JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 1, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.07.022

STRUCTURAL

Predictors and Clinical Outcomes of Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement

The PARTNER (Placement of AoRtic TraNscathetER Valves) Trial and Registry

Tamim M. Nazif, MD,* José M. Dizon, MD,* Rebecca T. Hahn, MD,* Ke Xu, PhD,† Vasilis Babaliaros, MD,‡ Pamela S. Douglas, MD,§ Mikhael F. El-Chami, MD,‡ Howard C. Herrmann, MD,‖ Michael Mack, MD,¶ Raj R. Makkar, MD,# D. Craig Miller, MD,** Augusto Pichard, MD,†† E. Murat Tuzcu, MD,‡‡ Wilson Y. Szeto, MD,‖ John G. Webb, MD,§§ Jeffrey W. Moses, MD,* Craig R. Smith, MD,* Mathew R. Williams, MD,* Martin B. Leon, MD,* Susheel K. Kodali, MD,* for the PARTNER Publications Office

ABSTRACT

OBJECTIVES The purpose of this study was to identify predictors and clinical implications of permanent pacemaker (PPM) implantation after transcatheter aortic valve replacement (TAVR).

BACKGROUND Cardiac conduction disturbances requiring PPM are a frequent complication of TAVR. However, limited data is available regarding this complication after TAVR with a balloon-expandable valve.

METHODS The study included patients without prior pacemaker who underwent TAVR in the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry and investigated predictors and clinical effect of new PPM.

RESULTS Of 2,559 TAVR patients, 586 were excluded due to pre-existing PPM. A new PPM was required in 173 of the remaining 1,973 patients (8.8%). By multivariable analysis, predictors of PPM included right bundle branch block (odds ratio [OR]: 7.03, 95% confidence interval [CI]: 4.92 to 10.06, $p < 0.001$), prosthesis diameter/left ventricular (LV) outflow tract diameter (for each 0.1 increment, OR: 1.29, 95% CI: 1.10 to 1.51, $p = 0.002$), LV end-diastolic diameter (for each 1 cm, OR: 0.68, 95% CI: 0.53 to 0.87, $p = 0.003$), and treatment in continued access registry (OR: 1.77, 95% CI: 1.08 to 2.92, $p = 0.025$). Patients requiring PPM had a longer mean duration of post-procedure hospitalization (7.3 ± 2.7 days vs. 6.2 ± 2.8 days, $p = 0.001$). At 1 year, new PPM was associated with significantly higher repeat hospitalization (23.9% vs. 18.2%, $p = 0.05$) and mortality or repeat hospitalization (42.0% vs. 32.6%, $p = 0.007$). There was no difference between groups in LV ejection fraction at 1 year.

CONCLUSIONS PPM was required in 8.8% of patients without prior PPM who underwent TAVR with a balloon-expandable valve in the PARTNER trial and registry. In addition to pre-existing right bundle branch block, the prosthesis to LV outflow tract diameter ratio and the LV end-diastolic diameter were identified as novel predictors of PPM after TAVR. New PPM was associated with a longer duration of hospitalization and higher rates of repeat hospitalization and mortality or repeat hospitalization at 1 year. (THE PARTNER TRIAL: Placement of AoRtic TraNscathetER Valves Trial; NCT00530894) (J Am Coll Cardiol Intv 2015;8:60–9) © 2015 by the American College of Cardiology Foundation.

The PARTNER (Placement of Aortic Transcatheter Valve) trial established transcatheter aortic valve replacement (TAVR) as a therapeutic alternative for inoperable and high-risk surgical candidates with symptomatic, severe aortic stenosis (AS) (1,2). Cardiac conduction disturbances requiring permanent pacemaker implantation (PPM) are a frequent complication of TAVR. The exact frequency of new PPM varies based on the valve system used and is significantly lower with the balloon-expandable Edwards SAPIEN valve (ESV) (Edwards Lifesciences, Irvine, California) than the self-expanding Medtronic CoreValve (MCV) (Medtronic, Minneapolis, Minnesota). Recent meta-analyses report average PPM rates ranging from 5.9% to 6.5% for ESV and from 24.5% to 25.8% for MCV (3–5).

SEE PAGE 70

Limited data are available regarding predictors and clinical implications of PPM after TAVR, particularly with respect to ESV. Furthermore, existing studies generally lack core laboratory analysis of diagnostic studies and independent adjudication of important adverse outcomes. The purpose of the current study was to determine the incidence, predictors, and clinical effect of PPM following TAVR with ESV in a large population of patients with core laboratory and clinical events committee (CEC)-adjudicated data from the PARTNER trial and registry.

METHODS

STUDY POPULATION AND DESIGN. The design and results of the PARTNER trial have been previously described (1,2). In the randomized trial, inoperable and high-risk surgical candidates with symptomatic, severe AS underwent TAVR with a 23- or 26-mm ESV by the transfemoral or transapical (high-risk patients only) approach. Following completion of enrollment in the randomized trial, additional patients underwent TAVR in a continued access registry, which utilized the same inclusion and exclusion criteria, screening committee, core laboratories, and CEC. The current analysis utilized an as-treated population of patients who underwent TAVR in the randomized trial and registry and excluded those with prior PPM. The rate of new PPM after TAVR was determined, and predictors were identified by univariate and multivariable analysis. Clinical and echocardiographic outcomes were compared between patients with and without new PPM.

