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FOCUS ON TAVR

Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement

Analysis From the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry

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CME Objective for This Article: At the end of the activity the reader should be able to: 1) appreciate the extent of conduction abnormalities post-TAVR; 2) evaluate the clinical outcomes following permanent pacemaker implantation in subjects undergoing TAVR procedures; and 3) consider the timing of conduction abnormalities post-TAVR.

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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the incidence, predictors, and clinical outcomes of permanent pacemaker (PPM) implantation following transcatheter aortic valve replacement (TAVR).

BACKGROUND Conduction abnormalities leading to PPM implantation are common complications following TAVR. Whether PPM placement can be predicted or is associated with adverse outcomes is unclear.

METHODS A retrospective cohort study of patients undergoing TAVR in the United States at 229 sites between November 2011 and September 2014 was performed using the Society of Thoracic Surgeons/American College of Cardiology TVT Registry and the Centers for Medicare and Medicaid Services database.

RESULTS PPM placement was required within 30 days of TAVR in 651 of 9,785 patients (6.7%) and varied among those receiving self-expanding valves (25.1%) versus balloon-expanding valves (4.3%). Positive predictors of PPM implantation were age (per 5-year increment, odds ratio: 1.07; 95% confidence interval [CI]: 1.01 to 1.15), prior conduction defect (odds ratio: 1.93; 95% CI: 1.63 to 2.29), and use of self-expanding valve (odds ratio: 7.56; 95% CI: 5.98 to 9.56). PPM implantation was associated with longer median hospital stay (7 days vs. 6 days; $p < 0.001$) and intensive care unit stay (56.7 h vs. 45.0 h; $p < 0.001$). PPM implantation was also associated with increased mortality (24.1% vs. 19.6%; hazard ratio [HR]: 1.31; 95% CI: 1.09 to 1.58) and a composite of mortality or heart failure admission (37.3% vs. 28.5%; hazard ratio HR: 1.33; 95% CI: 1.13 to 1.56) at 1 year but not with heart failure admission alone (16.5% vs. 12.9%; HR: 1.23; 95% CI: 0.92 to 1.63).

CONCLUSIONS Early PPM implantation is a common complication following TAVR, and it is associated with higher mortality and a composite of mortality or heart failure admission at 1 year. (J Am Coll Cardiol Intv 2016;9:2189–99)

Transcatheter aortic valve replacement (TAVR) is a therapeutic option for the management of patients with symptomatic severe aortic stenosis who have high surgical risk or are deemed inoperable as assessed by a multidisciplinary heart team (1,2). However, conduction abnormalities following TAVR requiring permanent pacemaker (PPM) placement have emerged as important short-term complications, noted in 6.0% to 6.4% for the balloon-expandable Edwards SAPIEN valve (ESV) and 25.4% to 28.0% for the self-expanding Medtronic CoreValve Revalving System (MCRS)

identified at https://www.ncdr.com/WebNCDR/tvt/home. Dr. Vemulapalli has received consulting fees and honoraria from Novella and Premiere; has received travel reimbursement from Abbott Vascular and Philips Medical Systems; and has received research grants from Abbott Vascular, the Agency for Healthcare Research and Quality, the American College of Cardiology, and Boston Scientific. Dr. Vora was funded by National Institutes of Health T-32 training grant T32 HL069749 and L30 HL124592. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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(3,4). Cardiac conduction abnormalities post-TAVR are hypothesized to be due to damage to the atrioventricular and infranodal tissues locally as a result of trauma, ischemia, hemorrhage, or edema during or after the implantation procedure (5). The higher radial force generated with deployment of the MCRS is believed to contribute to its higher rate of conduction abnormalities and pacemaker implantation compared with the ESV (6). Beyond valve type, identified predictors of post-TAVR need for PPM placement include male sex, pre-existing conduction abnormalities, larger prosthesis size, valve oversizing, and increasing implantation depth (4,7–9).

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Studies in non-TAVR patients have shown that isolated right ventricular pacing causes mechanical dyssynchrony similar to left bundle branch block, and this was associated with significant negative long-term outcomes, such as increased heart failure hospitalization and mortality (10–12). Whether PPM implantation post-TAVR is associated with similar adverse clinical outcomes is unclear (13,14). The aim of this study was to evaluate the incidence, predictors, and clinical outcomes of PPM placement post-TAVR in a real-world population using the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) TVT Registry and Centers for Medicare and Medicaid Services database.

METHODS

DATA SOURCES. The STS/ACC TVT Registry is a joint initiative of the STS and the ACC (15). Launched in December 2011, it tracks patient demographics, procedure details, and facility and physician information related to transcatheter valve replacement and repair procedures performed at 388 clinical sites in the United States. The TVT Registry uses a standardized dataset with written definitions, has requirements in place to ensure uniform data entry and transmission, and is subject to data quality checks. There were 2 main valve systems in use in the United States at the time of planning of this study. The balloon-expandable ESV was approved by the U.S. Food and Drug Administration in November 2011, while the self-expanding MCRS was approved in January 2014.

