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Permanent Pacemaker Implantation and Long-Term Outcomes of Patients Undergoing Concomitant Mitral and Tricuspid Valve Surgery

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ABSTRACT

BACKGROUND Tricuspid valve annuloplasty (TA) during mitral valve repair (MVr) is associated with increased risk of permanent pacemaker (PPM) implantation, but the magnitude of risk and long-term clinical consequences have not been firmly established.

OBJECTIVES This study assesses the incidence rates of PPM implantation after isolated MVr and following MVr with TA as well as the associated long-term clinical consequences of PPM implantation.

METHODS State-mandated hospital discharge databases of New York and California were queried for patients undergoing MVr (isolated or with concomitant TA) between 2004 and 2019. Patients were stratified by whether or not they received a PPM within 90 days of index surgery. After weighting by propensity score, survival, heart failure hospitalizations (HFHs), endocarditis, stroke, and reoperation were compared between patients with or without PPM.

RESULTS A total of 32,736 patients underwent isolated MVr (n = 28,003) or MVr + TA (n = 4,733). Annual MVr + TA volumes increased throughout the study period ($P < 0.001$, trend), and PPM rates decreased ($P < 0.001$, trend). The incidence of PPM implantation <90 days after surgery was 7.7% for MVr and 14.0% for MVr + TA. In 90-day conditional landmark-weighted analyses, PPMs were associated with reduced long-term survival among MVr (HR: 1.96; 95% CI: 1.75-2.19; $P < 0.001$) and MVr + TA recipients (HR: 1.65; 95% CI: 1.28-2.14; $P < 0.001$). In both surgical groups, PPMs were also associated with an increased risk of HFH (HR: 1.56; 95% CI: 1.27-1.90; $P < 0.001$) and endocarditis (HR: 1.95; 95% CI: 1.52-2.51; $P < 0.001$), but not with stroke or reoperation.

CONCLUSIONS Compared to isolated MVr, adding TA to MVr was associated with a higher risk of 90-day PPM implantation. In both surgical groups, PPM implantation was associated with an increase in mortality, HFH, and endocarditis. (J Am Coll Cardiol 2024;83:1656-1668) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Conduction abnormalities are a known complication of valvular heart surgery, with incidence rates varying as a function of patient age, baseline conduction system disease, preoperative arrhythmias, and the types and number of valve operations performed.[1,2] Mitral valve surgery, with or without tricuspid annuloplasty (TA), has a recognized risk of permanent pacemaker (PPM) implantation because of the proximity of the atrioventricular node to the valve annuli.[3,4] Recently, the CTSN (Cardiothoracic Surgical Trials Network) conducted a trial in patients with degenerative mitral regurgitation comparing mitral valve surgery (MVS) alone to MVS with concomitant TA in patients with less than severe tricuspid regurgitation (TR). Recipients of MVS + TA had a lower rate of the composite primary endpoint of death, reoperation for TR, or progression of TR at 2 years, driven largely by a reduction in TR progression.[5] However, the rate of PPM implantation was significantly higher for those who also underwent TA (16.0% for recipients of MVS + TA vs 3.2% for recipients of MVS alone at 2 years after randomization).[6] As such, the net value of TA at the time of MVS must account for the tradeoff between the potential benefit of less TR progression vs the longer-term risks associated with PPM implantation.

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Knowledge of the long-term clinical consequences associated with a PPM after valvular heart surgery is based mostly on evidence derived from observational studies, which have reported conflicting findings. Single-institution retrospective cohort studies in MVS patients have found no differences in 5-year survival among patients with or without PPMs.[7] On the contrary, several retrospective analyses in patients undergoing surgical aortic valve replacement have reported reduced survival related to long-term PPM implantation.[8,9] In addition, patients with PPMs are at risk for the development of TR as well as device-associated complications, including infection.[10-13] Establishing more precise estimates of these risks based on longer-term follow-up will help to inform clinical decision-making regarding the appropriate use of concomitant TA in patients undergoing MVS.

In this analysis, we used large, multicenter hospital discharge databases of all cardiac surgery in New York and California to assess the incidence of PPM implantation after mitral valve repair (MVr) with or without TA and the long-term clinical consequences thereafter.

METHODS

STUDY DESIGN. In this retrospective cohort study, we assessed the incidence of PPM implantation in patients who underwent MVr with or without concomitant TA during the years 2004 through 2019. We analyzed survival and major adverse events associated with receipt of a postoperative PPM. In the PPM group, we also analyzed pacemaker-related events, such as lead removal. We used New York's Statewide Planning and Research Cooperative System and the Department of Health Care Access and Information of California State mandatory all-payer discharge databases that include inpatient and outpatient records from all licensed hospitals and treatment facilities in these states. This study was approved by the privacy board of the New York State Department of Health, Committee for the Protection of Human Subjects of the State of California Health and Human Services Agency, and Institutional Review Board of Icahn School of Medicine at Mount Sinai New York. The approval included a waiver of informed consent.

PATIENT POPULATION AND HOSPITAL CHARACTERISTICS. We identified patients who underwent isolated MVr or MVr + TA using the International Classification of Diseases (ICD)-9th Revision-Clinical Modification procedure codes for patients discharged before

ABBREVIATIONS AND ACRONYMS

CL = confidence limit
CTSN = Cardiothoracic Surgical Trials Network
HFH = heart failure hospitalization
ICD = International Classification of Diseases
IPTW = inverse probability treatment weighting
MVR = mitral valve replacement
MVr = mitral valve repair
MVS = mitral valve surgery
PPM = permanent pacemaker
sHR = subdistribution HR
SMD = standardized mean difference
TA = tricuspid annuloplasty
TR = tricuspid regurgitation

