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ORIGINAL ARTICLE
Interventional cardiology and cardiac surgery

The degree of permanent pacemaker dependence and clinical outcomes following transcatheter aortic valve implantation: implications for procedural technique

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Aims Conduction abnormalities necessitating permanent pacemaker (PPM) implantation remain the most frequent complication post-transcatheter aortic valve implantation (TAVI), yet reliance on PPM function varies. We evaluated the association of right-ventricular (RV)-stimulation rate post-TAVI with 1-year major adverse cardiovascular events (MACE) (all-cause mortality and heart failure hospitalization).

Methods and results This retrospective cohort study of patients undergoing TAVI in two high-volume centers included patients with existing PPM pre-TAVI or new PPM post-TAVI. There was a bimodal distribution of RV-stimulation rates stratifying patients into two groups of either low [≤10%: 1.0 (0.0, 3.6)] or high [>10%: 96.0 (54.0, 99.9)] RV-stimulation rate post-TAVI. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated comparing MACE in patients with high vs. low RV-stimulation rates post-TAVI. Of 4659 patients, 408 patients (8.6%) had an existing PPM pre-TAVI and 361 patients (7.7%) underwent PPM implantation post-TAVI. Mean age was 82.3 ± 8.1 years, 39% were women. A high RV-stimulation rate (>10%) development post-TAVI is associated with a two-fold increased risk for MACE [1.97 (1.20, 3.25), $P = 0.008$]. Valve implantation depth was an independent predictor of high RV-stimulation rate [odds ratio (95% CI): 1.58 (1.21, 2.06), P=<0.001] and itself associated with MACE [1.27 (1.00, 1.59), $P = 0.047$].

Conclusion Greater RV-stimulation rates post-TAVI correlate with increased 1-year MACE in patients with new PPM post-TAVI or in those with existing PPM but low RV-stimulation rates pre-TAVI. A shallower valve implantation depth reduces the risk of greater RV-stimulation rates post-TAVI, correlating with improved patient outcomes. These data highlight the importance of a meticulous implant technique even in TAVI recipients with pre-existing PPMs.

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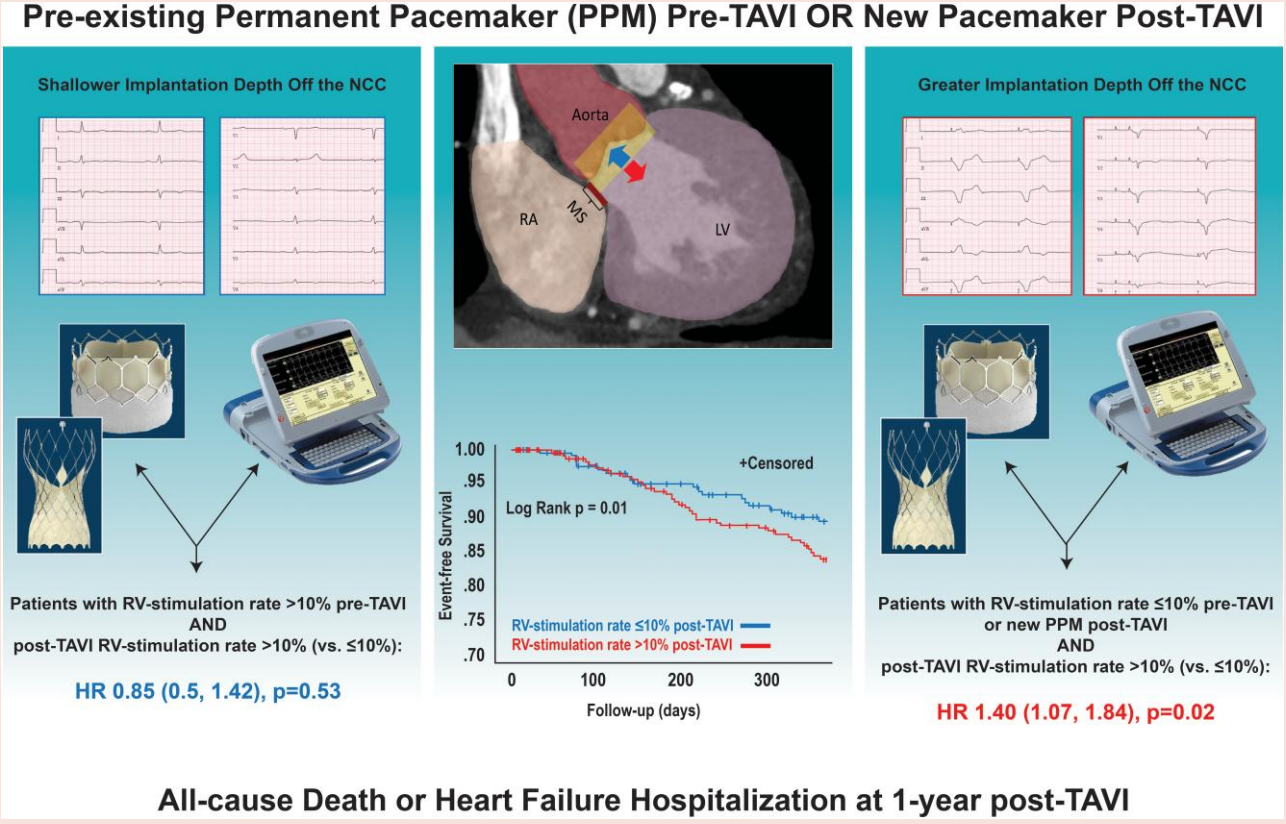
Graphical Abstract



Keywords Transcatheter aortic valve implantation • Permanent pacemaker • Right-ventricular stimulation • Implantation depth • MACE

Introduction

Conduction system disturbances, especially the need for permanent pacemakers (PPM), are still a relatively common occurrence following transcatheter aortic valve implantation (TAVI).[1,2] PPMs post-TAVI remain linked with greater hospital length of stay, more re-hospitalizations, and increased mortality.[3,4] High grade atrio-ventricular-bundle branch block is the typical indication for PPM post-TAVI and an extensive body of literature has defined predictors for its occurrence, including pre-existing bundle branch block, extensive valve and left-ventricular outflow tract calcification, and a shorter membranous septum length (MSL).[5–8] Valve choice, degree of oversizing, and implantation depth (ID) further impact PPM rates.[2,3,9,10] Many operators have subsequently introduced various procedural techniques that can lower the risk for permanent high-grade conduction abnormalities post-TAVI.[11–13] However, the mechanisms for adverse outcomes in patients with PPM post-TAVI remain elusive. Moreover, a significant proportion of PPM recipients demonstrate very little or no pacemaker dependence when followed beyond the 6–8 week period post-TAVI.[14,15]

The present analysis was aimed at evaluating the association between the degree of PPM dependence [by measuring right-ventricular (RV)-stimulation rates from PPM interrogations] in patients with PPM post-TAVI with 1-year all-cause mortality and heart failure hospitalization rates. We specifically evaluated whether changes in RV stimulation post-TAVI in patients with existing PPM pre-TAVI were linked with adverse clinical outcomes, and further explored factors that predisposed to greater PPM-dependence in these patients.