STUDY POPULATION. Patients who underwent TAVR for symptomatic severe aortic stenosis reported in the TVT Registry from November 21, 2011, to September 30, 2014, were included. Only the first TAVR (i.e., index procedure) during the hospital admission was considered. Centers reporting ≤30 cases were excluded to avoid high risk for adverse outcomes from those that recently joined the TVT Registry (16,17). Cases were included if we were able to link to the Centers for Medicare and Medicaid Services database using direct identifiers (name and Social Security number). Exclusion criteria were prior implantation of a pacemaker or implantable cardioverter-defibrillator; intraprocedural pacemaker implantation; unsuccessful procedures; conversion to open procedures; valve systems other than ESV or MCRS; procedure locations other than a hybrid operating room suite, hybrid catheterization suite, or catheterization laboratory; death during procedures; and patients with missing status on PPM implantation at 30-day assessment. Two cohorts were created: 1) PPM implantation, including patients undergoing PPM implantation within 30 days post-TAVR; and 2) no PPM implantation, including patients not undergoing PPM implantation within 30 days post-TAVR.

DEFINITIONS AND OUTCOMES. Valve oversizing percentage was based on a ratio of prosthesis area to aortic valve annular area and was defined as follows: [(prosthesis valve area in cm^2)/(native annular area in cm^2) − 1] × 100 (18).

Outcomes examined were grouped as in-hospital, 30-day, and 1-year outcomes. In-hospital outcomes reported were length of hospital stay and intensive care unit stay, which were collected as part of the TVT Registry. Thirty-day and 1-year outcomes studied were mortality, heart failure admission, a composite of mortality or heart failure admission, and stroke or myocardial infarction, as defined by the Valve Academic Research Consortium 2 endpoint criteria (19). These outcomes were identified using Medicare Denominator File and in-hospital administrative claims files. Follow-up for readmissions was censored at the end of fee-for-service coverage, loss of Part A or B coverage, or the end of follow-up period (October 31, 2014), whichever occurred first.

STATISTICAL ANALYSIS. Baseline characteristics are presented for patients with and without PPM implantation. Categorical variables are reported as counts and percentages, and the 2 cohorts were compared using the Pearson chi-square test or Fisher exact test. Continuous variables are reported as medians with interquartile ranges (IQRs) and were compared using the Wilcoxon rank sum test. The incidence of PPM implantation is reported in the overall population and within subgroups stratified by

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology
CI = confidence interval
ESV = Edwards SAPIEN valve
HR = hazard ratio
IQR = interquartile range
MCRS = Medtronic CoreValve Revalving System
OR = odds ratio
PPM = permanent pacemaker
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement

TABLE 1 Baseline, Electrocardiographic, Imaging, and Procedural Characteristics of the Study Population

	PPM (n = 651)	No PPM (n = 9,134)	p Value
Baseline characteristics			
Age (yrs)	84 (80-88)	84 (78-88)	0.031
Male	339 (52.2)	4,282 (46.9)	0.010
BMI (kg/m^2)	26.9 (23.9-30.6)	26.7 (23.4-31.1)	0.672
STS PROM score (%)	7.3 (4.8-11.2)	6.7 (4.5-10.3)	0.004
NYHA functional class III or IV	528 (82.0)	7,345 (81.3)	0.667
Prior PCI	249 (38.4)	3,174 (34.8)	0.069
Prior CABG	194 (29.8)	2,668 (29.2)	0.758
Prior other cardiac surgery	24 (3.7)	497 (5.5)	0.053
Prior aortic valve procedure	79 (12.1)	1,399 (15.3)	0.028
Aortic valve balloon valvuloplasty*	74 (93.7)	1,235 (88.6)	0.163
Prior stroke	73 (11.2)	1,108 (12.1)	0.482
Peripheral artery disease	221 (34.0)	2,893 (31.7)	0.228
Hypertension	593 (91.7)	8,152 (89.3)	0.057
Diabetes mellitus	236 (36.4)	3,171 (34.7)	0.399
Renal failure	37 (5.7)	445 (4.9)	0.351
Chronic lung disease	323 (50.9)	4,166 (46.1)	0.019
Home oxygen	71 (11.0)	1,304 (14.4)	0.018
Prior myocardial infarction	171 (26.4)	2,231 (24.5)	0.279
Electrocardiographic and imaging characteristics			
Atrial fibrillation/flutter	258 (39.6)	3,369 (36.9)	0.170
Conduction defect	263 (40.9)	2,407 (26.5)	<0.001
Coronary artery disease	510 (78.5)	7,011 (76.9)	0.353
Porcelain aorta	45 (6.9)	602 (6.6)	0.748
Left ventricular ejection fraction (%)	57 (49-65)	58 (50-65)	0.299
Right ventricular systolic pressure (mm Hg)	45 (35-54)	44 (35-55)	0.496
Left ventricular internal diastolic dimension (cm)	4.7 (4.1-5.2)	4.5 (4.0-5.1)	0.003
Aortic valve annular size (mm)	23 (22-25)	22 (21-24)	<0.001
Annular size assessment method†			<0.001
Transthoracic echocardiography	147 (24.2)	2,272 (27.4)	
Transesophageal echocardiography	170 (28.0)	3,094 (37.2)	
CTA	289 (47.6)	2,897 (34.9)	
Angiography	1 (0.2)	44 (0.5)	
Aortic valve area (cm^2)	0.70 (0.56-0.80)	0.66 (0.50-0.80)	0.033
Aortic valve mean gradient (mm Hg)	43 (36-51)	44 (37-53)	0.018
Moderate/severe mitral regurgitation‡	186 (34.1)	2,659 (34.9)	0.718
Procedural characteristics			
Prosthesis size (mm)			<0.001
23	160 (24.7)	3,918 (43.1)	
26	234 (36.1)	4,345 (47.8)	
29	146 (22.5)	567 (6.2)	
31	108 (16.7)	254 (2.8)	
Valve oversizing (%)	31.8 (15.4-46.0)	27.8 (9.3-39.7)	<0.001
Valve type			<0.001
Balloon-expanding ESV	373 (57.6)	8,265 (91.0)	
Self-expanding MCRS	275 (42.4)	821 (9.0)	
Procedure time (min)	116 (92-153)	128 (98-174)	<0.001
Procedure location			0.235
Hybrid operating room suite	404 (62.2)	5,636 (61.8)	
Hybrid catheterization laboratory	158 (24.3)	2,419 (26.5)	
Catheterization laboratory	88 (13.5)	1,066 (11.7)	