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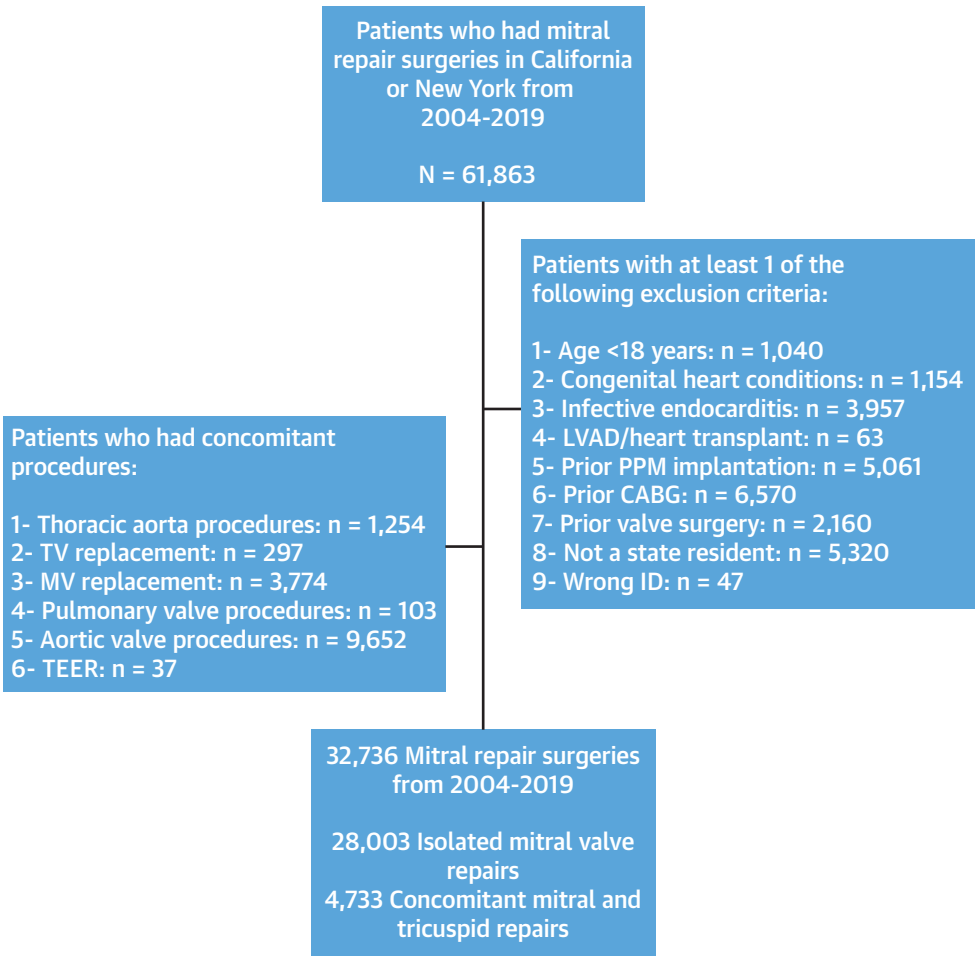
FIGURE 1 Flowchart Illustrating the Sample Selection Process and Exclusion Criteria



After application of exclusion criteria, 32,736 patients were included in the analysis: 28,003 had isolated MV repair, and 4,733 had MV repair with concomitant tricuspid annuloplasty. CABG = coronary artery bypass graft surgery; ID = unique patient identifier; LVAD = left ventricular assist device; MV = mitral valve; PPM = permanent pacemaker; TEER = transcatheter edge-to-edge repair of mitral valve; TV = tricuspid valve.

October 1, 2015, and the ICD-10th Revision-Procedures Coding System for patients discharged after that time (Supplemental Table 1). Using ICD codes, we identified all patients who underwent surgical repair of the mitral valve and were discharged between January 1, 2004, and December 31, 2019, in California and those in New York State as described previously.[1] All patients were followed through December 31, 2020. For each patient, we reviewed records back to January 1, 1995, in New York and to January 1, 1990, in California to identify a history of PPM implantation, previous heart surgery, and chronic comorbidities. Patients were excluded from the analysis if they had a history of coronary artery bypass grafting, any previous valve surgery, pacemaker or defibrillator implantation, infective endocarditis, left ventricular assist device implantation, heart transplantation, or any congenital heart disease. In addition, patients were excluded if the index procedure included thoracic aorta surgery or valve procedures other than mitral or tricuspid repair. In addition, we excluded patients <18 years of age as well as nonresidents of New York State or California at the time of the index procedure (**Figure 1**). In determining the specifications of our study cohort, we analyzed the trend in MVrs and found that the number of operations increased and subsequently plateaued in 2004 (Supplemental Figure 1). To minimize the potential influence of temporal improvements in surgical technique, we limited the study cohort to patients

discharged after January 1, 2004. The resultant study population included 32,736 patients.

To ensure that we captured past medical history relevant to the analysis, a minimum of 9 years of data before the index MVr was examined for each patient in the study. All codes used to define index procedures, PPM implantation, and outcomes are listed in Supplemental Table 1. The date of death was identified by linking the state's vital death records to the discharge data set. In addition, we searched for deaths in all hospital admissions as well as ambulatory and emergency department visit data.

Hospital surgical volume was defined as the number of MVr surgeries each performed in a specific year. High surgical volume for a given hospital was defined as at least 50 MVrs per year throughout the study period.

STUDY ENDPOINTS. The primary endpoint of the study was survival after index surgery. Secondary endpoints included stroke, heart failure hospitalization (HFH), infective endocarditis, and reoperation (MVr or mitral valve replacement [MVR] or mitral valve transcatheter edge-to-edge repair). HFH was identified when there was a postindex surgery hospitalization with heart failure as the primary diagnosis and no presurgical history of heart failure. Finally, the incidence of PPM-related complications, such as lead removal and device pocket relocation/revision, was assessed after both isolated MVr and concomitant MVr + TA.

STATISTICAL ANALYSIS. Baseline characteristics are reported as n (%) or median (Q1-Q3), as appropriate. Because of the large sample size, the differences in baseline characteristics between groups were evaluated using the absolute value of standardized mean differences (SMDs).

To control for confounding between patients who did and did not receive a postoperative PPM, we used inverse probability treatment weighting propensity analysis. We ran a logistic regression to estimate each patient's probability of receiving a PPM within 90 days of surgery. For each patient, age, sex, race, admission type, insurance status, all comorbidities, concomitant procedures (coronary artery bypass grafting or surgical ablation), year of procedure, and annual hospital surgical volume were included as covariates. Self-identified race was missing from 1.3% of records. Because we do not report specific racial/ethnic results, we treat the "missing/unknown" values as a separate category in our analysis. We stabilized weights by dividing the marginal probability of the observed treatment by the propensity score for the treatment received with trimming the 0.5% extreme weights (n = 9). The balance between treatment groups was assessed with the use of SMDs. A standardized difference of 10% or less was considered the ideal balance, and a standardized difference of 20% or less was deemed to be an acceptable balance.