ENDPOINTS. A blinded CEC adjudicated all adverse outcomes, including PPM. For this analysis, PPM was attributed to the TAVR procedure if it occurred within 30 days of valve implantation. Clinical data,

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
CEC = clinical events committee
ECG = electrocardiogram
ESV = Edwards SAPIEN Valve
LVEDd = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
MCV = Medtronic CoreValve
PPM = permanent pacemaker
RBBB = right bundle branch block
TAVR = transcatheter aortic valve replacement

From the *Columbia University Medical Center, New York, New York; †Cardiovascular Research Foundation, New York, New York; ‡Emory University School of Medicine, Atlanta, Georgia; §Duke Clinical Research Institute, Durham, North Carolina; ‖Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; ¶Baylor Healthcare System, Plano, Texas; #Cedars Sinai Medical Center, Los Angeles, California; **Stanford University School of Medicine, Stanford, California; ††Medstar Washington Hospital Center, Washington, DC; ‡‡Cleveland Clinic, Cleveland, Ohio; and the §§St. Paul's Hospital, Vancouver, British Columbia, Canada.
The PARTNER trial was funded by Edwards Lifesciences, and the protocol was developed jointly by the sponsor and the steering committee. The current analysis was designed and completed by the authors through the PARTNER Publications Office, which is colocated at Columbia University Medical Center/The Cardiovascular Research Foundation and The Cleveland Clinic. The PARTNER Publications Office is supported by an unrestricted grant from Edwards Lifesciences, administered by Medstar Health Research Institute. The sponsor had no involvement in the design or analysis of this substudy or in the decision to publish the results. Drs. Nazif, Pichard, Webb, and Kodali are consultants for Edwards Lifesciences. Dr. Hahn is a consultant for Edwards Lifesciences and has received research grant support from Phillips Healthcare. Dr. Babaliaros is a consultant for Direct Flow Medical, Bard Medical, and Intervalve; and is an investigator for Edwards Lifesciences. Dr. Douglas' institution has received research grant support from Edwards Lifesciences. Dr. El-Chami is a consultant to Boston Scientific; and has received a research grant from Medtronic. Dr. Herrmann has received grant support from Abbott Vascular, Boston Scientific Corporation, Edwards Lifesciences, Medtronic, Siemens, St. Jude Medical, and W.L. Gore and Associates; and is a consultant for Edwards Lifesciences, St. Jude Medical, and Siemens. Drs. Mack, Miller, Tuzcu, Smith, and Leon have received travel reimbursements from Edwards Lifesciences related to their activities as a member of the PARTNER Trial Executive Committee. Dr. Makkar has received grant support from Edwards Lifesciences, Medtronic, Abbott Vascular, and St. Jude Medical; is a consultant for Abbott Vascular, Cordis, and Medtronic; is a proctor for Edwards Lifesciences; and holds equity in Entourage Medical. Dr. Miller is supported by an R01 research grant from the National Heart, Lung, and Blood Institute (#HL67025); and has received consulting fees/honoraria from Abbott Vascular, St. Jude Medical, and Medtronic. Dr. Pichard is a proctor for Edwards Lifesciences. Dr. Szeto is a consultant for MicroInterventional Devices; and is an investigator for Edwards Lifesciences. Dr. Moses has served on the executive committee of the PARTNER trial. Dr. Williams is a consultant for Edwards Lifesciences and Medtronic. Dr. Kodali is a consultant to Meril; serves on the Scientific Advisory Board of and has equity in Thubrikar Aortic Valve, Inc.; is a principal investigator for and received research support from Claret Medical; and has received research and grant support from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 16, 2014; revised manuscript received July 24, 2014, accepted July 31, 2014.

electrocardiograms (ECGs), and transthoracic echocardiograms were obtained at baseline, hospital discharge/7 days, 30 days, 6 months, and 1 year. All ECGs and echocardiograms were interpreted by independent core laboratories using methodology previously described (6). Of note, left ventricular outflow tract (LVOT) diameter was measured in midsystole, no more than 0.5 cm apical to the annular measurement, and in a location avoiding a septal bulge, dystrophic calcification, or systolic anterior motion of the mitral leaflets. Pacemaker type and indication were extracted from operative reports and clinical notes. The indications were classified into the following categories: advanced atrioventricular block (complete and high-degree atrioventricular block), second-degree heart block (Mobitz 2 and Mobitz 1 with additional conduction disturbance), sick sinus syndrome (including tachycardia-bradycardia syndrome), and other bradycardia.

STATISTICAL ANALYSIS. Results are presented as means ± SD or counts and percentages. Continuous variables were compared with the Wilcoxon rank sum test, and categorical variables were compared with the chi-square or Fisher exact test. To identify independent predictors of PPM, multivariable logistic regression was performed with entry and stay criteria of 0.1 and 0.1. Candidate variables for the multivariable model were required to have clinical relevance and a p value <0.15 in the univariate analysis, which included all available baseline clinical, echocardiographic, ECG, and procedural data. Outcomes at 30 days and 1 year were analyzed with Kaplan-Meier estimates and compared between groups with the log-rank test. For all tests, a 2-sided alpha value <0.05 was required for statistical significance. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). Data extraction was performed on July 19, 2013.

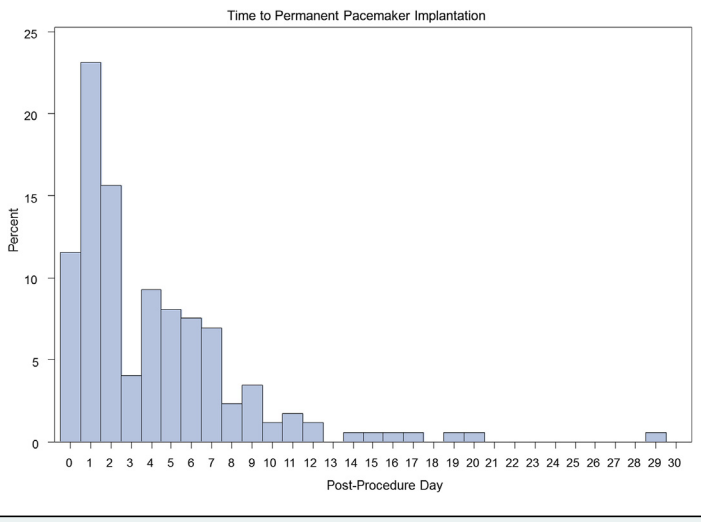

FIGURE 1 Timing of Pacemaker Implantation

The histogram displays the post-procedure day of pacemaker implantation in all cases.

RESULTS

PATIENT POPULATION AND BASELINE CHARACTERISTICS. A total of 2,559 patients underwent TAVR in the PARTNER trial and registry. Of these, 586 were excluded from the current analysis due to prior PPM, resulting in a final study population of 1,973 patients from the randomized trial (n = 409) and continued access registry (n = 1,564). PPM was required within 30 days of TAVR in 173 patients (8.8% of those without prior PPM and 6.8% of total population). The rate of PPM implantation was higher in the continued access registry than the randomized trial (9.6% vs. 5.6% of those without prior pacemaker). The mean time to PPM after TAVR was 4.1 ± 4.3 days, and the median was 3 days (interquartile range: 1 to 6 days) (Figure 1). In the vast majority of cases, PPM was performed during the index hospitalization (97.1%) and within 7 days of the procedure (86.1%).