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valve type, access site, and procedural risk classification. Comparison of PPM implantation incidence across subgroups was performed using the Pearson chi-square test or Fisher exact test. Time from TAVR to PPM implantation is reported as median and IQR. To identify predictors of PPM implantation post-TAVR, a multivariate logistic regression model was built using pre-specified baseline and procedural characteristics. Missing data on the predictors were handled by multiple imputation with 5 imputed datasets. Results are reported as odds ratios (OR) and 95% confidence intervals (CIs).

The associations between PPM implantation post-TAVR and in-hospital outcomes were assessed using linear regression models. Cumulative incidences of 30-day and 1-year outcomes were compared between patients with and without PPM implantation. Death was considered a competing risk for nonfatal outcomes, including heart failure admission, stroke, and myocardial infarction. Unadjusted and adjusted associations of PPM implantation with 30-day and 1-year outcomes were assessed using Cox proportional hazards models for mortality and composite of mortality or heart failure admission, and Fine and Gray's (20) proportional subdistribution hazards models for nonfatal outcomes. We accounted for the clustering of patients within sites using the generalized estimating equation method with an exchangeable correlation structure. For all outcomes, adjustment for confounders was made using the same covariates as in the short-term mortality predictive model recently developed for the TVT Registry (unpublished data; see the Online Appendix for a list of covariates), and results are presented as hazard ratios (HR) and 95% CIs. A 2-sided p value < 0.05 indicated statistical significance for all tests. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS OF STUDY POPULATION. Data from 229 U.S. sites were included in the final analysis, with a total of 9,785 eligible participants. The baseline characteristics of study participants stratified by PPM implantation are summarized in Table 1. Compared with those who did not undergo PPM implantation, patients who had PPMs implanted post-TAVR were more likely to be men (52.2% vs. 46.9%; p = 0.010), to have a higher STS Predicted Risk of Operative Mortality score (7.3% [IQR: 4.8% to 11.2%] vs. 6.7% [IQR: 4.5% to 10.3%]; p = 0.004), were less likely to have undergone prior aortic valve

procedures (12.1% vs. 15.3%; p = 0.028), and to require home oxygen (11.0% vs. 14.4%; p = 0.018).

ELECTROCARDIOGRAPHIC AND IMAGING CHARACTERISTICS. Electrocardiographic and imaging characteristics of participants are displayed in Table 1. Compared with those who did not undergo PPM implantation, patients who received PPMs were significantly more likely to have electrocardiographic evidence of prior conduction defects (40.9% vs. 26.5%; p < 0.001). Baseline imaging findings showed that patients requiring PPM placement had larger left ventricular internal diastolic dimensions (4.7 cm [IQR: 4.1 to 5.2 cm] vs. 4.5 cm [IQR: 4.0 to 5.1 cm]; p = 0.003), larger aortic valve annular sizes (23 mm [IQR: 22 to 25 mm] vs. 22 mm [IQR: 21 to 24 mm]; p < 0.001), larger aortic valve areas (0.70 cm^2 [IQR: 0.56 to 0.80 cm^2] vs. 0.66 cm^2 [IQR: 0.50 to 0.80 cm^2]; p = 0.033), and lower aortic valve mean gradients (43 mm Hg [IQR: 36 to 51 mm Hg] vs. 44 mm Hg [IQR: 37 to 53 mm Hg]; p = 0.018). Chosen imaging modality to assess annular size was different between the 2 groups (p < 0.001), with patients requiring PPM more likely to have undergone computed tomographic angiography (47.6% vs. 34.9%).