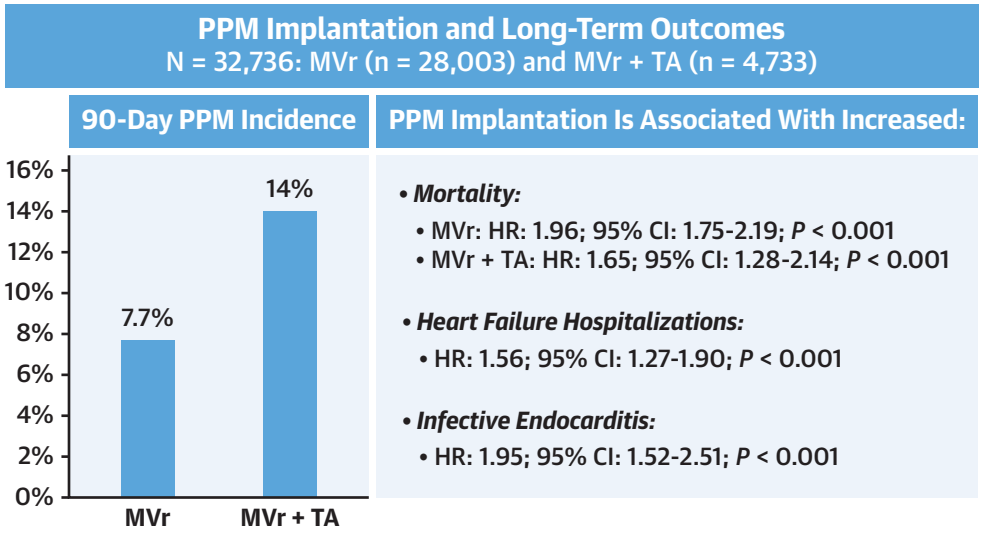
Four cohorts of patients were used in the analysis: all surgical procedures with or without PPM at 90 days, isolated MVr with or without PPM at 90 days, concomitant MVr + TA with or without PPM at 90 days, and all MVr procedures for patients with no history of heart failure. To distinguish between complications following surgery and those related to the PPM, landmark analysis was used to assess the adverse outcomes after PPM where time zero is 90 days postsurgery. A weighted Cox proportional hazards regression model with a robust variance estimator was used to compare long-term survival among groups. The cumulative incidence of secondary outcomes was analyzed using the subdistribution Fine and Gray method with death treated as a competing event.[14] The subdistribution HR is reported for secondary outcomes. The proportional hazard assumption was validated using Schoenfeld residuals.

For sensitivity analysis, a proportional hazards model was used with PPM implantation as a time-varying variable and the date of surgery as time zero. In addition, we repeated the landmark analysis by removing patients who had a history of atrial fibrillation or concomitant surgical ablation. In addition, we ran analyses that included all 32,736 patients to test the bivariable associations between PPM and survival, HFHs, and endocarditis (unadjusted analyses). Then, we conducted multivariable analyses with the following outcomes: survival, HFHs, and endocarditis with the mentioned covariates (sociodemographics, comorbidities, concomitant procedures, year of procedure, and annual hospital surgical volume). For trend analysis, the JoinPoint regression program version v4.8.0.1 was used to calculate annual percent change in surgery counts and PPM implantation rates. The statistical significance threshold for all tests was 0.05. Data extraction and statistical analysis were performed using SAS, version 9.4 (SAS Institute Inc).

RESULTS

STUDY POPULATION. A total of 32,736 patients were identified who had their initial MVr in California or New York State between 2004 and 2019 and had at least 9 years of available prior medical history. The median follow-up time was 6.6 years (Q1-Q3: 3.3-10.7

CENTRAL ILLUSTRATION Permanent Pacemaker Implantation and Long-Term Outcomes



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MVr = mitral valve repair; PPM = permanent pacemaker; TA = tricuspid annuloplasty.

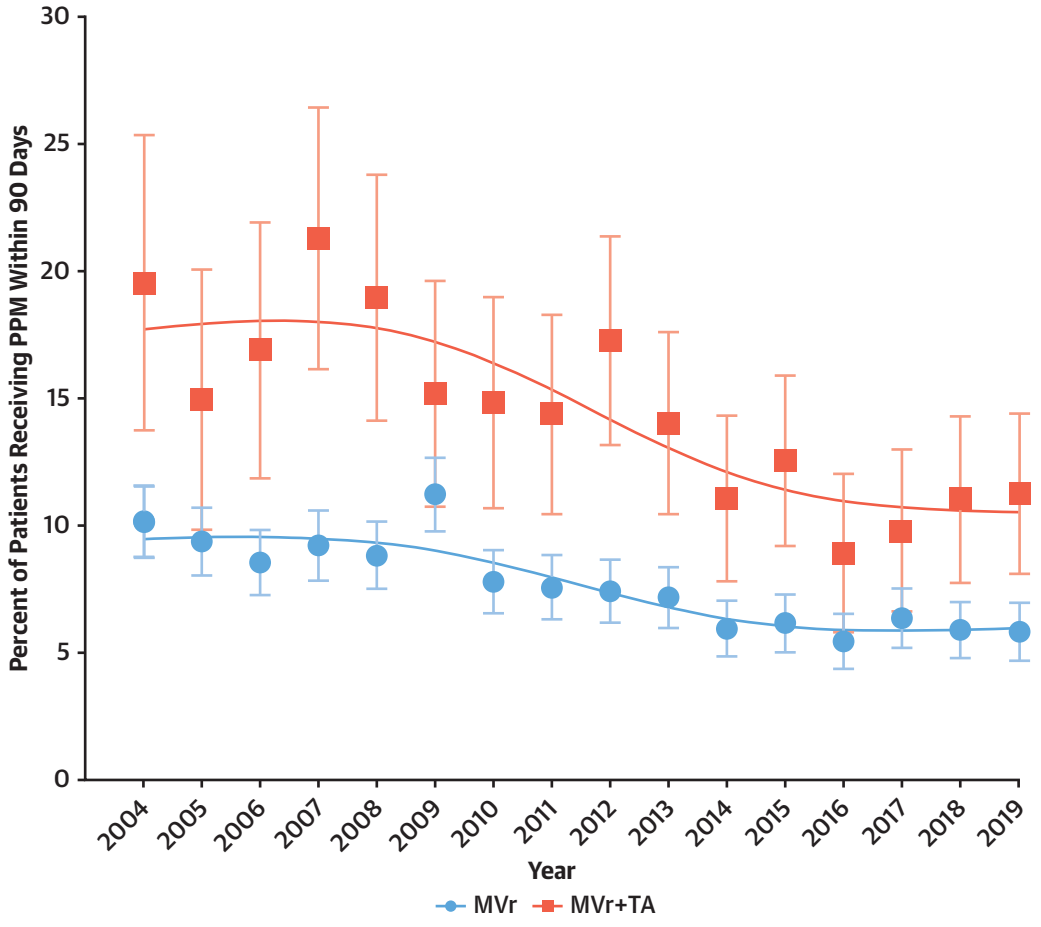
years). In these patients, 8.6% received a PPM within 90 days. In patients who had MVr alone (28,003; 85.5%), 7.7% (2,165) received a PPM within 90 days after surgery (Central Illustration). MVr and concomitant TA were performed in 15.5% (4,733) of patients, and 14% (661) received PPMs. As such, patients undergoing MVr + TA had a significantly higher incidence of PPM implantation compared to those undergoing MVr alone ($P < 0.001$). Figure 2 depicts the trend in PPM implantation rate after isolated MVr and concomitant MVr + TA. The incidence rate of PPM implantation within 90 days of surgery declined for both surgical groups, with an annual percent change of −4.05% for isolated MVr ($P < 0.001$) and −4.4% for concomitant MVr + TA ($P < 0.001$). The rate of PPM implantation for patients with no baseline history of atrial fibrillation was 6.8% (1,421 of 20,846) and for patients without concomitant surgical ablation was 8.5% (2,582 of 30,443).