Methods

Study design

We undertook a retrospective cohort study conducted at the Cleveland Clinic and the West German Heart and Vascular Center. Baseline patient characteristics, electrocardiogram (ECG), imaging, procedural characteristics, and clinical outcomes from prospective registries housed at both centers, including data captured within electronic medical records, were pooled and analyzed. The study was approved by the institutional review boards of both centers without the requirement of informed consent owing to the retrospective nature of the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient selection

We identified consecutive patients aged ≥18 years who underwent TAVI between January 2012 and September 2020 at both centers and included only those patients who had either a pre-existing PPM or implantable

cardioverter defibrillator (ICD) before TAVI implantation or new PPM/ICD implantation post-TAVI. No patient received a 'prophylactic' PPM before TAVI. Patients, who died within 30-days of TAVI implantation, patients treated with cardiac resynchronization therapy (CRT), and patients treated with subcutaneous ICD were excluded from our analysis. Eligible patients were divided into two groups: Patients with existing PPM/ICD pre-TAVI and patients with new PPM/ICD post-TAVI.

Baseline patient and procedural variables

Baseline patient and procedural variables in the present study included patient demographics, past history and comorbidities, ECG findings, echocardiographic parameters, aortic valve annular data, and procedural details. Only patients, who had at least one follow-up pacemaker interrogation >30 days post-valve implantation were included in this analysis. Pacing data and underlying rhythm were obtained from the patient records. All ECG data were interpreted as per the standard definitions and guidelines.[16,17] Aortic valve annular data were obtained using pre-TAVI contrast-enhanced ECG-gated computed tomography (CT) images. The calcium score of aortic valve leaflets was quantified using ECG-gated contrast CT images pre-TAVI, whereby a pre-specified threshold was applied to account for the hyperdensity of contrast medium according to a prior report.[18] Presence of calcification within the left-ventricular outflow tract was evaluated using pre-TAVI CT images. The contrast-enhanced CT images were also evaluated in the systolic phase (at 40% of the R-R interval) for the measurement of MSL.[19] MSL was determined in multiplanar reconstruction as the distance from the aortic valve annular plane to the tip of the muscular interventricular septum. The Aquarius iNtuition (TeraRecon Inc., Foster City, CA, USA) was used to collect these imaging variable data for patients from the Cleveland Clinic, whereas IntelliSpace Portal (Philips Healthcare, Best, the Netherlands) was used for patients from the West German Heart and Vascular Center. Eccentricity index and oversizing were calculated on formulas reported previously.[20] Implantation depth of a transcatheter heart valve relative to the base of the non-coronary cusp (NCC) was measured as the distance between the bottom of the NCC and the valve stent frame in the right anterior oblique caudal aortic root angiogram at the conclusion of TAVI procedure using SyngoDynamics (Siemens Healthcare, Malvern, PA, USA) for patients from the Cleveland Clinic and the CAAS Workstation (IntelliSpace Cardiovascular, Philips Healthcare, Best, The Netherlands) for patients from the West German Heart and Vascular Center.

Outcome measures

The primary outcome of major adverse cardiovascular events (MACE) was defined as a composite of all-cause death and heart failure hospitalization. All events within a time-frame of 30-days post TAVI implantation to 1-year were included. One-year follow-up was completed for all patients. The secondary outcome was the change in left-ventricular ejection fraction (LVEF) from pre-TAVI transthoracic echocardiography to available echocardiography imaging during follow-up.

Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using the Fisher exact test or chi-square test. Continuous variables were presented as median and interquartile range (IQR) or mean ± standard deviation and were compared using the Mann–Whitney *U* test or unpaired *t*-test as appropriate. Due to its skewed, bimodal distribution, RV-stimulation rate was categorized into two groups: ≤10% and >10%. The association between RV-stimulation rate and the primary endpoint was evaluated using unadjusted and multivariable (MV) adjusted Cox regression analysis. Since RV-stimulation rate at follow-up is a repeatedly measured covariate, the last observation carried forward method applied before doing survival modelling. Therefore, each patient was assigned a series of time intervals (based on the date of existing PPM interrogation), and the last available RV-stimulation rate before an event or censoring was used for all analyses. Variables adjusted for each model included the Society of Thoracic Surgeons (STS)-Score, history of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), LVEF at baseline, atrial fibrillation, and valve type. Associations were evaluated for the overall cohort as well as in subgroups of patients with RV-stimulation rate >10% pre-TAVI and in patients with RV-stimulation rate ≤10% pre-TAVI or no new PPM post-TAVI. Kaplan-Meier (KM) curves illustrate the cumulative MACE incidence in patients with RV-stimulation rate ≤ vs. >10% post-TAVI. Restrictive quadratic splines with knots 10% and 90% of RV stimulation rate were used to evaluate the association of RV stimulation rate as a continuous variable with the primary endpoint, using the median RV stimulation post-TAVI rate as reference. Linear regression analysis evaluated the association between RV-stimulation rate and changes in LVEF. Predictors of RV-stimulation rate post-TAVI (≤ vs. >10%) were evaluated using univariate and MV logistic regression analysis. Implantation depth in patients with RV-stimulation rate ≤ vs. >10% post-TAVI was compared using an unpaired *t*-test. The specific association between ID and RV-stimulation rate post-TAVI was evaluated using logistic regression analysis, controlling for right bundle branch block (RBBB), mean aortic valve gradient at baseline, and degree of valve oversizing. Further, we performed a sensitivity analysis, using 20% and 40% RV-stimulation rate as thresholds in the cohort of patients with low RV-stimulation rate pre-TAVI or new PPM post-TAVI using identical adjustment sets. Finally, additional analyses evaluated the association of RV-stimulation rate with both heart failure hospitalization and all-cause mortality separately. Again, identical adjustment sets were used. All tests were two-tailed with a significance level of 0.05. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study patients