The most common indication for PPM was high-degree or complete atrioventricular block (79%), followed by sick sinus syndrome (17.3%) (Figure 2A). The vast majority of devices were either dual-chamber (n = 131, 75.7%) or single-chamber (n = 34, 19.7%) right ventricular pacemakers, and very few were biventricular pacemakers (n = 5, 2.9%), implantable cardioverter-defibrillators (n = 1, 0.6%), or biventricular pacemaker-implantable cardioverter-defibrillators (n = 1, 0.6%) (Figure 2B). Among patients not requiring PPM within 30 days, only an additional 29 (1.9%) received PPM within 1 year, and there was no significant difference in this rate between patients treated in the trial or registry (1.5% vs. 2.0%, p = 0.57).

Baseline patient characteristics are shown, stratified by requirement for PPM, in Table 1. Overall, patients were elderly (mean age 84.3 ± 7.2 years), with a high burden of medical comorbidities. The patients were at high surgical risk, as reflected by Society of Thoracic Surgeons score (11.3 ± 4.0) and logistic EuroSCORE (25.5 ± 15.9). The groups were similar with respect to baseline clinical characteristics, with the exception of more frequent prior chest wall radiation (5.2% vs. 2.3%, p = 0.04) in the PPM group.

BASELINE ECG AND ECHOCARDIOGRAPHIC CHARACTERISTICS. Core laboratory analysis of a baseline ECG was available in 1,948 patients (98.7%),

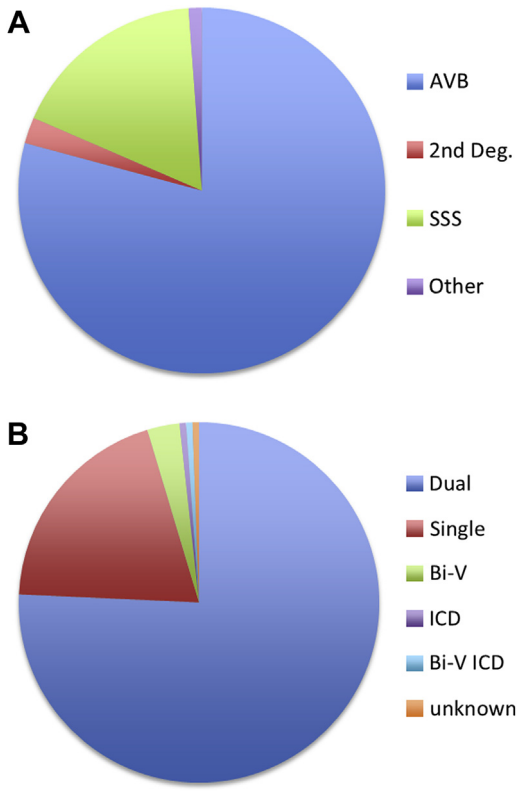

FIGURE 2 Pacemaker Indication and Device Type

(A) The indication for permanent pacemaker after transcatheter aortic valve replacement is displayed: advanced atrioventricular block (AVB); second-degree heart block (2nd Deg); sick sinus syndrome (SSS); and other bradycardia (Other). **(B)** The figure displays the type of pacemaker device implanted, including: dual chamber right ventricular pacemaker (Dual); single chamber right ventricular pacemaker (Single); biventricular pacemaker (Bi-V); and implantable cardioverter-defibrillator (ICD).

TABLE 1 Baseline Characteristics

	New PPM (n = 173)	No PPM (n = 1,800)	p Value
Age, yrs	84.8 ± 7.2	84.2 ± 7.2	0.33
Male	46.2	48.6	0.55
STS score	11.5 ± 4.1	11.3 ± 4.0	0.15
Logistic EuroSCORE	26.0 ± 17.3	25.4 ± 15.8 (1,001)	0.95
Frailty	13.0	13.0	1.00
NYHA functional class			
III	59.0	47.8	0.005
IV	31.2	47.4	<0.001
CAD	80.9	75.8	0.13
Prior MI	25.6	25.2	0.92
Prior PCI	40.1	37.7	0.53
Prior CABG	42.2	40.3	0.63
Prior BAV	22.8	21.4	0.67
Arrhythmia	48.6	42.2	0.11
PVD	41.4	43.4	0.63
Porcelain aorta	4.0	4.0	0.98
CVD	20.0	26.7	0.06
Hypertension	89.6	91.9	0.30
Dyslipidemia	84.4	83.0	0.65
Diabetes mellitus	35.8	36.3	0.90
Renal disease (cr ≥2)	16.8	16.2	0.86
Liver disease	2.9	2.8	0.81
COPD	48.0	45.9	0.61
Oxygen dependent	9.8	12.4	0.32
Pulmonary hypertension	39.4	37.9	0.69
Chest wall radiation	5.2	2.3	0.04

Values are mean ± SD or %.

BAV = balloon aortic valvuloplasty; CAD = coronary artery disease; cr = creatinine; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons.

and an echocardiogram in 1,936 patients (98.1%). ECG and echocardiographic characteristics of patients with and without new PPM are shown in Table 2. Patients who required PPM were more likely to have baseline ECG findings of bradycardia (sinus bradycardia, sinus pauses, or junctional bradycardia) (4.1% vs. 1.5%, p = 0.02), right bundle branch block (RBBB) (47.6% vs. 12.8%, p < 0.001), and left anterior fascicular block (16.5% vs. 8.5%, p < 0.009). By analysis of baseline echocardiograms, the PPM group also had smaller left ventricular end-diastolic diameter (LVEDd) (4.32 ± 0.71 cm vs. 4.47 ± 0.74 cm, p = 0.02) and LVOT diameter (1.98 ± 0.18 cm vs. 2.01 ± 0.18 cm, p = 0.02), and larger ratio of annulus diameter to LVOT diameter (1.09 ± 0.11 vs. 1.07 ± 0.10, p = 0.004). There were no significant differences between groups with respect to other important echocardiographic variables, including transvalvular peak and mean velocities, aortic valve area, annulus diameter, left ventricular ejection fraction (LVEF), and indexes of hypertrophy.