BASELINE CHARACTERISTICS. In the overall cohort (Table 1), the median age was higher among those who received a PPM within 90 days of surgery compared to those who did not (69 years [Q1-Q3: 62-77 years] vs 64 years [Q1-Q3: 55-72 years]; SMD: 45%). A greater proportion of men received PPM than women (56.7% vs 43.3%). Patients who received a PPM had more conduction system disorders at baseline (21.7% vs 7.9%; SMD: 61%). Greater than one-half (55.1%) of MVrs were performed in high-volume hospitals (≥50 MVrs per year). The incidence of PPM implantation in high-volume hospitals was 7.7% vs 9.8% in hospitals with <50 MVrs per year ($P < 0.001$). Patients with PPM implantation during the index hospitalization had longer hospital stays (median: 12 days [Q1-Q3: 9-18 days] vs 7 days [Q1-Q3: 5-11 days]).

Supplemental Tables 2 and 3 provide baseline characteristics of the cohort undergoing isolated MVr and those undergoing MVr + TA. Supplemental Table 4 stratifies these characteristics by history of heart failure. Before propensity score weighting, intergroup differences were observed in prior atrial fibrillation, diabetes, and coronary artery disease that was unrevascularized. After applying inverse probability treatment weights, a good balance was achieved in the baseline characteristics of patients across all groups as evidenced by SMDs, shown in Table 1 and Supplemental Tables 2 to 4.

SURVIVAL. In the landmark survival analysis, PPM implantation after all types of surgery (with and without TA) was associated with a higher long-term mortality risk compared with surgery without PPM implantation (HR: 1.90; 95% CI: 1.73-2.09; $P < 0.001$). Landmark survival analysis showed that for both the

FIGURE 2 The Trend in 90-Day PPM Implantation



The trend in 90-day PPM implantation for both isolated MVr and the combined MVr + TA procedure. The blue circles correspond to the mean annual rates of 90-day PPM implantation following isolated MVr, and the red squares correspond to the mean annual rates following MVr + TA. The error bars represent 95% confidence levels. The trend lines were constructed using LOESS (locally estimated scatterplot smoothing), a nonparametric method for smoothing a series in which no assumptions are made about the underlying structure of the data. The rates of PPM implantations decreased over time but were higher after MVr + TA than MVr. MVr = mitral valve repair; PPM = permanent pacemaker; TA = tricuspid annuloplasty.

isolated MVr group (HR: 1.96; 95% CI: 1.75-2.19; $P < 0.001$) and the MVr + TA group (HR: 1.65; 95% CI: 1.28-2.14; $P < 0.001$), PPM implantation was associated with a higher hazard of death than surgery without PPM implantation (**Figure 3**). Results of analyses without inverse probability treatment weighting (IPTW) are presented in Supplemental Figures 2 and 3.

SECONDARY OUTCOMES. In secondary landmark adjusted analysis, MVr patients who received a PPM had a higher cumulative incidence of infective endocarditis (subdistribution HR [sHR]: 1.95; 95% CI: 1.52-2.51; $P < 0.001$) and HFH (sHR: 1.56; 95% CI: 1.27-1.90; $P < 0.001$) compared to patients who did not have a PPM. There was no difference in the incidence of stroke (sHR: 1.05; 95% CI: 0.82-1.35; $P = 0.68$) or reoperation (sHR: 0.92; 95% CI: 0.70-1.21; $P = 0.54$) by PPM status (**Figure 4**). Results of landmark analysis are shown in Supplemental Figure 4.

Among patients who received PPMs within 90 days after surgery, the median time to PPM-related complications (ie, lead removal or pocket revision) was 6.4 years (Q1-Q3: 2.9-10.5 years) for isolated MVr and 5.9 years (Q1-Q3: 2.7-9.7 years) for MVr + TA ($P = 0.03$). The 16-year cumulative incidence of PPM complications was not different in the isolated MVr group compared to the concomitant MVr + TA group

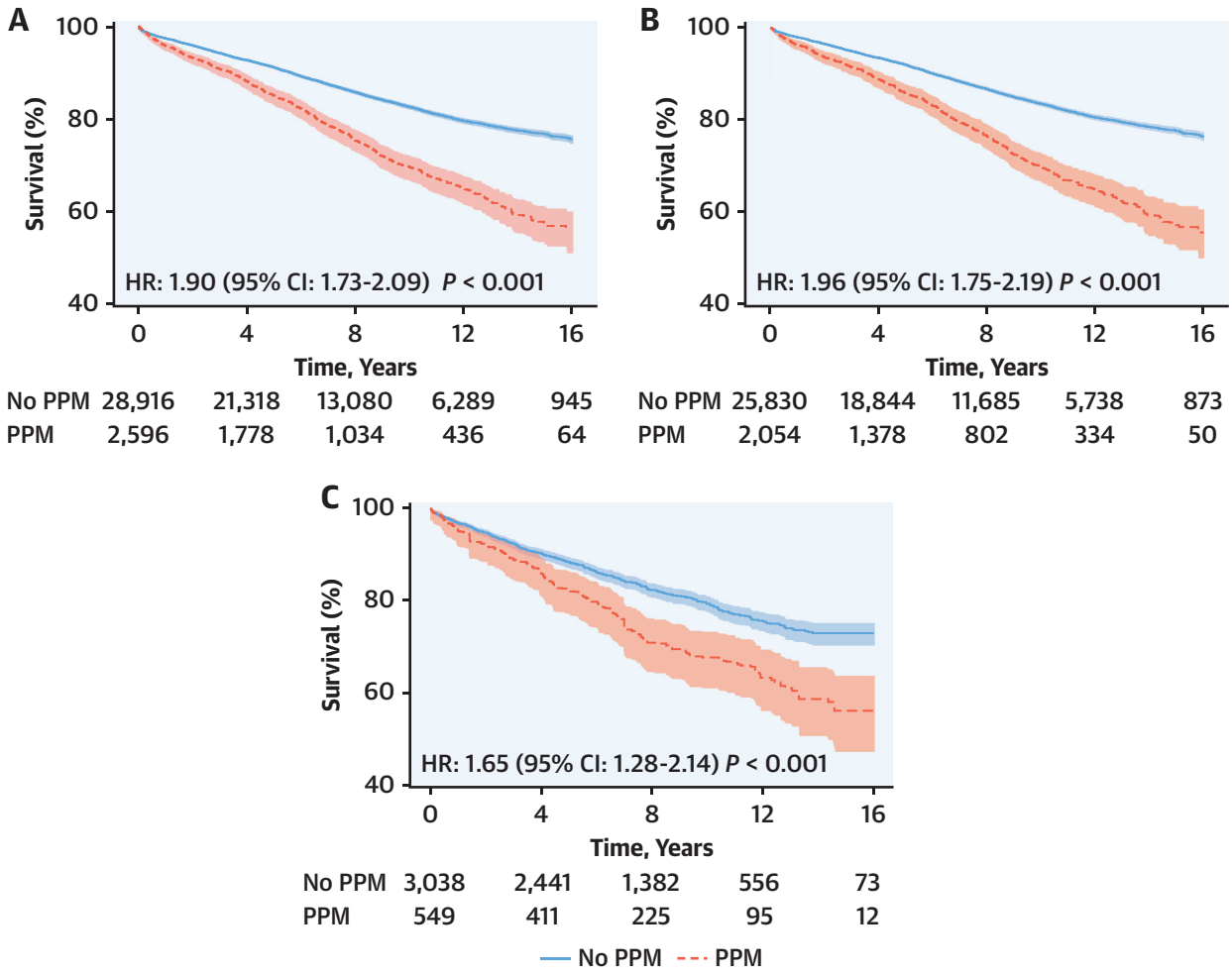
TABLE 1 Patient Baseline Characteristics in the Overall Cohort and According to PPM Implantation