PROCEDURAL CHARACTERISTICS. The procedural characteristics of participants with or without PPM placement are presented in Table 1. Participants who received PPMs were more likely to have larger prostheses implanted (p < 0.001) and higher proxies of valve oversizing (31.8% [IQR: 15.4% to 46.0%] vs. 27.8% [IQR: 9.3% to 39.7%]; p < 0.001).

INCIDENCE OF 30-DAY PPM IMPLANTATION. The incidence of 30-day PPM implantation is presented in Table 2. We found that 651 of 9,785 patients (6.7%) required PPMs within 30 days of TAVR. The median time from TAVR to PPM implantation was 3 days (IQR: 1 to 6 days) (Figure 1). The incidence of 30-day PPM implantation was higher with the self-expanding MCRS (25.1%) compared with the balloon-expanding ESV (4.3%). For patients undergoing transfemoral TAVR, the 30-day incidence was 7.3%, compared with 5.1% for transapical access. Patients who were considered inoperable or at extreme risk were less likely to need PPMs than high-risk patients (4.8% vs. 12.2%).

PREDICTORS OF 30-DAY PPM IMPLANTATION. Significant positive predictors of 30-day PPM implantation after multivariate adjustment (Table 3) were increasing age (OR: 1.07 per 5 years; 95% CI: 1.01 to 1.15; p = 0.033), prior conduction defect (OR: 1.93; 95% CI: 1.63 to 2.29; p < 0.001), aortic valve area when ≤0.75 cm^2 (OR: 1.21 per 0.25-cm^2 increment; 95% CI: 1.00 to 1.45; p = 0.045), and use of the MCRS (OR: 7.56; 95% CI: 5.98 to 9.56; p < 0.001). Negative predictors were prior aortic valve procedure (OR: 0.74; 95% CI: 0.57 to 0.95; p = 0.020), home oxygen use (OR: 0.67; 95% CI: 0.49 to 0.91; p = 0.009), and

TABLE 1 Continued

	PPM (n = 651)	No PPM (n = 9,134)	p Value
Procedural risk classification			<0.001
Inoperable/extreme risk	336 (51.9)	6,630 (72.8)	
High risk (≥8% risk for 30-day mortality)	294 (45.4)	2,124 (23.3)	
Intermediate risk (4%–7% risk for 30-day mortality)	14 (2.2)	96 (1.1)	
Low risk (<4% risk for 30-day mortality)	1 (0.2)	16 (0.2)	
Other	3 (0.5)	239 (2.6)	
Valve sheath access site			<0.001
Femoral	421 (64.7)	5,361 (58.8)	
Axillary/subclavian	9 (1.4)	39 (0.4)	
Transapical	155 (23.8)	2,858 (31.3)	
Transaortic	59 (9.1)	680 (7.5)	
Other	7 (1.1)	187 (2.0)	
Contrast volume (ml)	100 (65–150)	110 (70–160)	0.004
Fluoroscopy time (min)	18.1 (12.4–26.2)	17.1 (11.9–24.5)	0.067
Post-procedural aortic valve gradient	9 (6–12)	10 (7–13)	<0.001
Paravalvular leak§	27 (9.3)	358 (8.2)	0.499

Values are median (interquartile range) or n (%). *Percentages were calculated among patients who had undergone prior aortic valve procedures. †Percentages were calculated among patients with nonmissing data on aortic valve annular size. ‡Percentages were calculated among patients with mitral valve disease. §Percentages were calculated among patients who had aortic regurgitation on post-procedural echocardiography.

BMI = body mass index; CABG = coronary artery bypass graft; CTA = computed tomographic angiography; ESV = Edwards SAPIEN Valve; MCRS = Medtronic CoreValve Revalving System; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; STS PROM = Society of Thoracic Surgeons Predicted Risk of Operative Mortality.

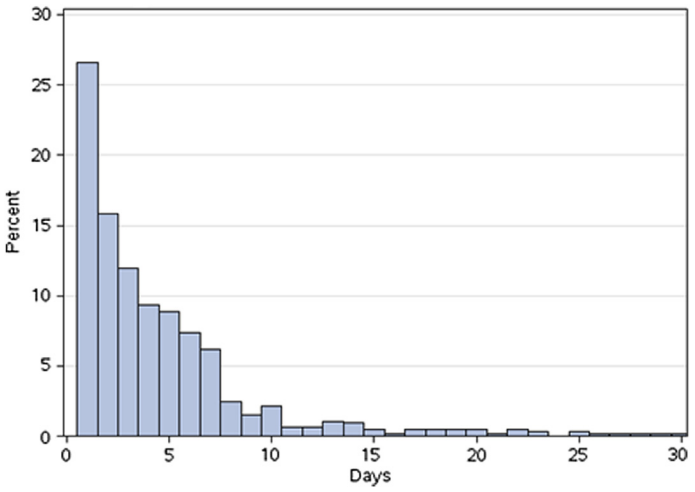
TABLE 2 Incidence of Permanent Pacemaker Implantation Post-Transcatheter Aortic Valve Replacement

	PPM	p Value
Overall	651 (6.7)	
Valve type		<0.001
Balloon-expanding ESV	373 (4.3)	
Self-expanding MCRS	275 (25.1)	
Valve sheath access site		<0.001
Femoral	421 (7.3)	
Axillary/subclavian	9 (18.8)	
Transapical	155 (5.1)	
Transaortic	59 (8.0)	
Other	7 (3.6)	
Procedural risk classification		<0.001
Inoperable/extreme risk	336 (4.8)	
High risk (≥8% risk for 30-day mortality)	294 (12.2)	
Intermediate risk (4%–7% risk for 30-day mortality)	14 (12.7)	
Low risk (<4% risk for 30-day mortality)	1 (5.9)	
Other	3 (1.2)	

Values are n (%).