A total of 4659 patients underwent TAVI across both centers between January 2012 and September 2020. Of these, 408 patients (8.6%) had an existing PPM pre-TAVI and 361 patients (7.7%) underwent PPM implantation within 30-days post-TAVI (median time between TAVI and PPM implantation 2.5 [1.0; 5.3] days). *Figure 1* depicts the detailed flow-chart of the patient cohort. The mean age was 82.3 ± 8.1 years, 39% were women (*Table 1*). Overall, there was a bimodal distribution of the RV-stimulation rate post TAVI (*Figure 2*). In patients with new PPM post-TAVI, 108 patients had a RV-stimulation rate of ≤10% [median (IQR) 1.0 (0.0, 3.0)%], whereas 253 patients had high RV-stimulation rates [>10%, median (IQR) 96 (55, 100)%]. Similarly, the group of patients with existing PPM pre-TAVI but low RV-stimulation rate before TAVI were sub-classified into a group of low RV-stimulation rate ≤10% post-TAVI [$n = 116$ patients, median (IQR) RV-stimulation rate 0.6 (0.0, 2.8)%] and a group of patients with high RV-stimulation following TAVI-implantation [>10%, $n = 54$, median (IQR) 90.1 (32.7, 99.0)%]. Patients with high RV-stimulation rate post-TAVI were on average older, less frequent women, had a lower STS-score, had more frequent cerebrovascular disease, and were more likely on dialysis (*Table 1*, Supplementary material online, *Table S1*). Likewise, patients with high RV-stimulation rate post-TAVI received on average larger valve sizes, with higher degree of valve oversizing and greater valve ID.

Table 2 shows the Cox regression analysis for the association of post-TAVI RV-stimulation rate (>10% vs. ≤10%) and MACE. In patients with high RV-stimulation rates already pre-TAVI, RV-stimulation rate post-TAVI was not linked with MACE. However, in patients with RV-stimulation rate ≤10% pre-TAVI or in new PPM recipients post-TAVI, an increase in RV-stimulation rate post-TAVI associated with a nearly 2-fold higher risk of MACE in MV adjusted models [Hazard ratio (95% confidence interval): 1.97 (1.20, 3.25), *P*-value = 0.008]. Additionally adjusting for age, degree of aortic valve regurgitation post-TAVI, and left ventricular outflow tract (LVOT) calcification did not alter the association [1.91 (1.15, 3.17), $P = 0.012$]. In sensitivity analysis, using 20% and 40% as alternative thresholds for RV-stimulation rate, robust effect sizes were observed (see Supplementary material online, *Table S2*). Kaplan Meier survival curves confirmed the adverse prognosis comparing high (vs. lower) RV-stimulation rates post-TAVI in patients

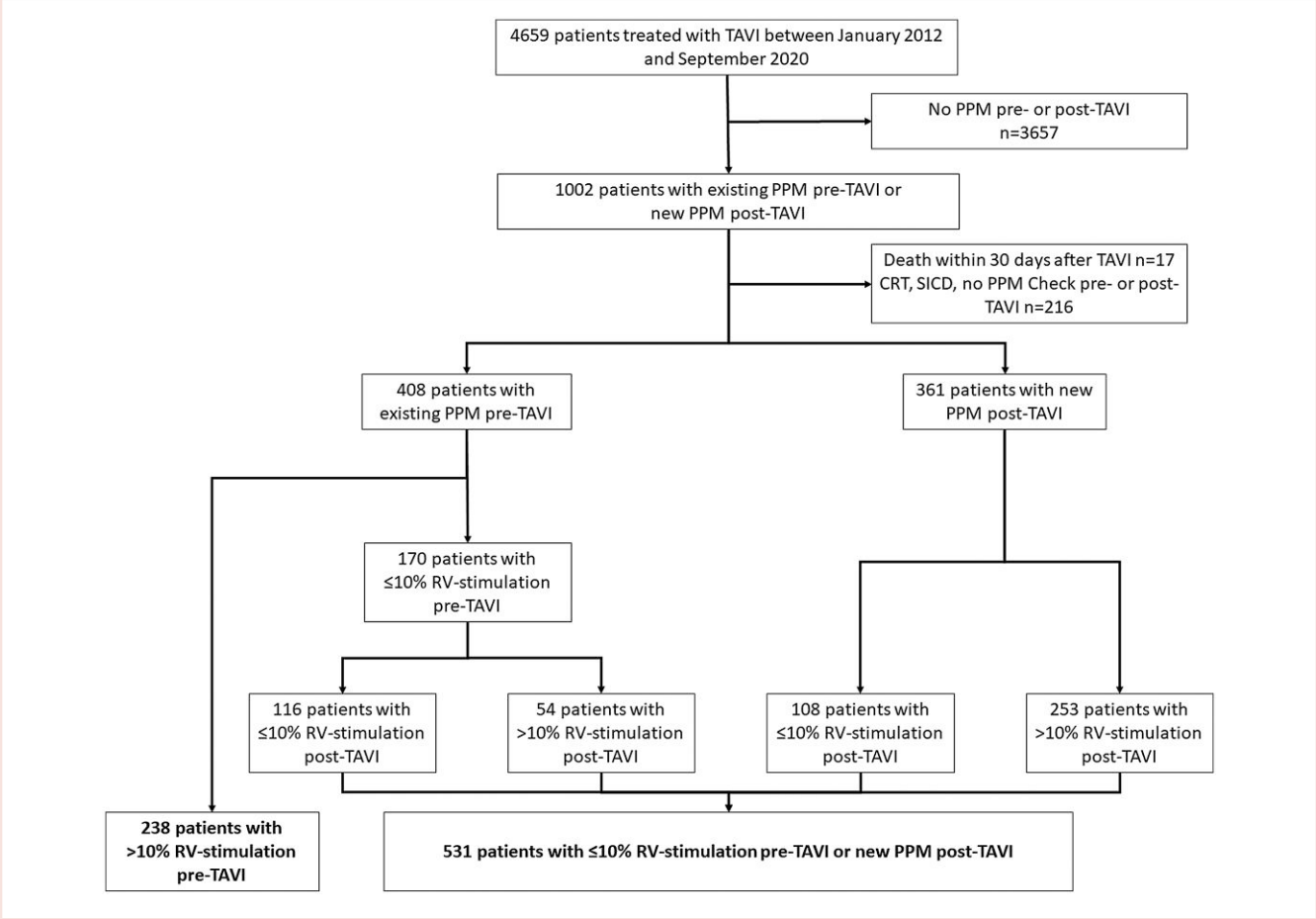


Figure 1 Flow-chart of the patient cohort. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; RV, right-ventricular; SICD, subcutaneous implantable cardioverter defibrillator; TAVI, transcatheter aortic valve implantation.