	Observed				Weighted by Propensity Score			
	All (N = 32,736)	Without PPM (n = 29,910)	With PPM (n = 2,826)	SMD, %	All (N = 32,729)	Without PPM (n = 29,974)	With PPM (n = 2,678)	SMD, %
Age, y	65 (56-73)	64 (55-72)	69 (62-77)	45	65 (56-73)	65 (56-73)	66 (58-74)	0.2
Sex								
Male	19,849 (60.6)	18,247 (61.0)	1,602 (56.7)	9	19,745 (60.3)	18,159 (60.7)	1,586 (56.1)	0.2
Female	12,887 (39.4)	11,663 (39.0)	1,224 (43.3)	—	12,907 (39.4)	11,815 (39.5)	1,092 (38.7)	—
Insurance status								
Medicare	15,039 (45.9)	13,278 (44.4)	1,761 (62.3)	37	15,146 (46.3)	13,804 (46.2)	1,341 (47.5)	2.1
Medicaid	3,133 (9.6)	2,846 (9.5)	287 (10.2)	2	3,131 (9.6)	2,871 (9.6)	261 (9.2)	0.1
Private insurance	13,542 (41.4)	12,855 (43.0)	687 (24.3)	40	13,364 (40.8)	12,368 (41.4)	996 (35.3)	1.8
Uninsured	404 (1.2)	368 (1.2)	36 (1.3)	0	392 (1.2)	368 (1.2)	24 (0.9)	0.9
Other insurance	618 (1.9)	563 (1.9)	55 (1.9)	0	619 (1.9)	564 (1.9)	55 (1.9)	0.7
Race/ethnicity								
White	23,136 (70.7)	21,258 (71.1)	1,878 (66.5)	10	23,018 (70.3)	21,159 (70.8)	1,859 (65.8)	0.3
Black	2,182 (6.7)	1,957 (6.5)	225 (8.0)	5	2,210 (6.8)	2,009 (6.7)	201 (7.1)	1.2
Hispanic	2,784 (8.5)	2,479 (8.3)	305 (10.8)	9	2,782 (8.5)	2,559 (8.6)	224 (7.9)	0.7
Asian	2,433 (7.4)	2,177 (7.3)	256 (9.1)	6	2,449 (7.5)	2,235 (7.5)	214 (7.6)	0.6
Other	1,774 (5.4)	1,642 (5.5)	132 (4.7)	5	1,688 (5.2)	1,621 (5.4)	147 (5.3)	2.6
Missing	427 (1.3)	397 (1.3)	30 (1.1)	1	424 (1.3)	391 (1.3)	33 (1.2)	0.3
Type of admission								
Scheduled	21,982 (67.1)	20,458 (68.4)	1,524 (53.9)	30	21,861 (66.8)	20,096 (67.2)	1,764 (62.5)	2.4
Unscheduled	10,754 (32.9)	9452 (31.6)	1,302 (46.1)	—	10,791 (33.0)	9,878 (33.0)	913 (32.3)	—
Comorbidities								
Hypertension	22,886 (69.9)	20,623 (69.0)	2,263 (80.1)	26	22,922 (70.0)	20,982 (70.2)	1,940 (68.7)	1.9
HFH	19,218 (58.7)	17,142 (57.3)	2,076 (73.5)	34	19,295 (59.0)	17,643 (59.0)	1,653 (58.5)	3.1
CAD, unrevascularized	19,238 (58.8)	17,152 (57.3)	2,086 (73.8)	35	19,285 (58.9)	17,641 (59.0)	1,644 (58.2)	1.4
CAD with PCI	769 (2.3)	637 (2.1)	132 (4.7)	14	779 (2.4)	705 (2.4)	74 (2.6)	3.6
Hyperlipidemia	17,339 (53.0)	15,626 (52.2)	1,713 (60.6)	17	17,388 (53.1)	15,904 (53.2)	1,484 (52.5)	2.1
CVD	2,977 (9.1)	2,599 (8.7)	378 (13.4)	15	3,040 (9.3)	2,759 (9.2)	281 (10.0)	5.5
Stroke	898 (2.7)	782 (2.6)	116 (4.1)	8	929 (2.8)	839 (2.8)	91 (3.2)	7
Carotid	286 (0.9)	230 (0.8)	56 (2.0)	10	291 (0.9)	256 (0.9)	35 (1.2)	2.3
PVD	4,019 (12.3)	3,549 (11.9)	470 (16.6)	14	4,045 (12.4)	3,683 (12.3)	363 (12.8)	0.4
Coagulopathy	2,873 (8.8)	2,599 (8.7)	274 (9.7)	3	2,871 (8.8)	2,632 (8.8)	239 (8.5)	0.1
Atrial fibrillation	11,890 (36.3)	10,485 (35.1)	1,405 (49.7)	30	11,987 (36.6)	10,925 (36.5)	1,062 (37.6)	1.3
Cardiac arrest	156 (0.5)	105 (0.4)	51 (1.8)	14	160 (0.5)	144 (0.5)	16 (0.6)	0.1
Cardioversion	600 (1.8)	515 (1.7)	85 (3.0)	8	623 (1.9)	559 (1.9)	64 (2.3)	2.1
Any conduction disorder	2,980 (9.1)	2,367 (7.9)	613 (21.7)	61	3,071 (9.4)	2,786 (9.3)	285 (10.1)	1.3
AV fascicular block	1,735 (5.3)	1,272 (4.3)	463 (16.4)	41	1,817 (5.6)	1,648 (5.5)	168 (6.0)	8.5
Sinoatrial disorder	646 (2.0)	280 (0.9)	366 (13.0)	49	697 (2.1)	640 (2.1)	57 (2.0)	8.7
Supraventricular tachycardia	841 (2.6)	750 (2.5)	91 (3.2)	2	854 (2.6)	771 (2.6)	83 (2.9)	0
Ventricular arrhythmias	1,526 (4.7)	1,237 (4.1)	289 (10.2)	24	1,564 (4.8)	1,419 (4.7)	145 (5.1)	5.1
History of catheter ablation	393 (1.2)	353 (1.2)	40 (1.4)	2	409 (1.2)	364 (1.2)	45 (1.6)	1.2
History of surgical ablation	27 (0.1)	23 (0.1)	4 (0.1)	2	27 (0.1)	24 (0.1)	2 (0.1)	0.4
Diabetes mellitus	7,187 (22.0)	6,203 (20.7)	984 (34.8)	32	7,271 (22.2)	6,620 (22.1)	651 (23.0)	3.6
COPD	7,375 (22.5)	6,577 (22.0)	798 (28.2)	14	7,423 (22.7)	6,778 (22.7)	644 (22.8)	1.4
CKD without dialysis	4,882 (14.9)	4,197 (14.0)	685 (24.2)	26	4,953 (15.1)	4,503 (15.1)	451 (16.0)	3.8
CKD with dialysis	798 (2.4)	680 (2.3)	118 (4.2)	11	812 (2.5)	739 (2.5)	73 (2.6)	1.3
Liver disease	2,623 (8.0)	2,332 (7.8)	291 (10.3)	9	2,639 (8.1)	2,420 (8.1)	220 (7.8)	4.3
Cancer	4,358 (13.3)	3,894 (13.0)	464 (16.4)	10	4,397 (13.4)	4,001 (13.4)	396 (14.0)	0.5
Tobacco use	9,598 (29.3)	8,676 (29.0)	922 (32.6)	8	9,619 (29.4)	8,787 (29.4)	832 (29.5)	0.9
Alcohol use	2,053 (6.3)	1,867 (6.2)	186 (6.6)	1	2,078 (6.3)	1,888 (6.3)	190 (6.7)	1
Drug use	1,260 (3.8)	1,146 (3.8)	114 (4.0)	1	1,271 (3.9)	1,159 (3.9)	112 (4.0)	0.8
Concomitant procedures								
Concomitant CABG	9,484 (29.0)	8,212 (27.5)	1,272 (45.0)	37	9,555 (29.2)	8,710 (29.1)	845 (29.9)	1.9
Concomitant surgical ablation	2,293 (7.0)	2,049 (6.9)	244 (8.6)	7	2,322 (7.1)	2,114 (7.1)	208 (7.4)	1.6
Annual hospital MVR volume								
High: ≥50/y	18,038 (55.1)	16,653 (55.7)	1,385 (49.0)	13	17,954 (54.9)	16,518 (55.2)	1,436 (50.8)	0.2