PROCEDURAL CHARACTERISTICS. Procedural variables are displayed, stratified by PPM requirement, in Table 3. Among patients who required PPM, there were numerically higher rates of transapical access (48.0% vs. 42.1%, p = 0.13) and use of the 26-mm (as opposed to 23-mm) prosthesis (51.2% vs. 44.3%, p = 0.09). The ratio of prosthesis diameter to LVOT diameter (valve/LVOT) was significantly greater (1.23 ± 0.11 vs. 1.21 ± 0.11, p = 0.001) in patients who required PPM. There were no significant differences in the rate of balloon valvuloplasty, rate of post-dilation, and post-dilation balloon size, but patients who required PPM were significantly more likely to require intra-aortic balloon pump support (7.0% vs.

TABLE 2 Baseline ECG and Echocardiographic Characteristics

	New PPM (n = 173)	No PPM (n = 1,800)	p Value
Electrocardiographic characteristics			
Sinus rhythm	73.7	73.8	0.97
Atrial tachyarrhythmia*	22.8	23.6	0.82
Bradycardia†	4.1	1.5	0.02
First-degree AVB	18.8	14.4	0.12
Intraventricular conduction disturbance:			
RBBB	47.6	12.8	<0.001
Incomplete RBBB	2.2	1.9	0.70
LBBB	7.1	9.0	0.39
Left anterior hemiblock	16.5	8.5	0.009
Left posterior hemiblock	0.0	0.1	1.00
IVCD	3.3	7.4	0.14
Echocardiographic characteristics			
AV peak velocity, m/s	4.21 ± 0.60	4.23 ± 0.64	0.52
AV mean gradient, mm Hg	45.20 ± 13.54	45.54 ± 14.49	0.36
Aortic valve area, cm^2	0.63 ± 0.19	0.65 ± 0.19	0.35
Aortic valve annulus, cm	1.88 ± 0.27	1.90 ± 0.27	0.58
LVOT diameter, cm	1.98 ± 0.18	2.01 ± 0.18	0.02
Annulus/LVOT	1.09 ± 0.11	1.07 ± 0.10	0.004
LV mass, g	240.1 ± 78.4	247.0 ± 75.2	0.35
IVSd diameter, cm	1.62 ± 0.35	1.60 ± 0.33	0.61
LVOT/IVSd (n)	1.09 ± 0.30 (98)	1.31 ± 0.30 (892)	0.34
LVED diameter, cm	4.32 ± 0.71	4.47 ± 0.74	0.02
LVEF	53.5	53.9	0.67

Values are % or mean ± SD. *Atrial fibrillation, atrial flutter, or atrial tachycardia. †Sinus bradycardia, sinus pauses, or junctional bradycardia.

AV = aortic valve; AVB = atrioventricular block; ECG = electrocardiogram; IVSd = interventricular septum diastolic diameter; LBBB = left bundle branch block; LV = left ventricular; LVED = left ventricular end-diastolic; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; PPM = permanent pacemaker; RBBB = right bundle branch block.

TABLE 3 Procedural Characteristics

	New PPM (n = 173)	No PPM (n = 1,800)	p Value
Access route			
Transfemoral	52.0	57.9	0.13
Transapical	48.0	42.1	0.13
Prosthesis size			
23 mm	48.8	55.7	0.09
26 mm	51.2	44.3	0.09
Prosthesis d./annulus d.	1.15 ± 0.08	1.14 ± 0.07	0.40
Prosthesis d./LVOT d.	1.25 ± 0.11	1.22 ± 0.10	<0.001
Post-dilation	9.3	10.6	0.60
Post-dilation balloon size	22.7 ± 2.8	23.0 ± 2.6	0.69
Hemodynamic support			
Cardiopulmonary bypass	5.8	5.0	0.63
Intra-aortic balloon pump	7.0	3.2	0.01
Conversion to open surgery	0	1.6	0.17
Time to discharge post-TAVR, days	7.3 ± 2.7	6.2 ± 2.8	<0.001

Values are % or mean ± SD.
d. = diameter; other abbreviations as in Table 2.

3.2%, p = 0.01). Following the procedure, the PPM group had a longer mean duration of hospitalization (7.3 ± 2.7 days vs. 6.2 ± 2.8 days, p = 0.001).

MULTIVARIABLE ANALYSIS. The candidate variables for the multivariable logistic regression analysis for predictors of PPM are shown in Table 4. Independent predictors of PPM included RBBB (odds ratio [OR]: 7.03, 95% confidence interval [CI]: 4.92 to 10.06, p < 0.001), valve/LVOT (OR: 1.29 per 0.1 increment, 95% CI: 1.10 to 1.51, p = 0.002), LVEDd (OR: 0.68 per 1-cm increment, 95% CI: 0.53 to 0.87, p = 0.003), and treatment in the continued access registry (OR: 1.77, 95% CI: 1.08 to 2.92, p = 0.025).

CLINICAL OUTCOMES. Clinical outcomes at 30 days and 1 year are presented in Table 5. At 30 days, new PPM was associated with a significantly higher rate of repeat hospitalization (10.6% vs 5.9%, p = 0.02), but not with mortality (7.5% vs. 5.8%, p = 0.40). Similarly, at 1 year, new PPM was not associated with significantly higher all-cause mortality (26.3% vs. 20.8%, p = 0.08), but was associated with significantly higher repeat hospitalization (23.9% vs. 18.2%, p = 0.05) and mortality or repeat hospitalization (42.0% vs. 32.6%, p = 0.007) (Figure 3). There were no significant differences between groups in heart failure symptoms and functional status as assessed by New York Heart Association functional class and 6-min walk time.