with RV-stimulation rate ≤10% pre-TAVI or in new PPM (log-rank $P = 0.01$) (*Figure 3*). For patients with RV-stimulation rate ≤10% pre-TAVI or new PPM post-TAVI, we evaluated the association of RV-stimulation rate post-TAVI rate with the primary endpoint. In quadratic splines analysis, we found a nearly linear relationship between RV-stimulation rate post-TAVI and risk of all-cause mortality or heart failure hospitalization (see Supplementary material online, *Figure S1*).

To investigate, how RV-stimulation rate may influence the combined endpoint of all-cause mortality and heart failure hospitalization, we evaluated the association between RV-stimulation rate and changes in LVEF after TAVI. In patients with a pre-TAVI PPM and a baseline RV-stimulation rate ≤10%, a post-TAVI RV-stimulation rate of >10% was associated with a significant reduction in LVEF from baseline to follow-up in both univariate and MV analyses [univariate: Parameter estimate (95% confidence interval): −2.63 (−5.15; −0.10), $P = 0.04$; MV: −2.42 (−4.78; −0.05), $P = 0.045$]. In contrast, for patients with a new PPM post-TAVI, the RV-stimulation rate at follow-up did not influence the change in LVEF (see Supplementary material online, *Table S3*). When separately evaluating the association of RV-stimulation rate with heart failure hospitalization and all-cause death, we observed a stronger link of high RV-stimulation rate with heart failure hospitalization, documenting the mechanistic influence of asynchrony in ventricular stimulation on heart failure in patients following TAVI implantation (see Supplementary material online, *Table S4*).

Table 3 evaluated the association of baseline and procedural characteristics with the onset of RV-simulation rate >10% post-TAVI in patients with RV-stimulation rate ≤10% pre-TAVI and in patients with new PPM post-TAVI. In an MV analysis, before RBBB, higher pre-TAVI mean aortic valve gradient and greater ID independently associated with high RV-stimulation rates. In contrast, in patients with RV-stimulation rate >10% pre-TAVI, ID did not associate with a high RV-stimulation rate post-TAVI [OR (95% CI): 1.19 (0.70, 2.03), $P = 0.51$]. Interestingly, the difference between the length of the MS and ID, but not MSL itself were linked with high pacing rates. Likewise, self-expanding as compared to balloon-expandable valve type was associated with high RV-stimulation rates post-TAVI in univariate analysis. However, after adjusting for other predictors, this association was no longer present.

Figure 4 compares the ID of patients with RV-stimulation rate of ≤ vs. >10% post-TAVI. In patients with RV-stimulation rate >10% pre-TAVI, ID was not significantly different when comparing patients with high vs. low RV-stimulation rates post-TAVI. In contrast, ID was noted to be significantly greater when RV-stimulation rates of ≤10% pre-TAVI increased to >10% post-TAVI. While ID was independently associated with RV-stimulation rate >10% post-TAVI in the overall cohort, this effect was primarily driven by patients with RV-stimulation rates of ≤10% pre-TAVI or new PPM post-TAVI (*Table 4*).

Table 5 describes the association between ID and MACE in our cohort of patients with existing PPM pre-TAVI or new PPM recipient's post-TAVI. In the overall cohort, ID is significantly associated with MACE. This effect was predominantly driven by patients with RV-stimulation rates ≤10% pre-TAVI and those with new PPM

Table 1 Baseline characteristics for the overall cohort as well as for patients with right-ventricular-stimulation rate ≤10% and >10% post-transcatheter aortic valve implantation

	Overall (N = 769)	RV-stimulation rate >10% post-TAVI (*n* = 523)	RV-stimulation rate ≤10% post-TAVI (*n* = 246)	*P* value
Age, years	82.3 ± 8.1	82.8 ± 7.8	81.2 ± 8.5	0.007
Female	302 (39.3)	186 (35.6)	116 (47.2)	0.002
Caucasian	748 (97.3)	509 (97.3)	239 (97.2)	0.9
Body mass index, kg/m^2	28.0 ± 5.7	27.8 ± 5.6	28.5 ± 5.8	0.1
STS risk score, %	6.44 ± 4.1	6.19 ± 3.7	6.99 ± 4.9	0.04
Prior CABG	190 (24.7)	118 (22.6)	72 (29.3)	0.004
Prior myocardial infarction	162 (21.1)	97 (18.6)	65 (26.4)	0.01
Prior PCI	320 (41.6)	224 (42.8)	96 (39.0)	0.3
Prior stroke	96 (12.5)	63 (12.1)	33 (13.4)	0.6
Peripheral artery disease	213 (27.7)	142 (27.2)	71 (28.9)	0.6
Cerebrovascular disease	144 (18.7)	112 (21.4)	32 (13.0)	0.005
Hypertension	704 (91.6)	484 (92.5)	220 (89.4)	0.1
Diabetes	287 (37.3)	185 (35.4)	102 (41.5)	0.1
Dyslipidemia	674 (87.7)	454 (86.8)	220 (89.4)	0.3
ESRD on dialysis	21 (2.7)	19 (3.6)	2 (0.8)	0.03
COPD	284 (36.9)	185 (35.4)	99 (40.2)	0.2
Oxygen dependent	69 (9.0)	51 (9.8)	18 (7.3)	0.3
History of atrial fibrillation/flutter	396 (51.5)	281 (53.7)	115 (46.8)	0.07
NYHA functional class III or IV	482 (62.7)	328 (62.7)	154 (62.6)	0.98
LVEF, %	53.3 ± 12.2	53.6 ± 11.4	52.6 ± 13.8	0.3
LVEDV, mL	109.6 ± 46.0	108.4 ± 43.0	112.1 ± 51.6	0.4
Aortic valve area, cm^2	0.71 ± 0.2	0.71 ± 0.2	0.70 ± 0.2	0.5
Aortic valve mean gradient, mmHg	40.2 ± 15.1	40.6 ± 15.8	39.4 ± 13.5	0.3
Aortic valve peak gradient, mmHg	67.1 ± 23.6	67.5 ± 24.5	66.4 ± 21.8	0.5
Bicuspid aortic valve	29 (3.8)	18 (3.4)	11 (4.5)	0.5
Failed bioprosthetic valve	54 (7.0)	37 (7.1)	17 (6.9)	0.9
Moderate or severe AR	183 (23.8)	119 (22.7)	64 (26.0)	0.8
Mean annular diameter, mm[a]	25.3 ± 2.7 [*n* = 629]	25.2 ± 2.7 [*n* = 421]	25.3 ± 2.7 [*n* = 208]	0.9
LVOT calcification	387/684 (55.3)	264/460 (57.4)	114/224 (50.9)	0.1
MSL, mm	4.52 ± 2.0 [*n* = 614]	4.63 ± 2.0 [*n* = 413]	4.31 ± 2.0 [*n* = 201]	0.07