Values are median (Q1-Q3) or n (%) unless noted otherwise.

AV = atrioventricular; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HFH = heart failure hospitalization; MVR = mitral valve replacement; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVD = peripheral vascular disease; SMD = standardized mean difference.

FIGURE 3 Survival Stratified by Permanent Pacemaker Implantation

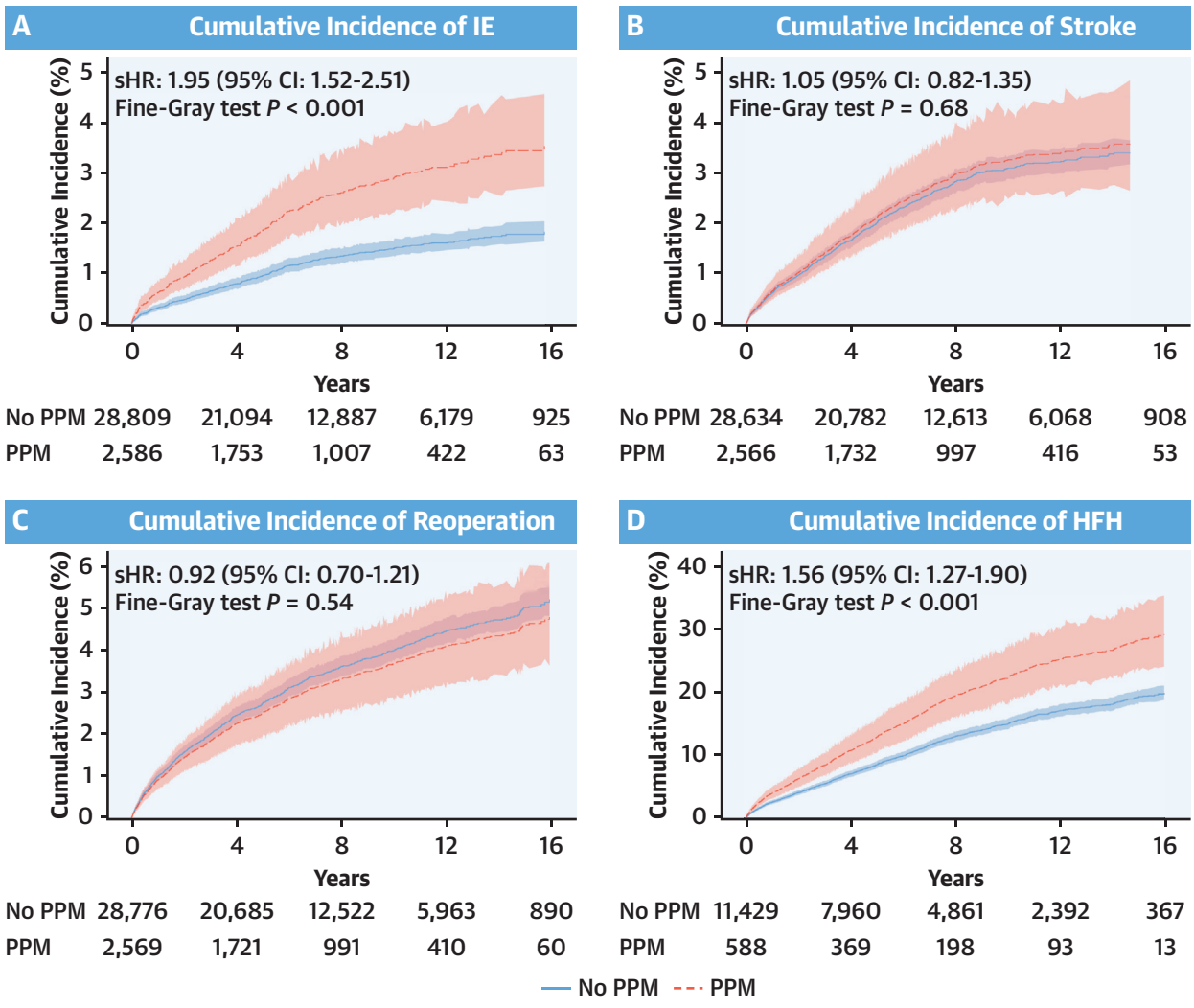


(A) Recipients of mitral valve repair (either as an isolated procedure or as a combined procedure with tricuspid valve annuloplasty). (B) Recipients of only isolated mitral valve repair. (C) Recipients of the combined mitral valve repair/tricuspid annuloplasty procedure. The figures reflect a landmark analysis of the propensity-weighted cohorts in which survival is plotted against time that starts 90 days following the intervention. The HRs are based on the landmark analysis. The shading around the curves represents the 95% CI. PPM = permanent pacemaker.

(sHR: 0.92; 95% CI: 0.63-1.35; $P = 0.67$) (Supplemental Figure 5). At 10 years of follow-up, the incidence of PPM complications reached 5.5% (95% CI: 4.6-6.7) after isolated MVr and 5.3% (95% CI: 3.6-7.4) after MVr + TA and did not differ between groups.

SENSITIVITY ANALYSIS. A proportional hazards model considering all patients, including those who experienced adverse events before 90 days (in contrast to the landmark analysis), was used to assess the association between PPM and the study outcomes with PPM implantation as a time-varying covariate. In this analysis, we report only the subdistribution HR.[14] The implantation of PPM within 90 days after surgery was associated with a higher hazard of mortality after both isolated MVr (HR: 1.37; 95% CI: 1.25-1.50; $P < 0.001$) and MVr + TA (HR: 1.23; 95% CI: 1.04-1.46; $P = 0.02$) surgery. In addition, a higher hazard of infective endocarditis (sHR: 1.56; 95% CI: 1.18-2.07; $P = 0.002$) and HFH (sHR: 