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Permanent Pacemaker Implantation Late after Transcatheter Aortic Valve Implantation

Short Title: Pacemaker Implantation Late after TAVI

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Abstract

Background: Impairment of atrioventricular (AV) conduction may occur late after transcatheter aortic valve implantation (TAVI) and progression to complete AV block is a matter of concern.

Objective: To describe the incidence of permanent pacemaker (PPM) implantation late after TAVI.

Methods: In a prospective TAVI registry, we retrospectively identified patients with PPM implantation after hospital discharge for TAVI and analyzed serial ECGs for AV conduction impairment prior to PPM implantation.

Results: Among 1,059 patients discharged after TAVI without PPM between January 2012 and December 2017, 62 patients (5.9%) underwent PPM implantation at a median of 305 days after discharge for TAVI. Indications for PPM implantation late after TAVI were AV conduction impairment in 46 patients (74.2%), sick-sinus-syndrome in 10 (16.1%), cardiac resynchronization or implantable cardioverter/defibrillator indication in two (3.2%), and a pace & ablate strategy in four (6.5%). Clinical symptoms leading to PPM implantation late after TAVI included syncope in 19 patients (30.7%), pre-syncope in seven (11.3%), and dyspnea in eight (12.9%). First-degree AV block and new left bundle branch block (LBBB) after TAVI as well as valve-in-valve procedure during follow-up were independent predictors for PPM implantation late after TAVI due to AV conduction impairment.

Conclusions: PPM implantation late after TAVI is infrequent and associated with clinical symptoms in half of patients. Impairment of AV-conduction was the indication in three quarters of patients. First-degree AV block and new LBBB after TAVI as well as valve-in-valve procedure during follow-up emerged as independent predictors.

Keywords: TAVI; pacemaker; LBBB; RBBB; AV block; syncope

Introduction

During the last decade, transcatheter aortic valve implantation (TAVI) has been established as a valuable treatment alternative to surgical aortic valve replacement across the spectrum of risk.[1] Despite significant advances in the TAVI procedure and valve design, atrioventricular (AV) and intraventricular conduction impairment after TAVI remain a frequent adverse event with a relevant proportion of patients developing new left bundle branch block (LBBB).[2] The management of these patients remains clinically challenging.[3] Permanent pacemaker implantation (PPM) is indicated in patients with advanced AV conduction impairment or in those deemed at high risk. Of note, the time course of AV conduction impairment behaves unpredictably in some patients and may develop more than 48 hours after TAVI or even after discharge. Reliable identification of patients at increased risk of deteriorating AV conduction is particularly relevant in the setting of early discharge.

Recently, an interdisciplinary expert consensus group summarized recommendations regarding the acute management of patients with AV conduction impairment after TAVI based on pre-existing and new AV conduction impairment.[3] While the proposed algorithm awaits prospective validation, there is a paucity of data regarding the long-term incidence of permanent pacemaker (PPM) implantation in patients discharged from TAVI. The present study investigates the incidence, indications and risk factors for PPM implantation in patients discharged after TAVI without a PPM.

Methods

Study Population

Patients undergoing TAVI for severe, symptomatic aortic valve stenosis at Bern University Hospital are consecutively enrolled in a prospective institutional registry, which is part of the SwissTAVI Registry (ClinicalTrials.gov NCT01368250).[4] For the present study, we included all TAVI patients treated at our institution between 01 January 2012 and 31 December 2017, irrespective of access route and valve type. Selection of device type was determined during review of anatomical and clinical characteristics prior to TAVI, and the peri-procedural management followed institutional protocols. Different iterations of valves from various manufacturers were implanted during the study period. Patients who received a PPM were grouped into one of three groups: i) PPM before TAVI; ii) PPM early after TAVI (i.e. implantation after TAVI but before discharge); and iii) PPM late after TAVI (i.e. implantation after discharge for TAVI).