Values are mean ± SD or *n* (%).
AR, aortic regurgitation; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, the New York Heart Association; PCI, Percutaneous coronary intervention; RV, right ventricular; STS, The Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
[a]Values obtained by multi-detector computed tomography.

post-TAVI, while no association was observed for patients with RV-stimulation rates of >10% pre-TAVI.

Discussion

To the best of our knowledge, the present analysis is the first to link the degree of pacing dependence pre- and post-TAVI with hard clinical events, with valve implant depth playing an important mechanistic role in driving the degree of RV stimulation, underscoring the propensity for MACE post-TAVI. We demonstrate: (i) a high RV-stimulation rate independently associated with all-cause mortality and heart failure hospitalization within a 1-year time-frame post-TAVI (ii), the link between greater degrees of RV-stimulation and MACE was not only present in new PPM recipients post-TAVI, but also in those individuals with pre-existing PPM and low (≤10%) degrees of RV-stimulation at baseline pre-TAVI, and (iii) valve ID was a major predictor of a high RV-stimulation rate post-TAVI which itself independently associated with MACE both in patients with existing PPM pre-TAVI as well as in new PPM recipients post-TAVI. These data reinforce the importance of a meticulous implant strategy, especially with regards to the target implant depth, in all TAVI recipients irrespective of the presence or absence of a pre-existing PPM, to optimize clinical outcomes.

Conduction disturbance with subsequent PPM implantation post-TAVI remains a relatively frequent complication that portends an adverse longer-term prognosis.[3,4,21] The existing body of literature to-date has primarily focused on new PPM implantations (as a binary outcome) as a predictor of an impaired longer-term prognosis. Yet up to 50% of individuals who undergo a PPM post-TAVI demonstrate little or no underlying PPM dependence beyond the 4–6 week mark

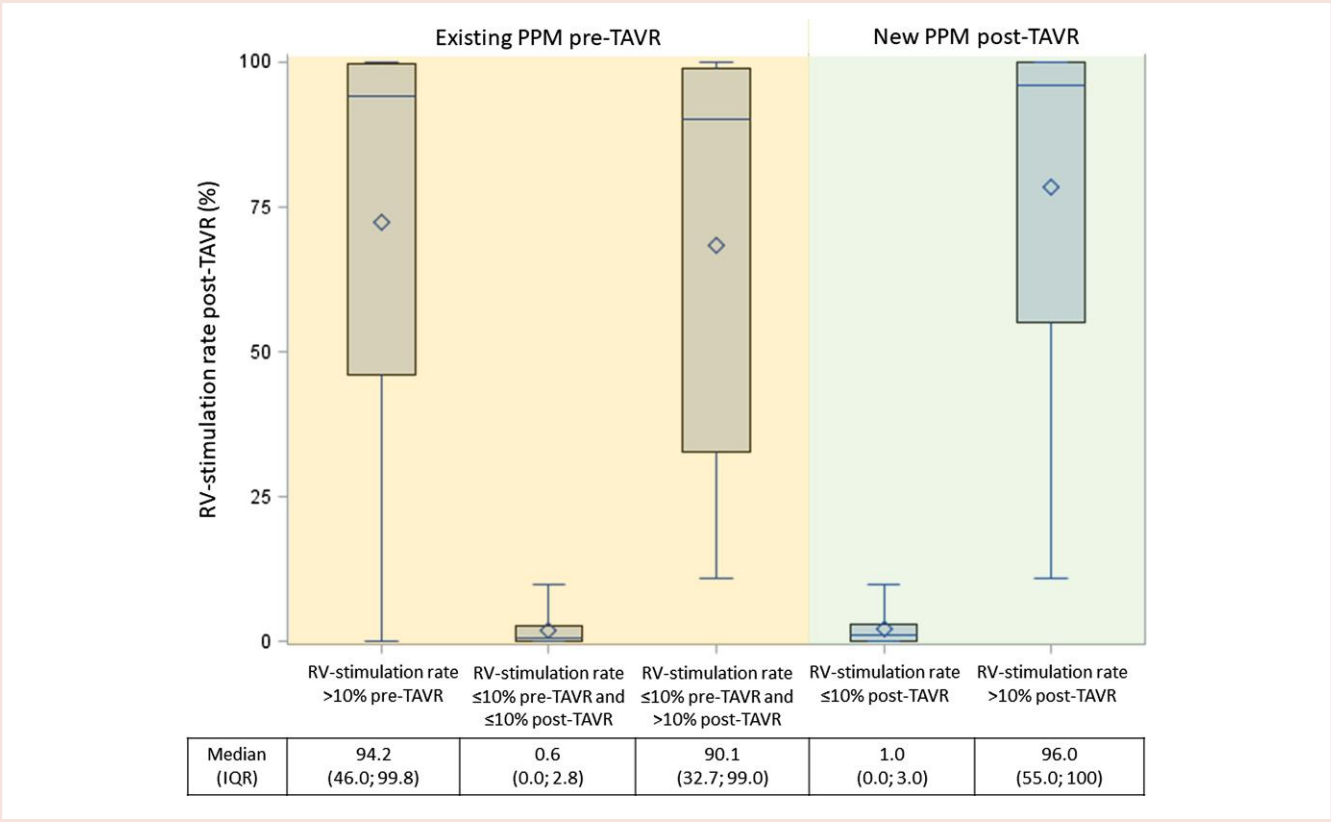


Figure 2 Right-ventricular-stimulation rate post-transcatheter aortic valve implantation for each group. Bimodal distribution of right-ventricular-stimulation rate post-transcatheter aortic valve implantation with either very low (≤10%) or very high (>10%) right-ventricular-stimulation rate. IQR, interquartile range; PPM, permanent pacemaker; RV, right-ventricular; TAVI, transcatheter aortic valve implantation.