1.75; 95% CI: 1.40-2.18; $P < 0.001$) was associated with PPM. There was no association between PPM and the postoperative incidence of reoperation or stroke (**Figure 5**). These results are summarized in a forest plot of surgical outcomes (Supplemental Figure 6). Finally, we analyzed the association between PPM and clinical outcomes in all 32,736 patients, where the results were similar

FIGURE 4 Cumulative Incidence of Secondary Outcomes Stratified by Pacemaker Implantation



(A) Incidence of IE. (B) Incidence of stroke. (C) Incidence of reoperation. (D) Incidence of heart failure hospitalization (HFH). Curves reflect a landmark analysis of the propensity-weighted cohorts in which the comorbidity risk is plotted against time that starts 90 days following the intervention. The shading around the curves represents the 95% CI. The HRs are displayed based on the landmark analysis. IE = infective endocarditis; sHR = subdistribution HR.

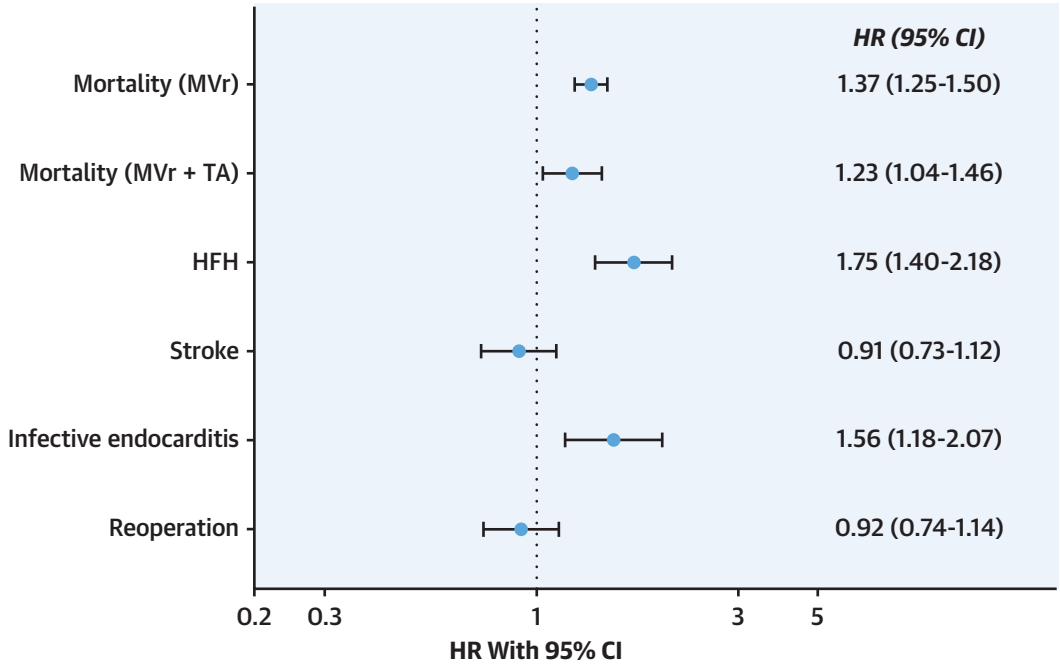
between the unadjusted and adjusted analyses (Supplemental Table 5).

The results were further confirmed in a sensitivity landmark analysis that excluded patients with a history of atrial fibrillation or who underwent concomitant surgical ablation. The distribution of baseline characteristics before and after application of IPTW is shown in Supplemental Table 6. We achieved a good balance of baseline characteristics for patients with and without implantation of PPM within 90 days after weighting by IPTW. In this analysis, implantation of PPM within 90 days after surgery was associated with greater mortality hazard (HR: 1.96; 95% CI: 1.72-2.25; $P < 0.001$) (Supplemental Figure 7), infective endocarditis (sHR: 2.12; 95% CI: 1.45-3.12; $P < 0.001$), and HFH (sHR: 1.76; 95% CI: 1.29-2.47; $P = 0.004$). There were no differences in the cumulative incidence of stroke (sHR: 1.03; 95% CI: 0.64-1.67; $P = 0.90$) or reoperation (sHR: 0.89; 95% CI: 0.62-1.29; $P = 0.53$).