Abbreviations as in Table 1.

FIGURE 1 Time From Transcatheter Aortic Valve Replacement to Permanent Pacemaker Implantation



The histogram displays frequency distribution of time to permanent pacemaker (PPM) implantation. TAVR = transcatheter aortic valve replacement.

TABLE 3 Significant Predictors* of 30-Day Permanent Pacemaker Implantation

	Odds Ratio (95% CI)	p Value
Age (per 5 yrs)	1.07 (1.01–1.15)	0.033
Prior aortic valve procedure	0.74 (0.57–0.95)	0.020
Home oxygen	0.67 (0.49–0.91)	0.009
Prior conduction defect	1.93 (1.63–2.29)	<0.001
Aortic valve area when ≤0.75 cm^2 (per 0.25 cm^2)	1.21 (1.00–1.45)	0.045
Self-expanding MCRS (vs. balloon-expanding ESV)	7.56 (5.98–9.56)	<0.001
Procedure time (per 30 min)	0.95 (0.92–0.99)	0.017
Procedural risk classification		<0.001
High risk (≥8%) vs. inoperable/ extreme risk	1.85 (1.54–2.21)	<0.001
Intermediate risk (4%–7%) vs. inoperable/extreme risk	1.78 (1.04–3.04)	0.035
Low risk (<4%) vs. inoperable/ extreme risk	0.55 (0.13–2.43)	0.433
Other vs. inoperable/extreme risk	0.26 (0.06–1.11)	0.069
Valve sheath access site		0.010
Axillary/subclavian vs. femoral	0.71 (0.32–1.54)	0.382
Transapical vs. femoral	1.36 (1.10–1.68)	0.004
Transaortic vs. femoral	1.52 (1.09–2.11)	0.013
Other vs. femoral	1.19 (0.59–2.40)	0.636

*Other predictors included in the model were sex, prior percutaneous coronary intervention, prior other cardiac surgery, hypertension, chronic lung disease, procedure location, contrast volume, post-procedural mean aortic valve gradient, and valve oversizing.

CI = confidence interval; other abbreviations as in Table 1.

procedure time (OR: 0.95 per 30-minute increment; 95% CI: 0.92 to 0.99; p = 0.017). Procedural risk classification (p < 0.001) and valve sheath access site (p = 0.010) were also found to predict need for PPM implantation.

IN-HOSPITAL OUTCOMES. Compared with those who did not undergo PPM implantation, patients receiving PPMs within 30 days of TAVR had a longer median hospital stay (7.0 vs. 6.0 days; p < 0.001) and a longer median intensive care unit stay (56.7 vs. 45.0 h; p < 0.001). Following multivariate adjustment, prolonged hospital and intensive care unit stays for the PPM group persisted, as shown in Table 4.

30-DAY AND 1-YEAR CLINICAL OUTCOMES. Cumulative incidences of 30-day and 1-year clinical outcomes are reported in Table 5. There were no differences in the cumulative endpoints at 30 days between the PPM and no-PPM groups. However, at 1 year, compared with those who did not undergo PPM implantation, patients who received PPMs had a higher cumulative incidence of heart failure admission (16.5% vs. 12.9%; p = 0.036), mortality (24.1% vs. 19.6%; p = 0.003), and a composite of mortality or heart failure admission (37.3% vs. 28.5%; p < 0.001). Cumulative incidence curves for important 1-year clinical outcomes are reported in Figures 2A to 2C. After multivariate adjustment, patients who underwent PPM implantation within 30 days of TAVR were at increased risk for mortality (HR: 1.31; 95% CI: 1.09 to 1.58; p = 0.003) and a composite of mortality or heart failure admission (HR: 1.33; 95% CI: 1.13 to 1.56; p < 0.001) at 1 year. However, there was no difference in heart failure admission at 1 year (HR: 1.23; 95% CI: 0.92 to 1.63; p = 0.162).

DISCUSSION

SUMMARY OF FINDINGS. The main findings are summarized as follows: 1) of 9,785 patients with severe aortic stenosis without prior PPM placement, 651 (6.7%) required PPM implantation within 30 days of TAVR; 2) after multivariate adjustment, positive predictors of PPM implantation were older age, prior conduction defect, self-expanding MCRS, high-risk patients, and transapical or transaortic access, while negative predictors were prior aortic valve procedure and home oxygen use; 3) PPM implantation was associated with longer hospital and intensive care unit stays; and 4) PPM implantation was associated with increased 1-year mortality and composite of mortality or heart failure admission for both adjusted and unadjusted analyses.