Table 2 Univariate and multi-variable Cox regression analysis for the association of post-transcatheter aortic valve implantation right ventricular-stimulation rate of >10% (vs. ≤10%) and major adverse cardiovascular events (all-cause death and heart failure hospitalization) in patients with right ventricular-stimulation rate ≤10% and >10% pre-transcatheter aortic valve implantation as well as patients with new permanent pacemaker post-transcatheter aortic valve implantation

	Overall (*n* = 769)		Patients with RV-stimulation rate >10% pre-TAVI (*n* = 238)		Patients with RV-stimulation rate ≤10% pre-TAVI (*n* = 170)		New PPM post-TAVI (*n* = 361)	
	Hazard Ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Univariate analysis	1.32 (0.90, 1.95)	0.16	0.50 (0.20, 1.29)	0.15	1.72 (0.79, 3.73)	0.2	1.70 (0.96, 3.02)	0.07
MV analysis[a]	1.46 (0.94, 2.27)	0.09	0.63 (0.21, 1.89)	0.41	2.52 (1.02, 6.23)	0.045	2.18 (1.01, 4.71)	0.045

CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MV, multi-variable; RV, right ventricular; TAVI, transcatheter aortic valve implantation.
[a]Adjusted for STS-Score, history of CAD, COPD, LVEF at baseline, atrial fibrillation, and valve type (ancillary for QRS-duration at baseline for patient with new PPM post-TAVI).

following PPM insertion.[3,22] It is conceivable that those TAVI recipients with new PPMs who demonstrate recovery of intrinsic conduction (with lesser/little pacing dependence) may follow a clinical trajectory that differs from those with longer-term total underlying PPM dependence. Additionally, in TAVI recipients with pre-existing PPMs, there are currently no data evaluating the clinical impact of a greater change in pacing dependence in the post-TAVI setting. The present analysis fills this knowledge gap by elucidating the deleterious effects of greater degrees of RV pacing, evident within the 1-year post-TAVI period. Importantly, this holds true not only for PPM-naïve TAVI recipients but

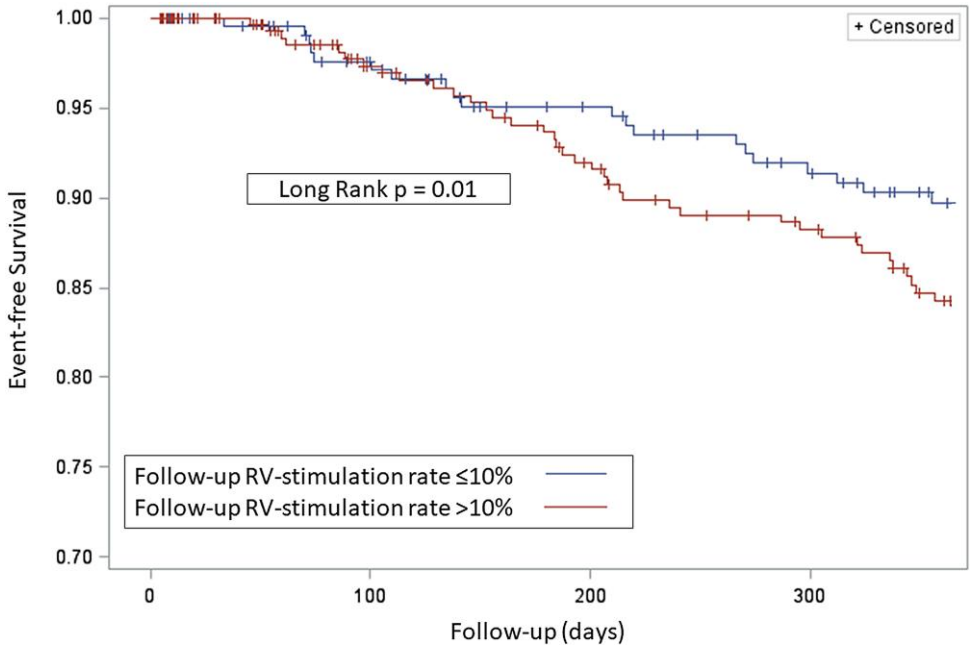


Figure 3 Kaplan-Meier survival curves for 1-year major adverse cardiovascular events (all-cause death and heart failure hospitalization) comparing right-ventricular-stimulation rates ≤10% vs. > 10% in patients with right-ventricular-stimulation rate ≤10% pre-transcatheter aortic valve implantation or in new permanent pacemaker. Higher major adverse cardiovascular events rate in patients with high right-ventricular-stimulation rate post-transcatheter aortic valve implantation (red line) as compared to patients with low right-ventricular-stimulation rate (blue line). MACE, major adverse cardiovascular events; RV, right-ventricular; TAVI, transcatheter aortic valve implantation.

Table 3 Univariate and multi-variable predictors of right ventricular-simulation rate >10% post-transcatheter aortic valve implantation in patients with right ventricular-stimulation rate ≤10% pre-transcatheter aortic valve implantation and in patients with new permanent pacemaker post-transcatheter aortic valve implantation

Predictor	Univariate		Multi-variable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
RBBB	2.19 (1.45; 3.31)	0.0002	2.19 (1.26; 3.81)	0.006
History of atrial fibrillation	1.09 (0.77; 1.54)	0.6	1.28 (0.80; 2.04)	0.3
Pre-TAVI mean aortic valve gradient	1.17 (0.98; 1.40)	0.08	1.35 (1.01; 1.80)	0.04
Pre-TAVI aortic valve area	1.13 (0.93; 1.36)	0.2	1.18 (0.91; 1.52)	0.2
Pre-TAVI LVEF	1.25 (1.05; 1.49)	0.01	1.25 (0.96; 1.63)	0.09
Implantation depth	1.60 (1.30, 1.97)	<0.0001	1.56 (1.14; 2.14)	0.006
MSL	1.16 (0.96; 1.40)	0.1	1.19 (0.94; 1.50)	0.1
Difference between MSL and implantation depths	0.78 (0.63; 0.95)	0.02	—	—
LVOT Calcification	1.33 (0.92; 1.92)	0.1	1.44 (0.90; 2.32)	0.1
Valve in valve	0.53 (0.22; 1.29)	0.2	2.48 (0.34; 18.1)	0.4
Valve size	1.11 (1.05; 1.19)	0.07	1.01 (0.91; 1.13)	0.8
Self-expanding vs. balloon-expandable valve	1.78 (1.21; 2.60)	0.003	0.98 (0.48; 2.00)	0.95
Pre-dilation	1.31 (0.93; 1.85)	0.1	0.97 (0.59; 1.60)	0.9
Post-dilation	0.38 (0.26; 0.57)	<0.0001	0.40 (0.23; 0.70)	0.001
Valve oversizing	1.42 (1.17; 1.75)	0.0006	1.23 (0.86; 1.77)	0.3