ECG AND ECHOCARDIOGRAPHIC OUTCOMES. Core laboratory ECG analysis was available for 97.9% of surviving patients at hospital discharge, 92.6% at 30 days, 86.0% at 6 months, and 82.5% at 1 year. ECG analysis revealed ventricular pacing in the new PPM group in 47.3% of patients at discharge/7 days, 50.7% at 30 days, 47.1% at 6 months, and 50.5% at 1 year. Echocardiograms were analyzed by the core laboratory for 100% of surviving patients at hospital discharge, 92.8% at 30 days, 86.3% at 6 months, and 78.7% at 1 year. The LVEF was similar between groups at baseline (53.5% vs. 53.9%, p = 0.67) and 1 year (55.4% vs. 56.8%, p = 0.18) (Figure 4). Left ventricular dimensions, including LVEDd and left ventricular (LV) end-systolic diameter, were also similar at 1 year.

DISCUSSION

This report of 1,973 patients without prior pacemaker from the PARTNER trial and registry is the largest existing study to analyze the incidence, predictors, and clinical effect of PPM after TAVR. It is particularly notable for CEC adjudication of important clinical

endpoints and core laboratory interpretation of ECGs and echocardiograms. The principal findings are that: 1) new PPM within 30 days of TAVR with ESV was required in 8.8% of patients without prior pacemaker; 2) by multivariable analysis, independent predictors of new PPM included baseline RBBB, larger prosthesis to LVOT diameter ratio, smaller LVEDd, and treatment in the continued access registry; 3) new PPM was associated with a longer duration of hospitalization after TAVR and significantly higher rates of repeat hospitalization and mortality or repeat hospitalization at 1 year; and 4) at 1 year, new PPM was not associated with significant differences in LVEF.

Cardiac conduction disturbances occur frequently after both surgical and transcatheter aortic valve replacement and may require PPM. This is likely due to both the high prevalence of comorbid conduction system disease in patients with AS and the close anatomic proximity of the infranodal conduction system to the aortic valvular complex (7,8). Mechanisms of conduction system injury have been shown to include direct trauma, compression, hemorrhage, and ischemia or infarction of the conduction system tissues (9–11). In recent series, the incidence of PPM after isolated surgical aortic valve replacement for AS has ranged from 3.2% to 7.1% (2,12–14). The requirement for PPM after TAVR with ESV is similar, with average rates ranging from 5.9% to 6.5% in large meta-analyses (3–5). The rate of new PPM of 8.8% among patients without prior pacemakers in the current study is well within the previously-reported range for ESV. Reported PPM rates with MCV are substantially higher, ranging from 24.5% to 25.8% in the meta-analyses (3–5). Similarly, in the recently reported CoreValve High Risk and Extreme Risk Trials, the new pacemaker rates were 19.8% and 21.6%, respectively, overall, or approximately 25% and 29% among patients without pre-existing pacemakers (15,16). The higher rate of new PPM with MCV is likely due to differences in stent design and properties (self-expanding vs. balloon-expandable) that influence the position of the valve frame within the LVOT and the radial force exerted on the conduction system (17).

PPM TIMING AND INDICATION. Limited data are available regarding PPM type, timing, and indication after TAVR, particularly with respect to ESV. In the current analysis, the majority of PPM were either single- or dual-chamber right ventricular pacemakers (>95%) implanted within a week of TAVR (86%) and during index hospitalization (97%). The indication for PPM was high-degree atrioventricular block in approximately 80% of cases. This correlates well with

TABLE 4 Univariate and Significant Multivariable Predictors of PPM after TAVR

	Univariate		Multivariable	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Continued access registry	1.78 (1.13–2.80)	0.013	1.77 (1.08–2.92)	0.025
Demographics				
Age >80 yrs	1.36 (0.90–2.05)	0.140		
CAD	1.36 (0.92–2.01)	0.128		
Arrhythmia	1.29 (0.95–1.77)	0.106		
Chest wall radiation	2.29 (1.10–4.79)	0.028		
Electrocardiographic				
Bradycardia	2.88 (1.23–6.73)	0.015		
First-degree AVB	1.38 (0.92–2.07)	0.121		
RBBB	6.23 (4.47–8.68)	<0.001	7.03 (4.92–10.06)	<0.001
Left anterior hemiblock	2.58 (1.65–4.02)	<0.001		
Echocardiographic				
LVED diameter (per 1-cm increment)	0.76 (0.61–0.95)	0.018	0.68 (0.53–0.87)	0.003
LVOT diameter	0.37 (0.15–0.87)	0.024		
Procedural				
Transapical access	1.27 (0.93–1.74)	0.133		
23 mm vs. 26 mm prosthesis	0.76 (0.55–1.04)	0.086		
Prosthesis d./LVOT d. (per 0.1 increment)	1.31 (1.13–1.51)	<0.001	1.29 (1.10–1.51)	0.002

CI = confidence interval; other abbreviations as in Tables 1 to 3.

TABLE 5 Multivariable Logistic Regression Analysis for Predictors of PPM—Clinical Outcomes

	New PPM (n = 173)	No PPM (n = 1,800)	p Value
30-Day Outcomes			
Mortality			
From any cause	7.5	5.8	0.40
From cardiovascular cause	3.6	4.4	0.57
Repeat hospitalization	10.6	5.9	0.02
Stroke	3.5	3.9	0.78
Myocardial infarction	0.6	1.0	0.58
Major vascular complication	6.9	7.6	0.77
Hemorrhagic event	7.6	11.5	0.12
Major bleeding	5.2	9.4	0.07
Minor bleeding	2.3	2.2	0.92
Renal failure requiring dialysis	5.4	2.4	0.03
1-Year Outcomes			
Mortality			
From any cause	26.3	20.8	0.08
From cardiovascular cause	7.6	9.0	0.52
Repeat hospitalization	23.9	18.2	0.05
Mortality or repeat hospitalization	42.0	32.6	0.007
Stroke	3.5	5.8	0.27
Myocardial infarction*	2.1	1.8	0.97

Values are %. *Excludes periprocedural myocardial infarction.
PPM = permanent pacemaker.