TABLE 4 Effects of Permanent Pacemaker Implantation on In-Hospital Clinical Outcomes

	PPM		No PPM		Adjusted Coefficient Estimate (95% CI)	p Value
	n	Median (IQR)	n	Median (IQR)		
Length of hospital stay (days)	589	7.0 (5.0–10.0)	8,307	6.0 (4.0–8.0)	1.6 (1.3–1.9)	<0.001
ICU stay (h)	532	56.7 (33.8–98.2)	7,909	45.0 (25.5–72.0)	19.5 (15.6–23.4)	<0.001

Covariates used for adjustment are listed in the Online Appendix.
ICU = intensive care unit; IQR = interquartile range; other abbreviations as in Tables 1 and 3.

INCIDENCE AND TIMING OF PPM IMPLANTATION. We found a 30-day PPM rate of 6.7% in this study. The self-expanding MCRS was used in 11.2% of the procedures in this study, and there was a PPM implantation rate of 25.1%, which is comparable with those of similar studies (8). Most of the procedures (88.3%) in the TVT Registry at the time of analysis used the balloon-expandable ESV, and we found a PPM rate of 4.3%, which is lower than previously reported rates of 6.2% to 8.8% in a similar cohort (13,21). This may be due to the sicker population in these 2 other studies, as evidenced by higher STS Predicted Risk of Operative Mortality scores. Interestingly, Mack et al. (22) in 2013, using the same TVT Registry (restricted to the ESV), reported a 6.6% PPM implantation rate post-TAVR. A possible explanation is that the learning curve for TAVR may have improved in the United States, thus leading to lower complication rates.

Conduction abnormalities usually occur either during or immediately after the TAVR procedure (6). Most studies reported a median time of 3 days from TAVR to PPM implantation, and almost 90% of PPMs were implanted within 7 days of TAVR (13,14,23). The timing of pacemaker implantation found in our study was similar (Figure 1). It should be noted that conduction abnormalities can occur at a later time, and these are believed to be due to edema and late expansion of the prosthesis (6,24).

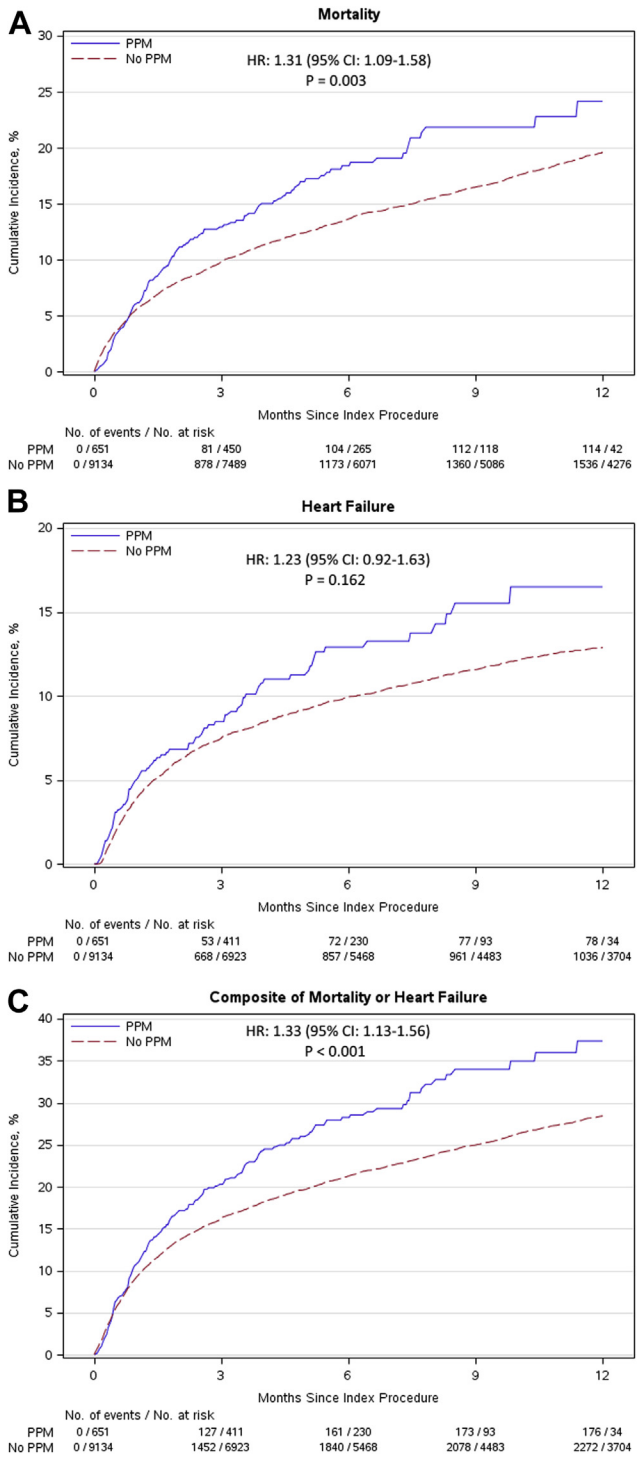
PREDICTORS OF PPM IMPLANTATION (MULTIVARIATE ADJUSTMENT). Consistent with previously reported studies, we found absence of prior aortic valve procedure, prior conduction abnormalities, transapical or transaortic access, and use of the self-expanding MCRS to be associated with increased odds of PPM placement in multivariate analysis (4,9,13). Although the TVT Registry does not collect information on the conduction abnormalities leading to PPM placement, the most commonly reported abnormality is preexisting right bundle branch block (6,13). We found age to be a predictor of post-TAVR PPM implantation.