DISCUSSION

The present study offers a comprehensive evaluation of the long-term impact of PPM implantation on

FIGURE 5 Association of PPM With Long-Term Surgical Outcomes



The HRs were estimated using a proportional hazards model in which PPM implantation was treated as a time-dependent variable, and the date of surgery was time zero. Recipients of a PPM implantation were at a higher risk of mortality, HFH, and endocarditis than those who did not have a PPM implantation. HFH = heart failure hospitalization; MVr = mitral valve repair, MVr + TA = mitral valve repair with concomitant tricuspid annuloplasty; PPM = permanent pacemaker.

survival, stroke, infective endocarditis, and HFH in a multicenter cohort of >32,000 patients following both isolated MVr with or without TA. MVr patients who received a PPM within 90 days of surgery were older, had more conduction abnormalities, and had a greater number of comorbidities including HF, diabetes, and chronic obstructive pulmonary disease compared with MVr patients who did not receive a PPM. After propensity score weighting to account for these differences, we observed that PPM implantation was associated with a significant reduction in long-term survival. Specifically, receiving a PPM was associated with increased risk of mortality in both MVr and MVr + TA patients. In addition, PPM implantation within 90 days of MVr surgery was associated with an increased risk of both infective endocarditis and HFH (**Central Illustration**).

Previously reported PPM rates following surgery in patients with degenerative mitral valve disease ranged from 2.5% to 14.5%.[5,7,15,16] The variability in reported PPM rates, in part, stems from differences in baseline characteristics of patients, use of concomitant procedures, single or multi-institutional analyses, and the duration of the observation period. In the largest observational study to date using STS (Society of Thoracic Surgeons) data, patients undergoing MVS without TA (n = 70,550) had a 6.2% 30-day PPM rate vs 14.5% in the MVS + TA group (n = 10,984).[16] In the CTSN randomized trial evaluating TA during MVS, which included rigorous follow-up to 2 years, there was an overall PPM implantation rate of 9.6%, with 3.2% for the MVS-alone group vs 16% among those randomized to the MVS + TA group.[5] In this trial, the overall PPM implantation rate within 30 days was 7.3%, with 3.0% in the MVS group vs 11.6% in the MVS + TA group. In the current analysis, the 90-day PPM rates (7.7% following MVr alone; 14% following MVr + TA) were closer to the rates observed in the CTSN tricuspid trial and STS database[16] than those from single-institution reports. Importantly, we observed a trend toward lower PPM rates over the 16 years of observation in the current study. In the final 3 years of the analysis (2016-2019), the PPM rate was 6.7% for all patients, 5.9% in the MVr-alone group vs 10.3% in the MVr + TA group. The observed reduction in PPM rates may be attributable to improved surgical

technique, changes in baseline patient characteristics, or their combination.

In our propensity-adjusted landmark analysis, patients who received a PPM after MVr with or without TA had significantly reduced long-term survival compared to those who did not receive a PPM. These findings have been observed in several other studies,[17-19] mostly focusing on the impact of PPMs after transcatheter aortic valve implantation or surgical aortic valve replacement. The relationship between PPM implantation and mortality is likely multifactorial but may in large part be related to chronic right ventricular pacing-related dyssynchrony,[20] progressive tricuspid regurgitation, and infection risk. In this analysis, we observed that MVr patients with a PPM had a 56% increased risk of HFH. We observed that at 10 years, 5.5% of patients who received a PPM had a PPM-related intervention, such as lead removal. Moreover, patients with a PPM had a significantly increased risk of endocarditis. Both PPM-related heart failure and endocarditis could negatively affect long-term survival in these patients.

The observed higher incidence of PPM implantation with MVr + TA compared to MVr alone, coupled with the observation that PPM implantation is associated with higher risks of all-cause mortality and HFH, could affect decision-making regarding the addition of TA to MVr in patients with moderate TR or less. However, such decision-making must be balanced by the potential long-term negative clinical consequences of untreated TR at the time of MVS. In the CTSN tricuspid trial, patients undergoing surgery for degenerative MR who had either moderate TR or mild/trace TR with tricuspid annular dilation were randomized to concomitant TA or MVr alone. Although the trial demonstrated a significant reduction in the composite primary endpoint at 2 years, largely because of a reduction in TR, the impact of concomitant TA on longer-term survival is not yet known. Moreover, it is unknown whether long-term outcomes may differ in patients with annular dilation and mild/trace TR than those with moderate TR at baseline, because both patient groups were included in the trial. Longer-term follow-up should help inform clinical decision-making regarding the addition of TA in individual patients.

Despite the temporal declines in PPM implantation rates observed in this multicenter analysis, our results underscore the desirability of avoiding PPM implantation after MVr. Of note, high-volume hospitals performing ≥50 mitral repairs a year had a modestly lower rate of PPM implantation compared with lower-volume hospitals (7.7% vs 9.8%). Several single-institution analyses have demonstrated even lower rates of 2.5% to 4.8%.[15,21] Meticulous attention to surgical technique with a focus on annuloplasty suture placement from the anteroseptal commissure to just proximal to the origin of the coronary sinus should allow safe placement of annuloplasty rings in most cases.

STUDY LIMITATIONS. Although our study included a robust inverse probability of treatment weighting propensity analysis, we were unable to adjust for several potentially confounding variables that are not present in the data sets used, including the classification of degenerative MR, severity of MR, and other valve lesions (including the severity of TR), dimensions, preoperative biventricular function, indication for surgery, or extent of coronary artery disease. Our data set does not include the indication for PPM implantation; only 52% of records included information regarding single- vs dual-chamber lead placement. Long-term data on PPM dependency are not included in these data sets. We used a landmark analysis in this study that ignored events occurring before 90 days.[22] We ran a time-varying sensitivity analysis to confirm our findings. We excluded out-of-state patients, which reduced the likelihood of out-of-state rehospitalizations, but were unable to measure out-of-state hospitalizations for those patients who were in-state residents at the time of surgery but may have subsequently been hospitalized in another state. This has the potential to underestimate the rate of secondary outcomes. However, we believe such out-of-state hospitalizations would affect both groups equally.

CONCLUSIONS

Among patients undergoing MVr, the addition of TA is associated with a higher incidence of PPM implantation compared with MVr alone. PPM implantation is associated with an increased risk of all-cause death, HFH, and endocarditis. Minimizing the need for postoperative PPM implantation for MVr patients, especially among those undergoing concomitant TA, is a target for continued quality and performance efforts.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing mitral valve repair with or without tricuspid annuloplasty, subsequent permanent pacemaker implantation is associated with reduced long-term survival and higher rates of heart failure hospitalization and infective endocarditis.

TRANSLATIONAL OUTLOOK: Advances in surgical technique that reduce the risk of pacemaker implantation could improve long-term outcomes of patients after mitral and tricuspid valve repair.

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KEY WORDS heart failure hospitalizations, mitral valve repair, mortality, tricuspid annuloplasty

APPENDIX For supplemental tables and figures, please see the online version of this paper.