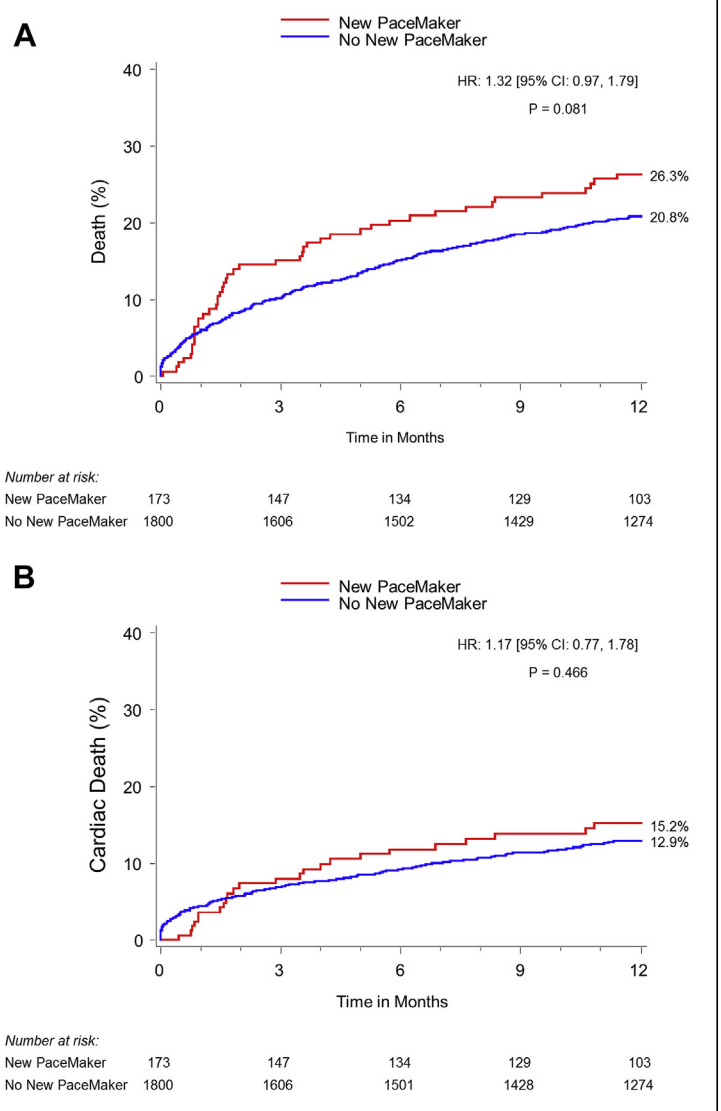

FIGURE 3 1-Year Clinical Outcomes

Kaplan-Meier curves are displayed for 1-year clinical outcomes, including: **(A)** death, **(B)** cardiovascular death, **(C)** repeat hospitalization, and **(D)** death or repeat hospitalization. CI = confidence interval; HR = hazard ratio.

Continued on the next page

a recent, smaller series, in which 82% of PPM after ESV were implanted within 1 week, and the indication was high-degree atrioventricular block in 75% (18). Interestingly, in the current analysis, the indication for PPM was sick sinus syndrome in more than 17%, which is higher than previously reported. Furthermore, the rate of PPM was higher in the continued access registry than the randomized trial (9.6% vs. 5.6%), and the association persisted after adjustment for differences in baseline characteristics. This suggests that differing physician thresholds for PPM may play an important role in PPM rates after TAVR, particularly outside the rigorous confines of a randomized trial.

Although the available data in this study did not permit definitive analysis of long-term pacemaker dependency, a review of the ECGs showed a paced rhythm in only approximately 50% of patients at each time point. This correlates with prior studies, predominantly including MCV, showing long-term pacemaker dependency rates <50% after TAVR (19–21). Given these considerations, recent studies have investigated the safety of more conservative strategies of PPM after TAVR (22). Further research is required to predict pacemaker dependency and to clarify the optimal PPM indications after TAVR.

PREDICTORS OF PPM. The largest prior analysis of predictors of PPM after TAVR, from a German registry, identified the use of MCV, porcelain aorta, and lack of prior valve surgery as predictors of PPM (23). Although the study included both MCV (n = 912) and ESV (n = 232), >90% of the PPM events were after MCV. With respect to ESV alone, the largest study is a Canadian registry of 411 patients without prior pacemaker that identified baseline RBBB as the only predictor of PPM (24). A number of other small registry studies have consistently identified MCV (as opposed to ESV) and baseline RBBB as predictors of PPM (3,25). Beyond these, the studies have variously identified an array of ECG, imaging, and procedural risk factors for PPM. Notable among these are the depth of implantation below the aortic valve annulus and the degree of calcification of the aortic annulus, mitral annulus, LVOT, or aorta (3,8,22,25–28). Important limitations of these studies include their small size and lack of core laboratory and CEC adjudication.

The current, large study with ESV confirms baseline RBBB as an important predictor of PPM and identifies prosthesis to LVOT diameter ratio and LVEDd as novel predictors of PPM. A prior, small study of MCV identified LVOT diameter as a predictor, but did not analyze the prosthesis to LVOT diameter ratio (29). In the current study, LVOT diameter was associated with PPM by univariate analysis, but only the prosthesis to LVOT diameter ratio was an independent predictor of PPM by multivariable analysis. Like implantation depth, this ratio is intuitively appealing as a potential marker of increased risk for injury to the conduction system as it courses through the septum near the LVOT. This may be particularly important in the setting of a "septal bulge," which can result in a smaller LVOT measurement and increased prosthesis to LVOT diameter ratio. It is important to note that

implantation depth and calcification data were not available in the present analysis. Further study is necessary to assess the interplay of these various anatomic and procedural factors in causing conduction abnormalities after TAVR.

CLINICAL IMPLICATIONS OF PPM. Isolated right ventricular apical pacing is not benign in patients with structural heart disease and has been associated with repeat hospitalization and mortality (30–32). However, few studies have investigated the effect of PPM after TAVR on clinical outcomes. A recent, large, mixed series of 1,556 TAVR recipients (ESV 858, MCV 698) showed no association of new PPM after TAVR with long-term mortality and mortality or repeat hospitalization (18). The other large series of 1,147 TAVR patients from the German registry showed no association of new PPM with 30-day mortality, but did not examine long-term outcomes (23). Two smaller series, predominantly with MCV, demonstrated no effect of PPM on 1-year all-cause mortality (22,33). The current analysis, representing the largest reported experience, showed no clear association of PPM after TAVR with 1-year mortality, but did demonstrate an association of new PPM with increased duration of hospitalization and increased rehospitalization and hospitalization or mortality after TAVR. The economic effect of the additional procedure, longer hospitalization, and rehospitalization must be considered given the current health care environment.