TABLE 5 Cumulative Incidence of Clinical Outcomes and Unadjusted and Adjusted Associations of Permanent Pacemaker Implantation With Clinical Outcomes

Outcomes	PPM		No PPM		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p Value*
	Number of Events	Rate, % (95% CI)	Number of Events	Rate, % (95% CI)			
30-day							
Mortality	39	6.0 (4.4–8.1)	507	5.6 (5.1–6.0)	1.07 (0.78–1.48)	1.04 (0.74–1.46)	0.822
Heart failure	32	4.9 (3.5–6.9)	352	3.9 (3.5–4.3)	1.29 (0.85–1.93)	1.20 (0.78–1.85)	0.406
Composite of mortality or heart failure	69	10.6 (8.5–13.3)	838	9.2 (8.6–9.8)	1.16 (0.90–1.49)	1.10 (0.84–1.45)	0.501
Stroke	14	2.2 (1.3–3.6)	229	2.5 (2.2–2.8)	0.86 (0.49–1.49)	0.74 (0.41–1.33)	0.320
MI	2	0.3 (0.1–1.2)	83	0.9 (0.7–1.1)	0.34 (0.09–1.31)	0.35 (0.09–1.36)	0.131
1-year							
Mortality	114	24.1 (19.6–29.7)	1,536	19.6 (18.7–20.5)	1.33 (1.13–1.58)†	1.31 (1.09–1.58)	0.003
Heart failure	78	16.5 (12.9–21.1)	1,036	12.9 (12.2–13.7)	1.25 (0.95–1.63)	1.23 (0.92–1.63)	0.162
Composite of mortality or heart failure	176	37.3 (31.9–43.7)	2,272	28.5 (27.5–29.5)	1.36 (1.17–1.57)†	1.33 (1.13–1.56)	<0.001
Stroke	18	3.1 (1.9–5.0)	345	4.1 (3.7–4.5)	0.79 (0.50–1.27)	0.74 (0.45–1.20)	0.217
MI	8	1.7 (0.8–3.4)	187	2.5 (2.1–2.9)	0.76 (0.37–1.52)	0.78 (0.38–1.61)	0.509

Covariates used for adjustment are listed in the Online Appendix. *p value for adjusted analyses. †p value for unadjusted analyses < 0.001.
HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Tables 1 and 3.

FIGURE 2 1-Year Clinical Outcomes



Cumulative incidence curves for 1-year mortality **(A)**, heart failure admission **(B)**, and composite of mortality or heart failure admission **(C)**. CI = confidence interval; HR = hazard ratio; PPM = permanent pacemaker.

Just 1 study to our knowledge has previously shown this association, and that study included only patients who had undergone transapical TAVR (21). Compared with inoperable or extreme-risk patients, high-risk patients were more likely to undergo PPM implantation post-TAVR. In the present study, about 1.1% of all TAVRs were in intermediate-risk patients. Data on this subset were recently published by the PARTNER (Placement of Aortic Transcatheter Valves) 2 investigators (25). Home oxygen use was associated with decreased need for post-TAVR PPM placement. A potential explanation for reduced PPM rates in these 2 sick cohorts, inoperable or extreme-risk patients and home oxygen users, might be less valve oversizing, as operators may rationalize that any valve implanted would probably outlast these patients.

IN-HOSPITAL OUTCOMES. Placement of a PPM was associated with a significantly prolonged hospital stay, similar to that reported by Nazif et al. (13). We also found that PPM implantation was associated with prolonged intensive care unit stay. This has economic significance, as the index admission cost (not including the cost of follow-up care) of each TAVR procedure, including hospitalization, was estimated at more than $73,000 in the PARTNER A trial (26). That trial noted a longer mean hospital stay (10.2 ± 7 days) and intensive care unit stay (3.2 ± 2 days) compared with the present analysis (7.1 ± 4.3 days and 2.4 ± 1.7 days, respectively). A French study found that the need for PPM implantation was associated with a 36% increase in cost associated with TAVR (27). In contrast, Babaliaros et al. (28) noted that length of hospital and intensive care unit stays but not PPM requirement were predictors of cost on multivariate analysis. Reduction of need for placement of PPM post-TAVR may be of significant benefit in controlling procedural cost.