All baseline clinical, procedural, and follow-up data of the registry were prospectively collected and entered into a web-based database managed at the Clinical Trials Unit of the University of Bern, Switzerland. Clinical follow-up data was obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries at 30 days, 1 year, and 3 and 5 years follow-up. Specific data on the types of implanted pacemakers, indications for pacemaker implantation, and clinical symptoms leading to pacemaker implant were collected retrospectively. All adverse events were systematically collected and adjudicated by a dedicated clinical events committee according to the Valve Academic Research Consortium (VARC-2) criteria.[5] SwissTAVI was approved by the local ethics committee and all study procedures were conducted in accordance with the Declaration of Helsinki as revised in 2013. All patients provided written informed consent for prospective

follow-up according to the protocol of the registry.

Monitoring of atrioventricular conduction after TAVI

12-lead ECGs were recorded at baseline, immediately after TAVI and daily thereafter until hospital discharge. Patients were continuously monitored after TAVI on the intermediate care unit overnight and/or with telemetry for at least 48 hours and thereafter as long as dictated by individual clinical course. Indications leading to PPM implantation after TAVI were established by electrophysiology attending physicians based on institutional and international guidelines. Trained cardiologists under the supervision of the senior author retrospectively analyzed 12-lead ECGs before and after TAVI and classified conduction disturbances according to internationally accepted criteria.[3]

For the purpose of the present study, we analyzed ECGs recorded the day before TAVI and ECGs recorded on day two after TAVI. If no ECG was available on day two after TAVI, we analyzed the next available ECG, up to day 5 after TAVI. We grouped all patients without PPM implantation before TAVI or early after TAVI into one of the following four categories, according to the presence and type of AV conduction disorder after TAVI: 1) no bundle branch block (BBB) after TAVI (group no BBB); 2) right bundle branch block (RBBB) after TAVI (group RBBB); 3) left bundle branch block (LBBB) present before TAVI (group LBBB); and 4) new LBBB after TAVI (group LBBB+). Patients without available ECGs after TAVI (n=37) were classified according to available ECGs before TAVI and patients without an ECG before and after TAVI (n=47) were grouped as no BBB after TAVI.

Primary and secondary endpoints

The primary endpoint of the present study was PPM implantation late after TAVI,

defined as the implantation of a PPM after discharge for TAVI. Secondary endpoints included the indication for PPM (sick-sinus-syndrome; AV conduction disease; pace & ablate strategy for rate control of permanent atrial fibrillation; cardiac resynchronization therapy; primary or secondary ICD indication) and the clinical manifestation leading to PPM implantation.

Statistical analysis

Continuous variables are expressed as means with standard deviations or medians with interquartile ranges (IQR), and categorical variables as numbers and frequencies. Continuous variables were compared using the Mann-Whithey U test or t-test in case of two-group comparison, as appropriate. For multiple group's comparison, Kruskall-Wallis or ANOVA was computed to test the difference for the continuous variables. Differences in proportions were tested with Pearson's $\chi 2$ test or Fisher's exact test. Predictors for PPM implantation late after TAVI were assessed in univariate analyses. Variables with a p-value of <0.1 in the univariate comparison were selected for the multivariable model. Further selection was based on clinical reasoning. Multiple imputation, applying the Rubin's rule to estimate the logistic models, was applied to impute the missing values of the chosen variables. All tests were performed at a two-sided 5% significance level with two-sided 95% confidence intervals (CIs). All analyses were performed using Stata (StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

Study population and procedural characteristics

A total of 1,498 patients underwent TAVI during the study period, of whom 131 patients (8.8%) had a prior PPM before TAVI, 272 patients (18.2%) received a PPM before hospital discharge, 25 patients (1.7%) died before discharge and 11 (0.7%) patients had no follow-up and/or withdrew consent (Figure 1). As a result, 1,059 patients were discharged after TAVI without a PPM (Figure 1). The median follow-up duration of these patients was 1,095 days (IQR 434; 1819). Table 1 and Supplementary Table 1 summarize baseline and procedural characteristics of the different groups. The type of transcatheter aortic heart valve implanted during the study period comprised balloon-expandable, self-expanding, or mechanically expandable valves in 727 (48.5%), 635 (42.4%), and 134 (8.9%) patients, respectively (Supplementary Table 2).

