4)	3 (1.2)	0.052
Other*	15 (5.0)	5 (11.9)	10 (3.9)	
Discharge post intervention (days)	5.5±4.0 5.0 (3.0;6.0)	8.6±5.8 7.0 (6.0;9.3)	5.0±3.4 5.0 (3.0;6.0)	**<0.001**
Length of stay in ICU plus IMC (hours)	23.2±53.1 4.0 (0.0;25.0)	65.7±66.1 46.0 (24.0;98.5)	16.3±47.3 2.0 (0.0;24.0)	**<0.001**
Length of stay at general ward (days)	5.5±3.1 5.0 (3.0;7.0)	6.9±3.8 7.0 (4.0;9.0)	5.3±2.9 5.0 (3.0;7.0)	**0.004**

Values are mean±SD deviation, median (IQR) or number pf patients (%).
Statistically significant values (p<0.05) are marked in bold.
*Complications: arrhythmia (n=7), partly with later PPI; neurological event (n=1); drug reaction (n=1); vascular events (n=3); second valve use (n=1); cardiac events: cardiac tamponade (n=1); cardiac decompensation (n=1).
ICU, intensive care unit; IMC, intermediate care; PPI, permanent pacemaker implantation; VARC-2, Valve Academic Research Consortium-2 .

Study limitations

The findings in this study are subject to several important limitations. Although the overall sample size in our study was large in comparison to other studies, the number of patients in the group undergoing PPI following TAVI was relatively small. The observational design of this study allowed an evaluation of TAVI patients in a real-world setting, yet there was a higher potential for missing data, and data on some variables in our study were incomplete. All patients in our registry received the Edwards SAPIEN 3/Ultra valves, though standard treatment protocols, post-treatment pathways and individual country and centre healthcare systems may vary, which might have influenced the presented data.

Clinical implications and outlook

Identification of patients at an increased risk of PPI after TAVI is of great clinical importance to prevent patient complications and to reduce the length of hospitalisation and treatment costs. Larger valve size and pre-existing RBBB remain the major predictive factors associated with pacemaker dependency following TAVI. Patient-related baseline markers may be challenging to address but should be thoroughly assessed in the preprocedural planning. The role of pacemaker placement, the timing of placement and prognosis of patients who require PPI are still unexplored and need to be addressed in future studies. There is an ongoing 1-year follow-up of this registry to further validate the reported results and to judge the long-term dependency of the patients on the pacemaker.

CONCLUSION

The overall incidence of postprocedural PPI was low, considering the strict inclusion of high-risk patients for PPI, which demonstrates the improvement of technical and procedural aspects of TAVI. On this basis, only valve sizing persisted to be a major, avoidable risk factor for PPI. The valve type, implantation depth and postdelivery balloon dilatation all affected PPI rates, but without statistical significance, potentially already reflecting the refined implantation techniques in the participating centres. For further investigation into the role of

modifiable risk factors, a study with a much larger sample size or a large database analysis is required. Nonetheless, the data confirm that careful clinical decision making before and after the intervention is key to achieving an uneventful postinterventional outcome.

Acknowledgements Data were captured using the s4trials Software provided by Software for Trials Europe GmbH, Berlin, Germany. The tremendous help of Dr Karin Bramlage with the statistics (IPPMed, Cloppenburg, Germany) is acknowledged.

Contributors TG is fully accountable for the overall content as guarantor. TR, JBaa, PB, JK, JBar, MD and TG were involved in the conception and design of the registry. MD, TR, JBaa, N-EN, JBar, LH and TG contributed patient data. MD, PB and VH drafted the manuscript. All the other authors revised the article for important intellectual content. All authors gave the final approval of the version to be published.

Funding This work was funded by a research grant from Edwards Lifesciences (Nyon, Switzerland) to the Institute for Pharmacology and Preventive Medicine (IPPMed, Cloppenburg, Germany).

Competing interests MD received travel honoraria by Medtronic; TR, JBaa, N-EN, JBar, PB, TR and TG received speaker fees and/or research grants and/or travel honoraria from Edwards Lifesciences. JK is an Edwards Lifesciences employee. The institution of PB and VH received funding for performing the study.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the ethics committee responsible for each site. Participants gave informed consent to participate in the study before taking part. The registry was conducted in accordance with the Declaration of Helsinki and complied with local laws and regulations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available from the corresponding author upon request.

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