Odds ratio and 95% confidence interval per standard deviation increase for the continuous variables.
CI, confidence interval; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; ID, implantation depth; MACE, major adverse cardiovascular events; OR, odds ratio; PPM, permanent pacemaker; RBBB, Right bundle branch block; RV, right ventricular; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

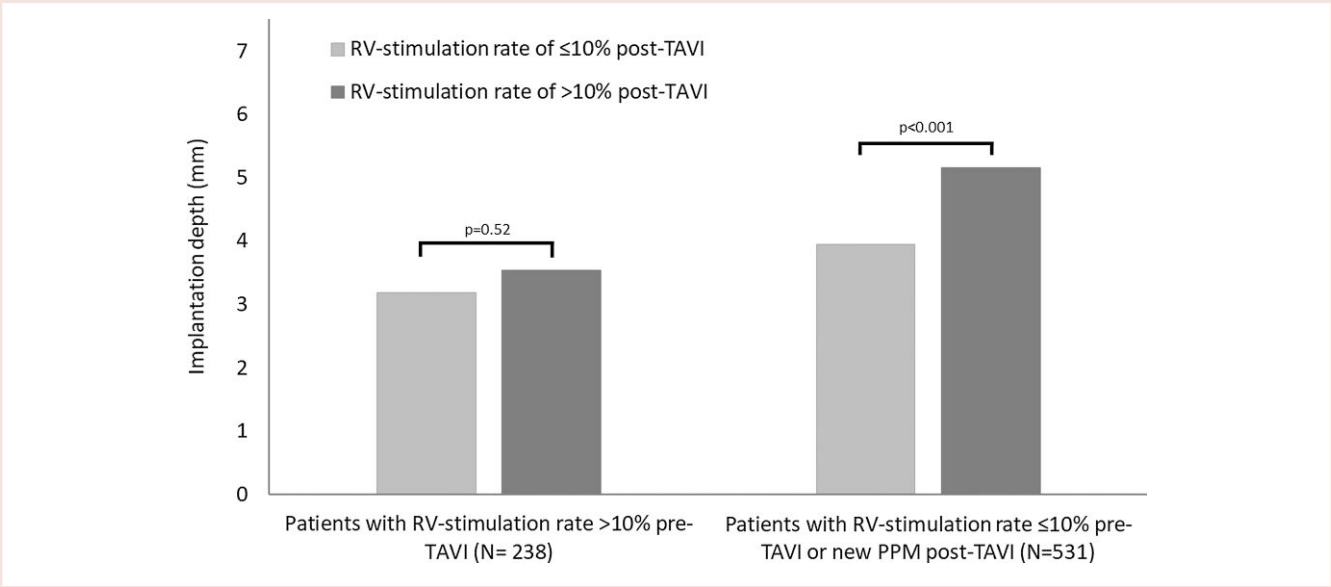


Figure 4 Implantation depth in patients with right-ventricular-stimulation rate of ≤ vs. >10% post-transcatheter aortic valve implantation. In patients with right-ventricular-stimulation rate >10% pre-transcatheter aortic valve implantation, there was no link between implantation depths and right-ventricular-stimulation rate post-transcatheter aortic valve implantation. In patients with existing permanent pacemaker and low right-ventricular-stimulation rate pre-transcatheter aortic valve implantation or patients with new permanent pacemakers post-transcatheter aortic valve implantation, implantation depth was significantly greater in patients with high right-ventricular-stimulation rates. PPM, permanent pacemaker; RV, right-ventricular; TAVI, transcatheter aortic valve implantation.

Table 4 Association of implantation depth with right ventricular-stimulation rate >10% (vs. ≤10%) post-transcatheter aortic valve implantation in patients with right ventricular-stimulation rate ≤10% and >10% pre-transcatheter aortic valve implantation

	OR (95% CI)	*P*-value
Overall (N = 769)	1.30 (1.04, 2.01)	0.02
Patients with RV-stimulation rate >10% pre-TAVI (N = 238)	1.17 (0.55, 2.52)	0.7
Patients with RV-stimulation rate ≤10% pre-TAVI or new PPM post-TAVI (N = 531)	1.58 (1.21, 2.06)	<0.001

Adjusted for RBBB, mean aortic valve gradient at baseline, and oversizing.
CI, confidence interval; OR, odds ratio; PPM, permanent pacemaker; RBBB, right bundle branch block; RV, right ventricular; TAVI, transcatheter aortic valve implantation.

also those with pre-existing PPMs. Valve ID, which independently associated with both the degree of pacemaker dependence in the post-TAVI setting, but also MACE, may in part contribute towards these findings. Likewise, we found that the difference between the length of the MS and ID but not the MSL itself was associated with high RV-stimulation rate, further supporting the important role of implantation depths on pacemaker dependence post-TAVI. In line with these observations, the MACE rates of patients with pre-existing PPM without an increase in pacing dependence post-TAVI along with TAVI recipients with new PPM implantation in the post-TAVI setting who maintain a low dependence on their PPM, are comparatively favourable. These findings suggest that the actual quantification of RV-stimulation may serve as a better predictor of overall patient outcome post-TAVI than simply reporting PPM implantation rates *per se*. Our results are in good agreement with a recent publication by Bruno *et al.*, describing that RV-stimulation rate >40% post-TAVI was associated with an increased risk of cardiovascular death or heart failure hospitalization.[23] Our results extend the existing literature by providing stable effect sizes independent of RV-stimulation threshold used and by identifying ID as key procedural characteristic to increase the risk of RV-stimulation rate and MACE itself. Our results therefore provide insights into implantation techniques for optimizing MACE in TAVI recipients.