PPM implantation late after TAVI

Late PPM implantation was observed in 62 patients (5.9%) discharged after TAVI without PPM. The median time to late PPM implantation amounted to 305 days (IQR 48, 712;) after discharge for TAVI. The incidence of PPM implantation late after TAVI was 21 per 1000 person years. Tables 1, 2 and Supplementary Table 1 summarize baseline, procedural and ECG characteristics of patients with PPM implantation late after TAVI. The main indications for PPM implantation were AV conduction impairment in 46 patients (74.2%; Table 3) and sick-sinus-syndrome in 10 patients (16.1%). Details on the type of AV conduction impairment and sick-sinus-syndrome are provided in Supplementary Table 3. We found no difference in median time to PPM implantation because of AV conduction impairment (241 days [34; 675]) versus sick sinus syndrome (403 days [176; 895]; p=0.372). Additional indications for PPM

implantation comprised cardiac resynchronization therapy in one patient (1.6%), implantable cardioverter/defibrillator in another one (1.6%), and a pace & ablate strategy for treatment of permanent atrial fibrillation in four patients (6.5%). Indications for late PPM implantation within 30 days versus later than 30 days after discharge from TAVI did not differ (Supplementary Table 4).

Clinical symptoms leading to PPM implantation were present in 34 patients (54.8%; Table 3 and Supplementary Table 5). These included syncope in 19 patients (30.7%), dyspnea/heart failure in eight (12.9%) and pre-syncope/dizziness in seven (11.3%). A coincidental ECG finding led to pacemaker implantation late after TAVI in 11 patients (17.7%), whereas a PPM was implanted due to another procedure (e.g. valve-in-valve) or indication (e.g. cardiac resynchronization) in 10 patients (16.1%;). The clinical circumstances leading to PPM implantation late after TAVI were unknown in seven patients (11.3%).

Predictors of PPM implantation late after TAVI

Six patients (5.5%) with LBBB present before TAVI, 30 patients (4.4%) with no BBB after TAVI, seven patients (9.3%) with RBBB after TAVI and 19 patients (10.0%) with new LBBB after TAVI underwent PPM implantation late after TAVI (Figure 1). In univariate analysis, first-degree AV block after TAVI, new LBBB after TAVI and valve-in-valve procedure during follow-up were significantly associated with PPM implantation late after TAVI due to AV conduction impairment, as were prolonged PR intervals and a broader QRS complex (Table 2). We found no difference in the rate of PPM implantation late after TAVI due to AV conduction impairment between balloon- and mechanically expandable versus self-expandable valves (OR 0.77, 95%-CI 0.25 to 2.41; p=0.652).

In multivariate analysis, first degree AV block after TAVI (OR 3.13, 95%-CI 1.68 to

5.83; p<0.001), new LBBB after TAVI (OR 2.19, 95%-CI 1.19 to 4.03; p=0.011), and valve-in-valve procedure during follow-up (OR 19.95, 95%-CI 4.39 to 90.75; p<0.001) emerged as independent predictors of PPM implantation late after TAVI due to AV conduction impairment (Table 4).

Overall PPM implantation rate

Overall, 465 patients of the entire TAVI population (31%) received a PPM either before TAVI, early before discharge or late after TAVI. Indications for late PPM implantation differed significantly between the three groups (Supplementary Table 6). Atrioventricular conduction disease was the most frequent indication for PPM implantation before TAVI (75.0%), early before discharge for TAVI (94.1%) and late after TAVI (74.2%), with significant differences among the groups (p<0.001). Sick-sinus-syndrome was a rare indication for PPM implantation early after TAVI (5.9%) and more frequent both before (21.1%) and late after TAVI (16.1%), with significant differences between the groups (p<0.001).