Ventricular conduction delays have been shown to have a negative effect on LV function in heart failure patients that may be successfully treated with cardiac resynchronization therapy (34,35). Isolated right ventricular pacing, which mimics left bundle branch block, has also been shown to negatively affect LV function (31,36). Several recent studies have shown that conduction disturbances, including both LBBB and PPM, after TAVR may negatively affect subsequent recovery of LVEF (18,37–39). However, the current analysis failed to show an effect of new PPM on LVEF recovery. There are several potential explanations for this, including fewer patients with baseline depressed LVEF in this cohort, the incomplete rate of long-term pacemaker dependency, and implantation of biventricular pacemakers in rare cases. It is worth noting that recent case reports have described success with cardiac resynchronization therapy after TAVR in patients with conduction disturbances, LV dysfunction, and persistent symptoms (40,41). Further studies of PPM after TAVR, particularly focusing on pacemaker-dependent patients and those with depressed LVEF, will be necessary to determine the effect of PPM on LVEF recovery and potential indications for biventricular pacing.

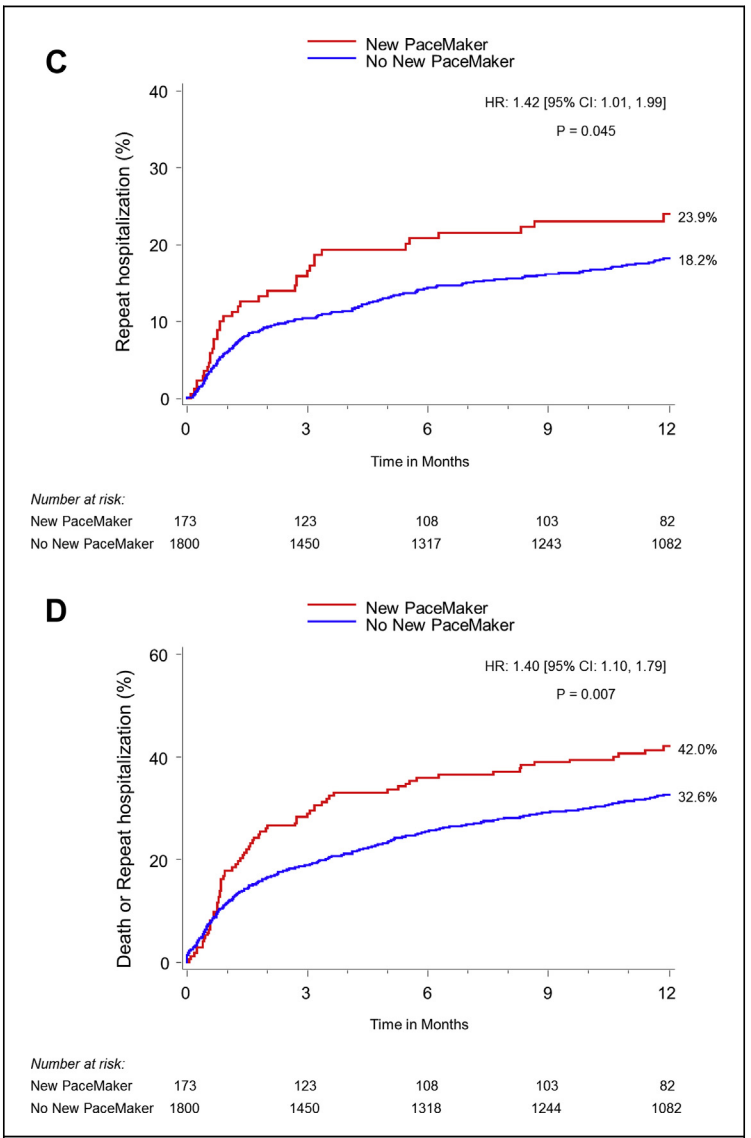

FIGURE 3 Continued

STUDY LIMITATIONS. This report consists of a retrospective analysis of existing data and is subject to all of the limitations inherent in this study design. A limitation of this analysis is that certain previously identified predictors of PPM after TAVR, such as depth of valve implantation and calcification, are not available in this dataset. Data on medications that could affect cardiac conduction are also not available. Another limitation is that comprehensive analysis of pacemaker dependency was not possible from the data, but was estimated from ECGs to be approximately 50% at each time point. To the extent that pacemaker dependency was incomplete, the clinical

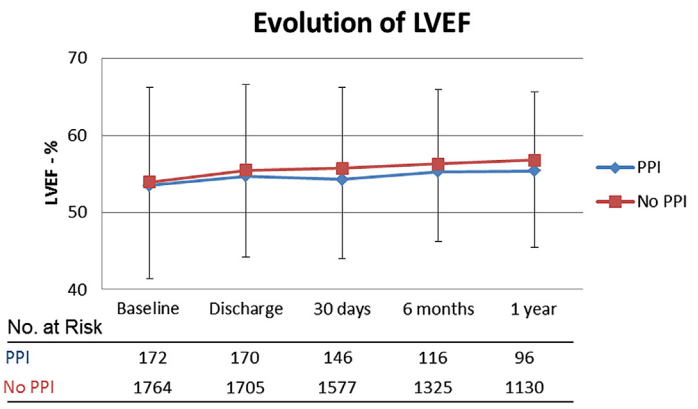

FIGURE 4 Evolution of Left Ventricular Function

The change in left ventricular ejection fraction over time is shown, stratified by permanent pacemaker.

effect of long-term right ventricular apical pacing may be underestimated. Finally, LV function was relatively preserved in this cohort (mean LVEF >50%), so a disproportionate effect of PPM in patients with depressed LV function cannot be ruled out.