Right ventricular stimulation induces abnormal electro-mechanical activation patterns, leading to worsening haemodynamic and myocardial remodelling parameters.[24,25] A broader QRS-duration due to RV-stimulation is linked with poorer left-ventricular contractility,[26] while long-term RV-stimulation can lead to pacing-induced cardiomyopathy.[27] The present results extend the existing knowledge base of the known adverse effects of high RV-stimulation rates in heart failure cohorts to TAVI recipients. We demonstrate that an increasing RV-stimulation rate correlated significantly with the risk of heart failure hospitalization and all-cause mortality, coinciding with a significant decline in LVEF. This phenomenon was evident in TAVI recipients with pre-existing PPM and low baseline pacing dependence. These results support the hypothesis of the direct impact that higher degrees of pacing dependence (i.e. % RV-stimulation) imparts upon patient outcomes post-TAVI. Novel, more physiologic means of pacing, including His-bundle and left bundle branch pacing, are aimed at minimizing the deleterious effects of RV-stimulation. Initial studies have outlined the feasibility of these techniques in patients post-TAVI, resulting in shorter QRS durations as compared to conventional RV-stimulation with early evidence, albeit limited, pointing to improvements in LVEF.[28,29] Interestingly, we observed a strong association between valve type (self-expanding vs. balloon-expandable valve) and high RV-stimulation rate post-TAVI in univariate analysis, which was no longer present in MV models. This finding may imply that other patient- and procedure-related characteristics such as prior RBBB, higher pre-TAVI mean aortic valve gradient, and greater ID may overrule the influence of

Table 5 Univariate and multi-variable Cox regression analysis for the association of implantation depth per 1 SD increase and incident major adverse cardiovascular events (all-cause death and heart failure hospitalization) in the overall cohort as well as in patients with right ventricular-stimulation rate >10% and ≤10% pre-transcatheter aortic valve implantation as well as patients with new permanent pacemaker post-transcatheter aortic valve implantation

	Overall ($n = 769$)		Patients with RV-stimulation rate >10% pre-TAVI ($n = 238$)		Patients with RV-stimulation rate ≤10% pre-TAVI or new PPM post-TAVI ($n = 531$)	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Univariate analysis	1.17 (0.98, 1.40)	0.086	0.93 (0.66, 1.31)	0.66	1.26 (1.02, 1.55)	0.03
MV analysis[a]	1.27 (1.00, 1.59)	0.047	0.85 (0.50, 1.42)	0.53	1.40 (1.07, 1.84)	0.02

CAD, Coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MS, membranous septum; MV, multi-variable; PPM, permanent pacemaker; RBBB, right bundle branch block; RV, right ventricular; STS, The Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

[a]Adjusted for STS-Score, history of CAD, COPD, LVEF at baseline, atrial fibrillation, and valve type.

valve type on pacemaker dependency after TAVI. Further studies in larger TAVI cohorts are needed to evaluate, whether conduction system pacing can lead to an improved prognosis in patients with a reliance on PPM post-TAVI, which has the potential to ultimately emerge as a standard of care for pacing post-TAVI.

Numerous analyses have described several predictors of a PPM requirement post-TAVI, which include pre-existing conduction disturbances (i.e. RBBB and LBBB), anatomical factors (i.e. calcification of the left-ventricular outflow-tract and short MSL), and procedural characteristics (i.e. ID and degree of valve oversizing).[1,2,5–7,9–12,30] The present manuscript confirms pre-existing RBBB, greater ID, and post-dilatation as independent predictors of high RV-stimulation rates post TAVI. In addition to its strong association with RV-stimulation rates, greater valve ID *per se* is associated with MACE in patients with existing PPM pre-TAVI and in new PPM recipient's post-TAVI. Given the intimate anatomical relationship between the intrinsic conduction system (His-Purkinje fibres) and MS that typically lies adjacent to the inter-leaflet triangle between the right and non-coronary cusps, there has been considerable debate as to how to optimize valve ID during TAVI to minimize valve-to-native conduction system interactions and subsequent PPM risk. This has led to a strong focus on implantation techniques that isolate the NCC for valve deployment ('cusp overlap' technique).[12,13] As such, implantation depths deeper than the length of the MS correlate with conduction disturbance and PPM requirements post-TAVI.[11,31] Our findings underscore the importance of a meticulous and targeted valve implantation technique to minimize the risk for new PPM post-TAVI, which importantly optimizes subsequent clinical outcomes. The present data also reinforces the notion that irrespective of the need for a PPM post-TAVI, there is still a clinical benefit to optimizing depth of implantation given that higher implant depths correlated with lesser pacing dependence and more favourable clinical outcomes compared with those with deeper implant depths and significant longer-term pacing dependence. These clinical benefits also extend to those with pre-existing PPM with low degrees of pacing dependence.

Several caveats of the present analysis warrant attention. We undertook a retrospective analysis of data from two high-volume centers in the U.S. and Europe, thus limiting somewhat the generalizability of our data. The RV-stimulation rate may vary at differing time points during follow-up. While we included all available PPM interrogations post-TAVI into our database and applied the last observation carried forward methods where the last available PPM interrogation before an event or censoring was used, we cannot rule out the RV-stimulation rate may have changed between the last interrogation and the event. However, the bimodal distribution of RV-stimulation rate, showing that the patients distributed into groups of either very high or very low RV-stimulation rate suggest stable RV-stimulation rates according to the presence or absence of continuous high-grade conduction disturbances. In addition, no assessment of quality of life was performed during standard of care and therefore was not available for this retrospective analysis. Finally, the implant depth measurement on a two-dimensional angiogram may not adequately reflect the true cusp overlap view due to the limitations of image detector angulation. However, both institutions aim for the near cusp overlap and removal of parallax (at both the time of implantation and again after final valve deployment) of the prosthesis, creating an appropriate reference point of the valve inflow relative to the nadir of the NCC.

Conclusions

Irrespective of the presence or absence of a baseline PPM pre-TAVI, greater degrees of pacing dependence post-TAVI correlated with higher risk for all-cause mortality and heart failure hospitalizations 1-year follow-up. The link between RV-stimulation rates and MACE was notable in patients with new PPM post-TAVI but also for patients with existing PPM but low RV-stimulation rates pre-TAVI. Valve ID was the driving mechanism underscoring these observations, which itself correlated with MACE. Implant techniques to plan and execute a specific valve ID are important for optimizing MACE in TAVI recipients, significantly impacting 1-year outcomes even in those with pre-existing PPMs.

Lead author biography

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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