Discussion

In a large cohort of consecutive TAVI patients, we assessed the incidence and indications of PPM implantation late after TAVI. The salient findings can be summarized as follows: the incidence of PPM implantation late after TAVI was almost 6%, corresponding to an incidence rate of 21 per 1000 person years. In our study, the predominant indication for late PPM implantation late after TAVI was AV conduction impairment (74.2%) followed by sick-sinus-syndrome (16.1%), CRT/ICD indication (3.2%) and a pace & ablate strategy (6.5%). Clinical symptoms leading to PPM implantation were present in 54.8% of the patients.

In a recent Finnish study, 6.2% of patients received a PPM 30 days to 5 years after TAVI, similar to the rate we found in our population.[6] The observed incidence of PPM implantation of 21 per 1000 person years in patients discharged after TAVI has to be compared to the incidence of PPM implantation in the general population of octogenarians. In Switzerland, the incidence rate of PPM implantation in octogenarians is 5 per 1000 person years.[7,8] Other countries report similar PPM incidence rates: 4 per 1000 person years in the population aged 75-84 years and 6 per 1000 person years in the population aged >85 years in Australia.[9] In Spain, the reported incidence for those aged 80-89 years is 6 per 1000 person years.[10,11] The PPM incidence rate of 21 per 1000 person years in patients discharged from TAVI is four times higher than would be expected in the general age matched population. Three factors may contribute to this excess of PPM implantation late after TAVI. First, TAVI patients generally have more advanced cardiovascular disease, predisposing them to the development of both sick-sinus-syndrome and AV conduction impairment, irrespective of valvular heart disease.[12,13] Second, severe aortic valve stenosis increases the risk of AV conduction impairment by progressive calcification of the region in the vicinity of the proximal His-Purkinje system. Severe aortic valve stenosis may also increase the risk of sick-sinus-

syndrome by promoting atrial remodeling via atrial pressure overload. This is exemplified by the fact that atrial fibrillation is highly prevalent in the TAVI population and that sick-sinus-syndrome frequently coexists with atrial fibrillation and shares the same risk factors.[14,15] Third, AV conduction impairment may be a direct sequelae of the TAVI procedure itself, or of subsequent procedures in the aftermath.[16]

Almost half of the patients with PPM implantation late after TAVI had no bundle branch block after TAVI, suggesting that the indication for PPM implantation was not directly related to the TAVI procedure. Moreover, a quarter of PPMs were implanted due to sick-sinus-syndrome or other procedures during follow-up, like valve-in-valve procedures and for CRT/ICD indications. These additional PPM implantations were most probably not directly associated with the initial TAVI procedures. In the general Swiss pacemaker population, approximately 17% of PPMs are implanted due to sick-sinus-syndrome, matching the rate of PPMs implanted for sick-sinus-syndrome late after TAVI.[8] Of note, 8.8% of the population undergoing TAVI already had a PPM implanted before TAVI. This illustrates that the TAVI population is at increased risk of AV conduction impairment or sick-sinus-syndrome, irrespective of the TAVI procedure and has been observed in previous populations of patients undergoing surgical aortic valve replacement.[17] In a study evaluating the prevalence of undiagnosed arrhythmias just before TAVI by 24h Holter ECG, advanced AV block was observed in 2.8% of patients and sinus node dysfunction or severe bradycardia in another 2.8% of patients.[18]

Notwithstanding, our data also provides evidence of PPM implantation late after TAVI as a direct consequence of the TAVI procedure itself in some patients. The presence of new LBBB after TAVI was among the strongest independent predictors of PPM implantation late after TAVI due to AV conduction impairment, in addition to the presence of first degree AV

block. Ongoing mechanical stress on the proximal His-Purkinje system, particularly in the case of self-expanding valves, may result in late progression of AV conduction impairment, even several weeks to months after valve implantation.[19] Of note, more than 40% of PPM implantations late after TAVI occurred within 6 months after TAVI with decreasing incidence thereafter. Patients with persistent LBBB after TAVI also have a higher incidence of syncope and complete AV block after hospital discharge.[20] Some studies reported increased mortality rates in patients with new LBBB after TAVI compared to patients without LBBB, but this finding was not consistent with other studies reporting no difference.[2,20,21] The recently published expert group recommendations have recognized patients with new LBBB after TAVI with QRS width >150 ms or PR prolongation >240 ms to be at increased risk of advanced AV conduction impairment.[3] However, the proper strategy for risk stratification of these patients awaits further definition and validation. Current recommendations include a broad range of strategies including performing an invasive electrophysiological study, continuous ECG monitoring or direct PPM implantation.