1-YEAR MORTALITY. Our study's 1-year increased all-cause mortality in those with PPM implantation has not been previously described. A smaller recent study of 1,973 patients (all receiving the ESV) from the PARTNER trial and a continued-access registry noted a trend toward increased 1-year mortality in patients with new PPMs, but it did not reach statistical significance. However, there was an increase in the composite endpoint of mortality or repeat hospitalization (13). That study differs from our study in 2 ways: 1) it included only patients with the balloon-expandable ESV; and 2) there was no multivariate adjustment. A follow-up study from the PARTNER

trial group using a propensity-matched analysis found that the presence of a new PPM also showed a trend toward increased mortality, rehospitalization, and a composite endpoint of mortality or rehospitalization (29). Another study of 1,556 patients (55% receiving the ESV) showed no difference in mortality, heart failure rehospitalization, or a composite of the 2 outcomes after a median follow-up period of 22 months. Interestingly, that study noted a lower rate of unexpected death in patients with PPMs (14). Other smaller studies have also not found an association between mortality and PPM implantation post-TAVR (8,9,21,23). After multivariate adjustment, we found that PPM implantation in TAVR patients was associated with a 31% increased risk for 1-year mortality and a 33% increased risk for a composite of mortality or heart failure admission at 1 year. One reason others showed nonsignificant trends while we demonstrated a difference may be due to the increased power as a result of our study's size, which was 5 times larger than the next largest mentioned previously. Unfortunately, our data did not have the specificity that would have enabled us to explore the cause of deaths in these patients. The study by Nazif et al. (13) found that noncardiovascular deaths may be the primary contributor to the increased mortality.

HEART FAILURE HOSPITALIZATION. Right ventricular pacing causes mechanical dyssynchrony similar to left bundle branch block, which was associated with increased heart failure hospitalization and mortality in non-TAVR patients (10–12,30). In TAVR patients, no study, including the present one, has demonstrated an association between right ventricular pacing and heart failure hospitalization (8,14). However, in the present study, there was a nonsignificant trend toward higher 1-year heart failure admissions. The potential reasons for an absence of negative outcomes in right ventricular paced TAVR patients were clearly elucidated in a recent editorial comment by Urena and Rodés-Cabau (31). First, TAVR patients are older and have more comorbidities than patients in these other studies. Thus, the differential effect of right ventricular pacing may not be readily apparent in the sicker TAVR population, which may not live long enough to see the deleterious effects (12,32). The longest follow-up after PPM implantation in TAVR patients is less than 2 years. Second, pacing dependency >40% is a predictor of the development of heart failure (11,33). More than one-half of TAVR patients requiring PPM implantation are not pacing dependent at follow-up (34). Third, isolated right ventricular pacing is more likely to be associated with adverse outcomes in patients with reduced left ventricular ejection fractions at baseline (10,30). Most TAVR studies, including this one, have a mean left ventricular ejection fraction that is >50%. Unfortunately, in our study, there was no information on the type of pacemaker inserted as well as pacing dependency at 1-year, and as such we are unable to explore this further.

STUDY LIMITATIONS. Despite the adjustment for potential confounders in multivariate analysis, we cannot rule out the possibility of selection bias in this cohort. Furthermore, study participants and physicians determining outcomes were not blinded to interventions. As this was a registry, the granularity of the data limited further analysis to explore other potential associations. For example, there was no information on indication for PPM placement post-TAVR as well as the type of PPM implanted. Similarly, there was no information on cause of death that may have allowed us explore the reasons for a potential increase in mortality following PPM implantation in TAVR patients. Finally, the question of pacing dependency and its relation to later adverse left ventricular function remains a potential unmeasured confounder in our study cohort, as these data were not available to us.

CONCLUSIONS

In a real-world clinical registry, we found that conduction abnormalities leading to PPM placement are frequent complications following TAVR for symptomatic severe aortic stenosis. Several factors, including patient or procedural characteristics, may predict which patients are likely to develop this complication. PPM placement may be associated with negative long-term outcomes, such as mortality and a composite of mortality or heart failure. As TAVR indications expand to include lower risk patients with aortic stenosis, interventions to curtail the need for PPM placement are needed, as well as further studies to confirm or refute its association with adverse outcomes reported in this study.

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PERSPECTIVES

WHAT IS KNOWN? Conduction abnormalities leading to PPM implantation are common complications following TAVR; however, it is unclear if there is an association with adverse outcomes.

WHAT IS NEW? PPM placement may be associated with negative short-term outcomes such as prolonged length of hospital stay and intensive care unit stay and long-term outcomes such as mortality and a composite of mortality or heart failure.

WHAT IS NEXT? More studies are needed to examine closely the association between PPM placement (including the role of pacing dependency) and negative clinical outcomes. In addition, the use of biventricular pacemaker as an alternative to right ventricular pacemaker in preventing decline in left ventricular function and subsequent heart failure hospitalization needs to be examined.

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KEY WORDS aortic stenosis, heart failure, mortality, pacemaker, registry, transcatheter aortic valve replacement

APPENDIX For a list of covariates in the short-term mortality predictive model, please see the online version of this article.

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