CONCLUSIONS

Among patients who underwent TAVR with a balloon-expandable valve in the PARTNER trial and registry, PPM was required within 30 days in 8.8% of patients without a prior pacemaker. Independent predictors of new PPM included RBBB, prosthesis to LVOT diameter ratio, smaller LVEDd, and treatment in the continued access registry. New PPM was associated with significantly longer post-procedure hospitalization and increased repeat hospitalization and mortality or repeat hospitalization at 1 year. PPM did not adversely affect the recovery of LVEF after TAVR, although pacemaker dependency was only approximately 50% at follow-up.

ACKNOWLEDGMENT The authors would like to thank Maria Alu (Columbia University Medical Center) for her assistance in preparing this manuscript.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Susheel Kodali, Columbia University Medical Center/New York Presbyterian Hospital, 177 Ft. Washington Avenue, Room 501, New York, New York 10032. E-mail: skodali@columbia.edu.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

3. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. J Cardiovasc Electrophysiol 2012;23:391–7.

4. Khatri PJ, Webb JG, Rodes-Cabau J, et al. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. Ann Intern Med 2013;158:35–46.

5. Jilaihawi H, Chakravarty T, Weiss RE, Fontana GP, Forrester J, Makkar RR. Meta-analysis of complications in aortic valve replacement: comparison of Medtronic-Corevalve, Edwards-Sapien and surgical aortic valve replacement in 8,536 patients. Catheter Cardiovasc Interv 2012;80:128–38.

6. Douglas PS, Waugh RA, Bloomfield G, et al. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. J Am Soc Echocardiogr 2013;26:348–58, e3.

7. Friedman HS, Zaman Q, Haft JI, Melendez S. Assessment of atrioventricular conduction in aortic valve disease. Br Heart J 1978;40:911–7.

8. Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. Circ Cardiovasc Interv 2008;1:74–81.

9. Fukuda T, Hawley RL, Edwards JE. Lesions of conduction tissue complicating aortic valvular replacement. Chest 1976;69:605–14.

10. Moreno R, Dobarro D, Lopez de Sa E, et al. Cause of complete atrioventricular block after percutaneous aortic valve implantation: insights from a necropsy study. Circulation 2009;120:e29–30.

11. Sinhal A, Altwegg L, Pasupati S, et al. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. J Am Coll Cardiol Intv 2008;1:305–9.

12. Bagur R, Manazzoni JM, Dumont E, et al. Permanent pacemaker implantation following isolated aortic valve replacement in a large cohort of elderly patients with severe aortic stenosis. Heart 2011;97:1687–94.

13. Dawkins S, Hobson AR, Kalra PR, Tang AT, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. Ann Thorac Surg 2008;85:108–12.

14. Erdogan HB, Kayalar N, Ardal H, et al. Risk factors for requirement of permanent pacemaker implantation after aortic valve replacement. J Cardiac Surg 2006;21:211–5, discussion 216–7.

15. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

16. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–81.

17. Tzamtzis S, Viquerat J, Yap J, Mullen MJ, Burriesci G. Numerical analysis of the radial force produced by the Medtronic-CoreValve and Edwards-SAPIEN after transcatheter aortic valve implantation (TAVI). Med Eng Phys 2013;35:125–30.

18. Urena M, Webb JG, Tamburino C, et al. Permanent pacemaker implantation following transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. Circulation 2014;129:1233–43.

19. Goldenberg G, Kusniec J, Kadmon E, et al. Pacemaker implantation after transcatheter aortic valve implantation. Am J Cardiol 2013;112:1632–4.

20. van der Boon RM, Van Mieghem NM, Theuns DA, et al. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. Int J Cardiol 2013;168:1269–73.

21. Pereira E, Ferreira N, Caeiro D, et al. Transcatheter aortic valve implantation and requirements of pacing over time. Pacing Clin Electrophysiol 2013;36:559–69.

22. De Carlo M, Giannini C, Bedogni F, et al. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. Am Heart J 2012;163:492–9.

23. Ledwoch J, Franke J, Gerckens U, et al. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: analysis from the german transcatheter aortic valve interventions registry. Catheter Cardiovasc Interv 2013;82:E569–77.

24. Bagur R, Rodes-Cabau J, Gurvitch R, et al. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. J Am Coll Cardiol Intv 2012;5:540–51.

25. Fraccaro C, Napodano M, Tarantini G. Conduction disorders in the setting of transcatheter aortic valve implantation: a clinical perspective. Catheter Cardiovasc Interv 2013;81:1217–23.

26. Khawaja MZ, Rajani R, Cook A, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). Circulation 2011;123:951–60.

27. Binder RK, Webb JG, Toggweiler S, et al. Impact of post-implant SAPIEN XT geometry and position on conduction disturbances, hemodynamic performance, and paravalvular regurgitation. J Am Coll Cardiol Intv 2013;6:462–8.

28. Munoz-Garcia AJ, Hernandez-Garcia JM, Jimenez-Navarro MF, et al. Factors predicting and having an impact on the need for a permanent pacemaker after CoreValve prosthesis implantation using the new Accutrak delivery catheter system. J Am Coll Cardiol Intv 2012;5:533–9.

29. Baan J Jr., Yong ZY, Koch KT, et al. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. Am Heart J 2010;159:497–503.

30. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002;288:3115–23.

31. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–7.

32. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368:1585–93.

33. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493–501.

34. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.

35. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.

36. Tse HF, Yu C, Wong KK, et al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. J Am Coll Cardiol 2002;40:1451–8.

37. Hoffmann R, Herpertz R, Lotfipour S, et al. Impact of a new conduction defect after transcatheter aortic valve implantation on left ventricular function. J Am Coll Cardiol Intv 2012;5:1257–63.

38. Nazif TM, Williams MR, Hahn RT, et al. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. Eur Heart J 2014;35:1599–607.

39. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol 2012;60:1743–52.

40. Meguro K, Lellouche N, Teiger E. Cardiac resynchronization therapy improved heart failure after left bundle branch block during transcatheter aortic valve implantation. J Invasive Cardiol 2012;24:132–3.

41. Osmancik P, Stros P, Herman D, Kocka V, Paskova E. Cardiac resynchronization therapy implantation following transcatheter aortic valve implantation. Europace 2011;13:290–1.

KEY WORDS cardiac conduction, pacemaker, PARTNER, TAVR, transcatheter aortic valve replacement