Half of the patients with PPM implantation late after TAVI had a symptomatic presentation, with syncope being present in 31%. In comparison, syncope was the clinical manifestation in 24% of patients in the general Swiss pacemaker registry and in 41% of patients in the corresponding Spanish registry.[8,11] Follow-up of TAVI patients with new LBBB and first degree AV block after TAVI in regular intervals, particularly in the first 6 months after TAVI, using serial 12-lead ECGs and/or Holter ECGs, may be appropriate and cost-efficient strategies to avoid syncope or worse clinical manifestation of a new-onset PPM indication.

Several limitations of our study merit consideration. First, this was a retrospective single center study. Second, despite the large size of the overall cohort, the number of endpoints was relatively low. Accordingly, the results of the multivariate predictor analysis for PPM

implantation late after TAVI have to be interpreted cautiously. Larger studies are needed to confirm these findings. Third, patients may have died suddenly during follow-up because of complete AV block, which may have resulted in an underestimation of the true incidence of complete AV block in patients discharged from TAVI without a PPM.

Conclusions

In summary, the incidence of PPM implantation after discharge for TAVI was 5.9% overall, corresponding to 21 per 1000 person years. The majority of PPMs implanted late after TAVI were due to AV conduction impairment. Over half of the patients had a symptomatic, clinical presentation with syncope being the most frequent one. New LBBB after TAVI, first-degree AV block and valve-in-valve procedure during follow-up were independent predictors for PPM implantation late after TAVI due to AV conduction impairment.

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Figure legend

Figure 1. Study flow chart.

BBB, bundle branch block; ECG, electrocardiogram; FU, follow-up; LBBB, left bundle branch block; LBBB+, new left bundle branch block after TAVI; NS-IVCD, nonspecific intraventricular conduction delay; PPM, permanent pacemaker; RBBB, right bundle branch block; TAVI, transcatheter aortic valve implantation.

Tables

Table 1. Baseline and procedural characteristics.

	Total n=1059	No PPM n=997	PPM late after TAVI n=62	P value	No PPM related to AVCI n=1013	PPM related to AVCI n=46	P value
Age, years	81.7±6.3	81.8±6.3	80.6±6.0	0.151	81.8±6.3	81.4±5.9	0.706
Female sex	559 (52.8%)	526 (52.8%)	33 (53.2%)	1.000	535 (52.8%)	24 (52.2%)	1.000
Body mass index, kg/m^2	26.4±5.2	26.4±5.2	26.4±5.2	0.965	26.4±5.2	26.0±5.7	0.639
Hypertension	905 (85.5%)	854 (85.7%)	51 (82.3%)	0.458	866 (85.5%)	39 (84.8%)	0.832
Diabetes mellitus	264 (24.9%)	246 (24.7%)	18 (29.0%)	0.450	251 (24.8%)	13 (28.3%)	0.602
History of CVI	131 (12.4%)	127 (12.7%)	4 (6.5%)	0.167	129 (12.7%)	2 (4.3%)	0.109
Coronary artery disease	661 (62.4%)	622 (62.4%)	39 (62.9%)	1.000	631 (62.3%)	30 (65.2%)	0.757
Previous PCI	273 (25.8%)	259 (25.9%)	14 (22.6%)	0.654	262 (25.9%)	11 (23.9%)	0.864
Previous MI	146 (13.8%)	140 (14.0%)	6 (9.7%)	0.447	143 (14.1%)	3 (6.5%)	0.189

Atrial fibrillation	359 (33.9%)	334 (33.5%)	25 (40.3%)	0.272	342 (33.8%)	17 (37.0%)	0.637
STS Score	5.4±3.8	5.4±3.8	4.9±2.5	0.379	5.4±3.8	5.1±2.5	0.699
Logistic Euro Score	17.1±13.2	17.0±13.2	18.6±13.6	0.368	17.0±13.1	18.6±14.6	0.427
Echocardiography							
LVEF, %	55±15	55±15	52±16	0.084	55±15	53±16	0.396
Aortic valve area, cm2	0.7±0.3	0.7±0.3	0.7±0.3	0.206	0.7±0.3	0.7±0.2	0.519
MTPG pre TAVI, mmHg	41±18	41±18	38±17	0.160	41±18	39±17	0.393
Procedural characteristics							
Procedure time, min.	62±29	61±30	65±26	0.402	61±30	65±27	0.373
Balloon-expandable valve	554 (52.4%)	525 (52.7%)	29 (46.8%)	0.363	533 (52.7%)	21 (45.7%)	0.368
Mechanically expanding valve	71 (6.7%)	66 (6.6%)	5 (8.1%)	0.601	66 (6.5%)	5 (10.9%)	0.229
Self-expanding valve	432 (40.9%)	404 (40.5%)	28 (45.2%)	0.507	412 (40.8%)	20 (43.5%)	0.760
Pre dilation	726 (68.7%)	688 (69.0%)	38 (61.3%)	0.205	696 (68.8%)	30 (65.2%)	0.627
Post dilation	299 (28.2%)	286 (28.7%)	13 (21.0%)	0.244	290 (28.7%)	9 (19.6%)	0.240
Hospital stay, days	6.1±3.2	6.1±3.2	6.0±2.7	0.834	6.1±3.2	5.4±1.9	0.138

MTPG post TAVI, mmHg	9±5	9±5	8±3	0.197	9±5	7±3	0.176
Follow-up and procedures during follow-up							
Mean follow-up, days	1071±585	1060±586	1237±554	0.021	1065±586	1199±560	0.128
Valve-in-valve	8 (0.8%)	5 (0.5%)	3 (4.8%)	0.009	5 (0.5%)	3 (6.5%)	0.004
PCI	33 (3.1%)	28 (2.8%)	5 (8.1%)	0.021	30 (3.0%)	3 (6.5%)	0.169

Shown are means with standard deviations or numbers with percentages in parentheses, as appropriate. P-values refer to No PM vs. PM late after TAVI and No PPM because of AVCI vs. PPM because of AVCI. AVCI, atrioventricular conduction impairment; CVI, cerebrovascular ischemia; LAAO, left atrial appendage occlusion; LVEF, left ventricular ejection fraction; MTPG, mean transprosthetic gradient; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

415 Table 2. ECG before and after TAVI in patients discharged from TAVI without a PPM.

	Total n=1059	No PPM n=997	PPM late after TAVI n=62	P value	No PPM related to AVCI n=1013	PPM related AVCI n=46	P value
ECG before TAVI	n=989	n=933	n=56		n=947	n=42	
Heart rhythm				0.420			0.367
SR	786 (79.5%)	745 (79.8%)	41 (73.2%)		756 (79.8%)	30 (71.4%)	
AF	200 (20.2%)	185 (19.8%)	15 (26.8%)		188 (19.9%)	12 (28.6%)	
Other	3 (0.3%)	3 (0.3%)	-		3 (0.3%)	0 (0%)	
First degree AV-Block	159 (20.3%)	149 (20.1%)	10 (24.4%)	0.549	151 (20.0%)	8 (26.7%)	0.359
Intraventricular conduction impairment				0.009			0.047
LBBB	110 (11.2%)	104 (11.1%)	6 (10.7%)	1.000	106 (11.2%)	4 (9.5%)	1.000
RBBB	62 (6.3%)	55 (5.9%)	7 (12.5%)	0.079	57 (6.0%)	5 (11.9%)	0.178
NS-IVCD	21 (2.1%)	17 (1.8%)	4 (7.1%)	0.027	18 (1.9%)	3 (7.1%)	0.056

Intervals							
PR, ms	174±34	174±34	180±36	0.261	174±34	180±33	0.336
QRS, ms	105±22	105±21	113±25	0.004	105±22	111±25	0.056
QTc, ms	429±30	429±30	433±28	0.366	429±30	430±27	0.762
Heart rate, per minute	75±15	75±15	74±14	0.613	75±15	74±15	0.720
ECG after TAVI	n=977	n=922	n=55		n=935	N=42	
Heart rhythm				0.419			0.375
SR	764 (78.2%)	724 (78.5%)	40 (72.7%)		733 (78.4%)	31 (73.8%)	0.450
AF	206 (21.1%)	192 (20.8%)	14 (25.4%)		196 (21.0%)	10 (23.8%)	0.699
Other	7 (0.7%)	6 (0.7%)	1 (1.8%)		6 (0.6%)	1 (2.4%)	0.265
First degree AV-Block	236 (30.9%)	214 (29.6%)	22 (55.0%)	0.001	216 (29.5%)	20 (64.5%)	<0.001
Intraventricular conduction impairment				0.003			0.002
LBBB	104 (10.6%)	98 (10.6%)	6 (10.9%)	1.000	100 (10.7%)	4 (9.5%)	1.000
LBBB+	191 (19.5%)	172 (18.7%)	19 (34.5%)	0.008	174 (18.6%)	17 (40.5%)	0.001
RBBB	71 (7.3%)	64 (6.9%)	7 (12.7%)	0.110	66 (7.1%)	5 (11.9%)	0.222

NS-IVCD	26 (2.7%)	23 (2.5%)	3 (5.5%)	0.176	24 (2.6%)	2 (4.8%)	0.309
Intervals							
PR, ms	182±41	181±41	199±38	0.005	180±41	206±35	0.001
QRS, ms	116.9±27.5	116±27	130±27	<0.001	116±27	132±28	0.001
QTc, ms	437±39	436±40	444±27	0.161	436±40	447±27	0.091
Heart rate, per minute	81±21	81±22	81±15	0.880	81±22	80±16	0.861

Shown are means with standard deviations or numbers with percentages in parentheses, as appropriate. P-values refer to No PPM vs. PPM late after TAVI and No PPM because of AVCI vs. PPM because of AVCI. AF, atrial fibrillation; AVCI, atrioventricular conduction impairment; LBBB, left bundle branch block; LBBB+, new LBBB after TAVI; NS-IVCD, nonspecific intraventricular conduction disturbance; PPM, permanent pacemaker; RBBB, right bundle branch block; SR, sinus rhythm; TAVI, transcatheter aortic valve implantation.

420 Table 3. Indications for PPM implantation late after TAVI and corresponding clinical

421 manifestations.

	AV conduction impairment n=46	Sick-sinus-syndrome n=10	Other indications n=6	P value
Symptomatic presentation	25 (54.3%)	9 (90.0%)	-	0.001
Syncope	13 (52.0%)	6 (66.7%)	-	
Dizziness/pre-syncope	4 (16.0%)	3 (33.3%)	-	
Dyspnea/heart failure	8 (32%)	-	-	
Non-symptomatic presentation	21 (45.7%)	1 (10%)	6 (100%)	

422 Shown are numbers with percentages in parentheses. AV, atrioventricular; PPM, permanent

423 pacemaker; TAVI, transcatheter aortic valve implantation.

424

Table 4. Multivariate analysis of the outcome PPM implantation late after TAVI due to atrioventricular conduction disturbance.

	Coefficient (95%-CI)	OR (95%-CI)	P value
ECG after TAVI			
LBBB+	0.79 (0.18 to 1.39)	2.19 (1.19 to 4.03)	0.011
First degree AV-Block	1.14 (0.52 to 1.76)	3.13 (1.68 to 5.83)	<0.001
Repeat unplanned interventions after TAVI			
Valve-in-valve	2.99 (1.48 to 4.51)	19.95 (4.39 to 90.75)	<0.001

The analysis included all patients discharged from TAVI without a PPM (n = 1095). Patients with PPM implantation late after TAVI due to a "pace and ablate" strategy were excluded from the outcome. AV, atrioventricular; LBBB+, new left bundle branch block after TAVI; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation.