Impact of Right Ventricular Pacing in Patients With TAVR Undergoing Permanent Pacemaker Implantation

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Abstract

Background
Long-term right ventricular pacing (VP) has been related to negative left ventricular remodeling and heart failure (HF), but there is a lack of evidence regarding the prognostic impact on transcatheter aortic valve replacement (TAVR) patients.
Objectives
The aim of the PACE-TAVI registry is to evaluate the association of high percentage of VP with adverse outcomes in patients with pacemaker implantation after TAVR.
Methods
PACE-TAVI is an international multicenter registry of all consecutive TAVR patients who underwent permanent pacemaker implantation for conduction disturbances in the first 30 days after the procedure. Patients were divided into 2 subgroups according to the percentage of VP (<40% vs ≥40%) at pacemaker interrogation. The primary endpoint was the composite of cardiovascular mortality or hospitalization for HF.
Results
A total of 377 patients were enrolled, 158 with VP <40% and 219 with VP ≥40%. After multivariable adjustment, VP ≥40% was associated with a higher incidence of the primary endpoint (HR: 2.76; 95% CI: 1.39-5.51; *P* = 0.004), first HF hospitalization (HR: 3.37; 95% CI: 1.50-7.54; *P* = 0.003), and cardiovascular death (HR: 3.77; 95% CI: 1.02-13.88; *P* = 0.04), while the incidence of all-cause death was not significantly different (HR: 2.17; 95% CI: 0.80-5.90; *P* = 0.13). Patients with VP ≥ 40% showed a higher New York Heart Association functional class both at 1 year (*P* = 0.009) and at last available follow-up (*P* = 0.04) and a nonsignificant reduction of left ventricular ejection fraction (*P* = 0.18) on 1-year echocardiography, while patients with VP <40% showed significant improvement (*P* = 0.009).
Conclusions
In TAVR patients undergoing permanent pacemaker implantation, a high percentage of right VP at follow-up is associated with an increased risk for cardiovascular death and HF hospitalization. These findings suggest the opportunity to minimize right VP through dedicated algorithms in post-TAVR patients without complete atrioventricular block and to evaluate a more physiological VP modality in patients with persistent complete atrioventricular block.

Key Words
heart failure, permanent pacemaker implantation, transcatheter aortic valve replacement.

Abbreviations and Acronyms

AV – atrioventricular; AVB - atrioventricular block; CRT - cardiac resynchronization therapy; CV – cardiovascular; HF - heart failure; LAFB - left anterior fascicular block; LV - left ventricular; LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; RBBB - right bundle branch block; PM – pacemaker; PPI - permanent pacemaker implantation; PS - propensity score(s); TAVR - transcatheter aortic valve replacement; VP - ventricular pacing.

Transcatheter aortic valve replacement (TAVR) represents a first-line treatment for many patients with severe aortic stenosis and is comparable with surgical replacement even in patients at low and intermediate risk.[1-3] However, permanent pacemaker implantation (PPI) has emerged as a relevant issue, as it is more frequent in TAVR patients compared with those treated with aortic valve replacement, even among lower risk patients and with new generation devices.[1-4]
Currently, data regarding the impact of PPI on long-term outcomes after TAVR are conflicting, and recent evidence suggests that PPI after TAVR might be associated with higher risk for all-cause mortality and heart failure (HF) hospitalization.[5,6]
Long-term right ventricular pacing (VP) in the setting of structurally normal hearts has been linked to electromechanical dyssynchrony, negative left ventricular remodeling, and increased risk for atrial fibrillation and HF, while the correlation with adverse outcomes appears still unsettled.[7] Historically, a pacemaker (PM) pacing percentage ≥40% has been correlated with adverse outcomes at follow-up, including increased cardiovascular (CV) hospitalizations and new-onset atrial fibrillation.[8,9]
Data on the impact of the amount of VP in TAVR patients are scarce and limited to high-risk patients, whereas the increased use of transcatheter valves in patients at intermediate or low surgical risk warrants an evaluation in patients with long life expectancy.[10,11]
Thus, the aim of the PACE-TAVI registry was to evaluate the association of PM dependency or of a high percentage of VP with adverse outcomes after TAVR.

Methods

Study population

PACE-TAVI is an international, multicenter, retrospective, observational study including all consecutive patients with severe aortic stenosis treated with TAVR who subsequently underwent PPI because of major conduction disease in the first 30 days after the procedure at 9 high-volume TAVR centers in Europe. A list of participating centers is provided in Supplemental Figure 1. If required, study investigators received approval from local institutional boards or ethics committees. Clinical, procedural, PM interrogation, and echocardiographic and laboratory variables along with follow-up data were recorded in a dedicated database.

Study protocol and definitions

Patients were divided into 2 subgroups according to the percentage of VP (<40% vs ≥40%) at 6-month follow-up. For patients with unavailable 6-month PM interrogation, data from 1- to 6-month PM interrogation were used.
The percentage of VP was analyzed both continuously and dividing the population into quartiles of right VP percentage (Figure 1, Supplemental Figure 2). When stratifying in quartiles according to VP, a VP cutoff of 40% proved to be the best to predict the primary endpoint outcomes on Kaplan-Meier survival analysis, as reported in Figure 1. The cutoff was also consistent with previous reports both in TAVR and non-TAVR patients.[9,10] Preprocedural, predischarge, and 1-year echocardiographic data were collected. New York Heart Association (NYHA) functional class was assessed at baseline, at 1 year, and at last available follow-up. All patients received right ventricular apical pacing PMs.
The primary endpoint was the composite of CV death or first hospitalization for HF according to the percentage of VP.
The individual components of the primary endpoint, all-cause death, and changes in left ventricular ejection fraction (LVEF) and NYHA functional class at 1 year were the secondary endpoints.
Hospitalization for HF was defined according to the American College of Cardiology/American Heart Association task force definition: hospital admission (lasting at least 24 hours or extending over a calendar date) with a primary diagnosis of HF with new or worsening symptoms of HF on presentation, objective evidence of new or worsening HF, and initiation or intensification of treatment specifically for HF.[12] Our study received the proper ethical oversight.

Statistical analysis

Continuous and categorical variables were reported as mean ± SD or median (IQR) and as frequencies and percentages, respectively. Differences in clinical and procedural features between patients according to VP (<40% and ≥40%) during the hospitalization or in the first 30 days after the discharge were investigated by performing the 2-tailed Kruskal-Wallis test for continuous data and by applying the chi-squared test for categorical data, with a threshold for significance of 0.05 and not adjusting for multiple comparisons. The actuarial survival curves and the related cumulative incidence curves were obtained using the Kaplan-Meier method. Univariate and multivariable survival analyses were performed with Cox proportional hazards models, yielding HRs and associated 95% CIs. Demographic, echocardiographic, electrocardiographic, and procedural factors with *P* values ≤0.10 in the univariate analysis for each endpoint were entered into the multivariable models. Moreover, a propensity score (PS) was generated for each patient from a multivariable logistic regression model on the basis of pretreatment covariates as independent variables with VP ≥40% or <40% at follow-up as dependent outcome. Pairs of patients were derived using greedy 1:1 matching with a caliper of width of 0.2 SDs of the logit of the PS. A Cox regression model, stratified by the propensity to have VP ≥40% or <40%, was used to analyze outcomes. All variables used for PS analysis as well as the *P* values of their differences in the PS population are reported in Supplemental Table 1. To assess whether the distributions of baseline covariates were similar between treatment arms after the application of the PS methods, the distribution of PS for each treatment group was visually examined, demonstrating good overlap between groups (Supplemental Figure 3). In addition, the pstest command in Stata (StataCorp) was used to test balance in the PS population, and the results are reported in Supplemental Table 1. For the predictors of VP ≥40% at follow-up, a backward stepwise logistic multivariable regression was performed, including all variables with *P* values ≤0.10 in the univariate analysis. *P* values <0.05 were considered to indicate statistical significance. All the analyses were performed using Stata version 17.

Results

Baseline characteristics

A total of 393 consecutive patients underwent PPI after TAVR at the included centers. Sixteen patients were excluded because cardiac resynchronization therapy (CRT) devices (n = 10 [2.5%]) or His-bundle pacing PMs (n = 6 [1.5%]) were implanted; thus, 377 patients constituted the final population, 247 (65.6%) with dual-chamber and 130 (34.4%) with single-chamber PMs. Of these, 158 (42%) had VP <40% and 219 (58%) had VP ≥40% at 6-month follow-up. Baseline clinical, echocardiographic, and procedural characteristics of the entire cohort and according to VP at follow-up are reported in Table 1 and Supplemental Tables 2 and 3. Patients with VP ≥40% were older (mean age 83.5 ± 5.3 years vs 82.3 ± 5.8 years; *P* = 0.04) and had lower LVEFs (mean 55.6% ± 11.3% vs 57.8% ± 11.2%; *P* = 0.03) and larger left ventricular (LV) volumes (mean LV end-diastolic volume 107.5 ± 42.9 mL vs 98.70 ± 39.8 mL [*P* = 0.04], mean end-systolic diameter 36.08 ± 10.1 mm vs 33.54 ± 9.9 mm [*P* = 0.007]). Self-expanding prostheses were more commonly implanted in patients with VP ≥40% (152 [69.4%] vs 89 [56%]; *P* = 0.03). Baseline electrocardiographic and PPI characteristics are reported in Table 2. On baseline electrocardiography, patients with VP ≥40% more often had conduction disorders (right bundle branch block [RBBB] in 17.4% vs 10.8% [*P* = 0.01] and RBBB with left anterior fascicular block [LAFB] in 17.8% vs 12%% [*P* = 0.01]). Time to PPI was shorter in patients with VP ≥40% (3.74 ± 5.4 days vs 5.01 ± 4.6 days; *P* = 0.001). The reason for PPI was predominantly complete atrioventricular block (AVB) in patients with VP ≥40% (67.6% of patients), while paroxysmal complete AVB was the indication in patients with VP <40% (32.3% of patients) (*P* < 0.001). At follow-up PM interrogation, patients with VP ≥40% had a higher programmed lower rate (55.1 ± 8.6 beats/min vs 52.5 ± 10 beats/min; *P* < 0.001) and lesser use of the algorithm for intrinsic atrioventricular (AV) conduction preservation (12.3% vs 28.1%; *P* = 0.001).

Primary endpoint

Median follow-up time was 685 days (IQR: 366-1,139 days). During follow-up, 61 patients (28.2%) with VP ≥40% and 17 (11.0%) with VP <40% reached the primary endpoint (*P* < 0.001). In the unadjusted Kaplan-Meier time-to-event curves, patients with VP ≥40% had a significantly higher cumulative incidence of the primary endpoint compared with patients with VP <40% (*P* < 0.001, log-rank test) (Central Illustration). After multivariable adjustment, VP ≥ 40% was significantly associated with a higher incidence of the primary endpoint (adjusted HR: 2.76; 95% CI: 1.39-5.51; *P* = 0.004) (Central Illustration). Predictors of the primary endpoint are reported in Supplemental Table 4. The results were consistent also in the PS-matched population (HR: 4.19; 95% CI: 1.27-13.90; *P* = 0.02) (Supplemental Figure 4). The results were consistent also when excluding patients (n = 53 [13%]) with available PM interrogation before 6 months (Supplemental Figure 5).

Secondary endpoints

During follow-up, a first HF hospitalization occurred in 51 patients (23.3%) with VP ≥40% and 12 (7.6%) with VP <40% (*P* < 0.001), CV death in 22 patients (10.2%) with VP ≥40% and 6 (3.9%) with VP <40% (*P* = 0.02), and all-cause death in 73 patients (33.3%) with VP ≥40% and 42 (26.6%) with VP <40% (*P* = 0.16). Unadjusted Kaplan-Meier cumulative incidence of first HF hospitalization, CV death, and all-cause death according to VP percentage are reported in the Central Illustration and Figure 2. After multivariable adjustment, VP ≥40% was significantly associated with a higher incidence of first hospitalization for HF (adjusted HR: 3.37; 95% CI: 1.50-7.54; *P* = 0.003) and CV death (adjusted HR: 3.77; 95% CI: 1.02-13.88; *P* = 0.04), whereas it was not associated with a statistically significantly higher incidence of all-cause mortality (adjusted HR: 2.17; 95% CI: 0.80-5.90; *P* = 0.13) (Central Illustration, Figure 2). The results were consistent also in the PS-matched population (Supplemental Figures 4 and 6).

Subgroup analysis

Subgroup analysis according to baseline LVEF, intrinsic heart activity, reason for PM implantation, and type of PM implanted after TAVR are reported in Supplemental Figures 7 to 10.
In the unadjusted Kaplan-Meier time-to-event curves, with VP ≥40%, patients with intrinsic rhythm on PM interrogation, with reasons for PM implantation other than complete AVB and with a single-chamber PM implanted, had a trend toward a higher incidence of the primary endpoint compared with other patients (Supplemental Figures 7 to 10).

LVEF and NYHA functional class at follow-up

LVEF predischarge and at 1 year post-TAVR was available respectively in 346 (92%) and 251 (74%) patients alive at 1 year. At predischarge, LVEF was not different between the 2 groups (57% ± 9% for VP ≥40% and 58% ± 9% for VP <40%; *P* = 0.16), while after 1 year, patients with VP ≥40% had lower LVEFs compared with those with VP <40% (54% ± 10% vs 60% ± 8%; *P* < 0.001) (Figure 3). Patients with VP <40% had a significant improvement of LVEF (from 58.0% ± 9.3% to 60.10% ± 8.0%; *P* = 0.008) at 1-year echocardiography, whereas patients with VP ≥40% showed a nonsignificant reduction of LVEF (from 56.8% ± 9.14% to 54.3% ± 10.2%; *P* = 0.18) (Figure 3). In the exploratory analysis of patients with reduced LVEF at baseline (n = 49 [13%]), both groups had improvements at hospital discharge (*P* = 0.002 and *P* = 0.0003, respectively), whereas only patients with VP <40% showed a significant improvement at 1-year echocardiography (*P* = 0.009) (Figure 3). NYHA functional class data were available for 320 patients (85%) at 1 year and 349 patients (93%) at last available follow-up. Compared with baseline, both groups showed lower NYHA functional class, both at 1 year and at last available follow-up (Figure 4). Compared with patients with VP <40%, those with VP ≥ 40% showed higher NYHA functional class both at 1 year (*P* = 0.009) and at last available follow-up (*P* = 0.04) (Figure 4).

Predictors of percentage of pacing at follow-up

Unadjusted, adjusted, and fully adjusted ORs of predictors of VP ≥40% are presented in Table 3. Among all baseline and procedural characteristics, LVEF (fully adjusted OR per 1 percentage point: 0.95; 95% CI: 0.91-0.99), the presence of RBBB (fully adjusted OR: 6.13; 95% CI: 1.30-28.87) and RBBB with LAFB (fully adjusted OR: 7.82; 95% CI: 1.30-46.95) on baseline electrocardiography, QRS duration on baseline electrocardiography (fully adjusted OR per 1 ms: 1.03; 95% CI: 1.01-1.07), type of implanted prostheses (fully adjusted OR for balloon-expandable prostheses: 0.43; 95% CI: 0.20-0.93), and complete AVB as reason for PM implantation (fully adjusted OR: 6.25; 95% CI: 2.81-13.90) were found to be independent predictors of VP ≥ 40% at follow-up. The results were consistent both in the adjusted and fully adjusted models, the latter also including complete AVB as reason for implantation and AV delay management mode (Table 3).

Discussion

To our knowledge, this is the first study enrolling a large cohort of patients undergoing PPI after TAVR focusing on the effects of the amount of right VP on adverse events at follow-up.

The main findings of the present study are as follows: 1) patients with VP ≥40% at 6-month follow-up had a significantly higher incidence of the primary composite endpoint of CV mortality and HF hospitalization; 2) patients with VP ≥40% had worse NYHA functional class at follow-up; and 3) baseline electrocardiography (RBBB and RBBB with LAFB, QRS duration), poor LVEF, self-expanding prostheses, and complete AVB following TAVR were found to be independent predictors of VP ≥40% at follow-up.

Despite advances in TAVR, PPI after TAVR is one of the most common complications of the procedure.[4] The extension of TAVR indications to a lower risk and younger population requires better understanding of the long-term prognostic impact of PPI after TAVR.[2] In the PARTNER (Placement of Aortic Transcatheter Valve) 3 trial, the rate of PPI after TAVR was 6.6%, while in the Evolut Low Risk Trial, it was 17.4%.[13,14] In the UK TAVR trial, the rate of PPI was 14.2% 1 year after TAVR, considering all Conformité Européenne–approved valves.[3] However, the impact of PPI on long-term outcomes after TAVR is debated.[5,6,15]

In 2 recent meta-analyses, both groups reported a higher risk for all-cause death and 1-year HF hospitalization in patients undergoing PPI, while no difference was observed in cardiac mortality.[5,15] Cardiac death rate was frequently not reported, and there were few studies with long-term follow-up data. In contrast, a recent nationwide analysis of the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry on 481 patients with PPI after TAVR showed no difference in all-cause and CV death and a nonsignificant increase in HF hospitalization in patients undergoing PPI during a median follow-up period of 2.7 years.[6]

However, no information about the amount of right VP was available in the studies, and data in the literature on the impact of different percentages of right VP in TAVR patients are limited, especially at long-term follow-up.

Only 2 small studies have investigated the effects of different percentages of right VP on outcomes after TAVR.[10,11] Nadeem et al,[10] in a cohort of 30 patients with VP ≥40%, found a trend toward increased all-cause mortality and a significantly higher incidence of HF compared with patients with VP <40%, while Hochstadt et al[11] found no difference in all-cause mortality in 91 patients with VP ≥40% compared with those with lower VP burden.[10,11] In these studies, the sample size was relatively low, and data about CV mortality and HF hospitalization were not provided, making it impossible to draw a clear conclusion.

We found a higher incidence of CV death and of first HF hospitalization, but we failed to detect a significant increase in all-cause death.

The effect of right VP on LVEF has been recognized for many years.[9] Right VP, in fact, causes an abnormal LV electric activation sequence, which leads to systolic dyssynchrony and, subsequently, increased LV volume, increased mitral regurgitation, and decreased LVEF.[9] This is prominent in

patients with preexisting LV dysfunction, in which biventricular pacing has demonstrated a lower incidence of adverse outcomes at follow-up, and it is indeed the currently recommended therapy for patients who are expected to need permanent pacing.[16,17] Moreover, in MOST (Mode Selection Trial in Sinus-Node Dysfunction), the risk for HF hospitalization increased by 20% for every 10% increase in right VP, and in patients with VP larger than 40%, the risk for HF hospitalization was 2.5 times higher than in those with VP <40%.[9,18]

However, data on the impact of a high percentage of VP on HF development and timing in patients with aortic stenosis are limited. In our study, patients with VP ≥ 40% showed an increased incidence of HF and higher NYHA functional class a few months after the procedure, possibly because of poorer LV remodeling associated with a large amount of right VP.[19]

Although other studies have shown an independent association between PPI post-TAVR and HF decompensations requiring hospitalization, our study is the first to demonstrate the association between a high percentage of right VP and the risk for HF hospitalization, suggesting that VP percentage could be one of the causes of the increased risk for HF hospitalizations observed in patients who undergo PPI post-TAVR.[20]

Some previous studies have shown a negative effect of PPI on ventricular function among TAVR patients, even after 1 year of follow-up, and especially in patients with high percentage of right VP. Our study confirms the deleterious effect of a high percentage of right VP on LVEF, particularly in patients with pre-TAVR reduced LVEFs.[10,20]

VP ≥40% is reported in about 50% of patients undergoing PPI after TAVR, a figure similar to the 58% observed in our cohort.[21,22] However, patients who underwent implantation because of persistent third-degree AVB are unlikely to have recovery of AV conduction over long-term follow-up, whereas patients who undergo implantation for different indications are more likely to need only a small amount of right VP during follow-up.[10,22,23] Accordingly, complete AVB as a reason for PPI was found to be the strongest independent predictor of VP ≥ 40% at follow-up, together with implantation of a self-expanding valve and baseline RBBB, as already observed in other studies.[22,24] In contrast, patients with PPI indications other than complete AVB showed a relatively low percentage of pacing at follow-up (mean VP 72.0% ± 39.5% vs 32.5% ± 39.6%).[22] These findings support the recommendations of the latest European Society of Cardiology guidelines on cardiac pacing, in which PPI after TAVR is recommended only in patients with persistent high-degree AVB or new-onset alternating bundle branch block, while in other cases (such as paroxysmal AVB, complete left bundle branch block post-TAVR, or PR interval prolongation), PPI should be carefully evaluated, as the conduction system could recover from the acute-phase injury and PPI may not be needed in these patients.[17]

Interestingly, we observed a trend toward a higher incidence of the primary endpoint, especially in the first months after PM implantation, in patients with VP ≥40% and intrinsic rhythm at follow-up and in patients with VP ≥40% who underwent implantation for reasons other than complete AVB. It is possible that in patients with preserved intrinsic heart activity, the competition between physiological electric activity and the PM leads to different wave fronts, which could be deleterious for the heart, especially when already remodeled as in the setting of aortic stenosis.[25,26]

Moreover, because of its detrimental long-term effect, it appears mandatory to reduce as much as possible the percentage of right VP in post-TAVR patients without persistent AVB, especially in those with low LVEFs. Future research and dedicated randomized studies are needed to define the most suitable VP mode alternative to right VP in post-TAVR patients with an expected large amount of VP at follow-up, such as patients with persistent complete AVB after the procedure, even in the presence of a preserved or mildly reduced LVEF. In preclinical and/or clinical studies in different settings, more contemporary pacing strategies that can preserve ventricular synchrony (ie, physiological pacing, such as biventricular or conduction system pacing) were all associated with a decreased risk for pacing-induced cardiomyopathy, albeit at the potential prize of higher cost, difficulty of implantation, and increased rate of complications.[27]

Current guidelines state that de novo CRT should be considered in patients with reduced LVEFs and expected high percentage of VP (Class 2a, Level of Evidence: B), but we observed a detrimental effect of VP pacing also in TAVR patients with preserved LVEFs.[17] The 6 patients with His pacing included in our registry, but excluded from the analysis, had no HF hospitalizations or death during follow-up, while the 10 patients with CRT devices implanted (all with LVEF <40%) had 3 HF hospitalizations but no CV death during follow-up.
Finally, closer PM follow-up after discharge should be scheduled for TAVR patients undergoing PPI to evaluate AV conduction recovery and optimize the stimulation settings in the perspective of VP minimization. An AV delay management algorithm should be always activated to favor spontaneous AV conduction over VP, whenever possible without compromising LV preload in patients with advanced AVB, a strategy that has proved detrimental in many clinical settings.[28] Future studies are needed to better characterize patients who are likely to benefit from a most suitable VP mode aimed at avoiding LV desynchrony and dysfunction.

Study limitations

First, this was an observational and retrospective study, and although we used both multivariable and propensity matching analysis, potential bias due to the effect of unmeasured and unknown variables cannot be excluded.
Second, there was no definite protocol on PM programming across the centers, but clinical practice at all participating centers provided that PM programming was according to European Society of Cardiology guidelines for cardiac pacing in order to avoid VP whenever possible.
Patient follow-up was limited to up to 60 months (5 years), with a median follow-up duration of 2.7 years.
Finally, LVEF data and NYHA functional class at follow-up were not present for the totality of patients, and no central core laboratory was available for echocardiographic reading and measurements.

Conclusions

TAVR patients undergoing PPI after the procedure because of conduction disorders and with VP ≥40% are at increased risk for CV death and HF hospitalizations compared with patients with VP <40%. These finding suggest minimizing the percentage of right VP at follow-up through proper programming in post-TAVR patients without complete persistent AV block. Additionally, studies to evaluate the potential benefit of a more physiological VP mode in TAVR patients with an expected high percentage of VP are warranted.

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Perspectives

WHAT IS KNOWN? Recent evidence suggests that PPI after TAVR might be associated with higher risk for adverse outcomes at follow-up, but the mechanism is still unknown. Long-term right VP could be one of the possible causes.
WHAT IS NEW? TAVR patients undergoing PPI with right VP ≥40% at 6-month follow-up are at increased risk for CV death and HF hospitalization compared with patients with VP <40%.
WHAT IS NEXT? Right VP should be minimized through dedicated algorithm in post-TAVR patients without complete AVB, while a more physiological VP mode should be pursued for patients with persistent complete AVB.

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Table 1. Baseline and Procedural Characteristics

	All Patients (N = 377)	**VP <40% (n = 158)**	**VP ≥40% (n = 219)**	***P* Value**
Female	190 (50.4)	89 (56.3)	101 (46.1)	0.05
Age, y	83 ± 5.52	82.3 ± 5.8	83.5 ± 5.3	**0.04**
Current smoking	14 (3.7)	6 (3.8)	8 (3.7)	0.94
Dyslipidemia	224 (59.4)	99 (62.7)	125 (57.1)	0.28
Type II diabetes	103 (27.3)	38 (24)	65 (29.7)	0.23
Hypertension	329 (87.3)	141 (89.2)	188 (85.8)	0.33
History of syncope	49 (13)	17 (10.8)	32 (14.6)	0.27
Previous CAD	143 (37.9)	63 (39.9)	80 (36.5)	0.25
Previous MI	60 (15.9)	25 (15.8)	35 (15.9)	0.97
Previous PCI	99 (26.5)	42 (26.8)	57 (26.3)	0.92
Previous CABG	37 (9.8)	16 (10.1)	21 (9.6)	0.86
Prior AVR/TAVR	9 (2.4)	5 (3.1)	4 (1.8)	0.21
Prior BAV	10 (2.7)	3 (1.9)	7 (3.2)	0.16
Atrial fibrillation				0.62
Paroxysmal	62 (16.5)	26 (16.5)	36 (16.4)	
Permanent	54 (14.3)	19 (12)	35 (16)	
NYHA functional class III or IV at baseline	80 (21.2)	27 (17.1)	53 (24.2)	0.10
Baseline creatinine, mg/dl	1.33 ± 1.1	1.30 ± 1.1	1.36 ± 1.1	0.07
Hb, g/dL	12.1 ± 1.7	12.3 ± 1.69	12.0 ± 1.7	0.13
WBC count, $\times 10^9$	6.71 ± 2.2	6.68 ± 1.9	6.73 ± 2.4	0.98
INR	1.27 ± 0.48	1.26 ± 0.48	1.27 ± 0.48	0.42
STS mortality score	5.49 ± 3.5	5.02 ± 2.7	5.8 ± 4.0	0.38
Ejection fraction, %	56.54 ± 11.3	57.82 ± 11.2	55.63 ± 11.3	**0.03**
Ejection fraction ≤40%	49 (13.0)	17 (10.8)	32 (14.6)	0.27
Peak gradient, mm Hg	76.20 ± 21.7	74.34 ± 21.9	77.56 ± 21.5	0.06
Mean gradient, mm Hg	46.63 ± 14.2	45.93 ± 14.4	47.13 ± 14.1	0.19
LVESV, mL	48.78 ± 28.9	45.60 ± 27.6	51.10 ± 29.8	0.05
LVEDV, mL	103.82 ± 41.8	98.70 ± 39.8	107.5 ± 42.9	**0.04**

	All Patients (N = 377)	VP <40% (n = 158)	VP ≥40% (n = 219)	*P* Value
ESD, mm	35.02 ± 10.1	33.54 ± 9.9	36.08 ± 10.1	**0.007**
EDD, mm	47.74 ± 9.8	46.61 ± 8.5	48.56 ± 10.6	0.08
Moderate or severe MR	17 (5)	8 (5)	9 (4.1)	0.62
Moderate or severe TR	57 (15.1)	24 (15.2)	33 (15.1)	0.97
PASP, mm Hg	39.73 ± 12.6	39.40 ± 14.4	39.94 ± 11.3	0.23

Values are n (%) or mean ± SD. *P* values in **bold** denote statistical significance.
AVR = aortic valve replacement; BAV = balloon aortic valvuloplasty; CABG = coronary artery bypass graft; CAD = coronary artery disease; EDD = end-diastolic diameter; ESD = end-systolic diameter; Hb = hemoglobin; INR = international normalized ratio; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation; VP = ventricular pacing; WBC = white blood count.

Table 2. Electrocardiographic and Pacemaker Characteristics

	All Patients (N = 377)	VP <40% (n = 158)	VP ≥40% (n = 219)	*P* Value
Sinus rhythm	259 (68.7)	106 (67.1)	153 (69.9)	0.81
AVB	98 (26)	37 (23.4)	61 (27.9)	0.33
First degree	86 (22.8)	29 (18.4)	57 (26)	0.79
Second degree type II	5 (1.3)	3 (1.8)	2 (1.0)	0.43
Not specified	7 (1.9)	5 (3.2)	2 (0.9)	
IV conduction disorder	180 (48)	64 (40.5)	116 (53)	**0.01**
RBBB	55 (14.6)	17 (10.8)	38 (17.4)	
RBBB with LFAB	58 (15.4)	19 (12)	39 (17.8)	
LAFB	29 (7.7)	16 (10.1)	13 (5.9)	
LBBB	32 (8.5)	12 (7.6)	20 (9.1)	
Not specified	6 (1.8)	0 (0)	6 (2.8)	
QRS duration, ms	115 ± 24	112 ± 22	117 ± 25	0.12
Time to PM implantation, d	4.26 ± 5.1	5.01 ± 4.6	3.74 ± 5.4	**<0.001**
Reason for PM implantation				

	All Patients (N = 377)	VP <40% (n = 158)	VP ≥40% (n = 219)	*P* Value
Complete AVB	194 (51.5)	46 (29.1)	148 (67.6)	
Paroxysmal complete AVB	68 (18)	51 (32.3)	17 (7.8)	
New-onset alternating BBB	18 (4.8)	13 (8.2)	5 (2.3)	
Bradycardic AF	28 (7.4)	12 (7.6)	16 (7.3)	
New type II degree AVB	32 (8.5)	13 (8.2)	19 (8.7)	
New-onset LBBB	15 (4)	11 (7)	4 (1.8)	
Other reasons	22 (5.8)	12 (7.6)	10 (4.6)	
Type of PM implanted				0.20
Single chamber	130 (34.4)	61 (38.6)	69 (31.5)	
Dual chamber	247 (65.6)	99 (62.7)	148 (67.6)	
Type of stimulation				**0.004**
VVI (R)	124 (32.9)	59 (37.4)	65 (29.7)	
DDD (R)	197 (52.3)	71 (44.9)	126 (57.6)	
VDD (R)	15 (4)	6 (3.8)	9 (4.1)	
AAI>DDD (R)	37 (9.8)	22 (13.9)	15 (6.8)	
Missing data	4 (1)	0 (0)	4 (1.8)	
Percentage of RVAP	52.8 ± 44.2	5.8 ± 8.6	90.5 ± 16.0	**<0.001**
Absence of intrinsic heart activity	91 (25.6)	0 (0)	91 (46.2)	**<0.001**
Lower rate frequency rate, beats/min	54.0 ± 9.4	52.5 ± 10	55.1 ± 8.6	**<0.001**
Upper rate frequency rate, beats/min	128.0 ± 8.7	128.4 ± 9.1	127.7 ± 8.5	0.43
Rate response	90 (28.1)	33 (23.6)	57 (31.7)	0.11
AV delay management on	55 (19.5)	36 (28.1)	19 (12.3)	**0.001**

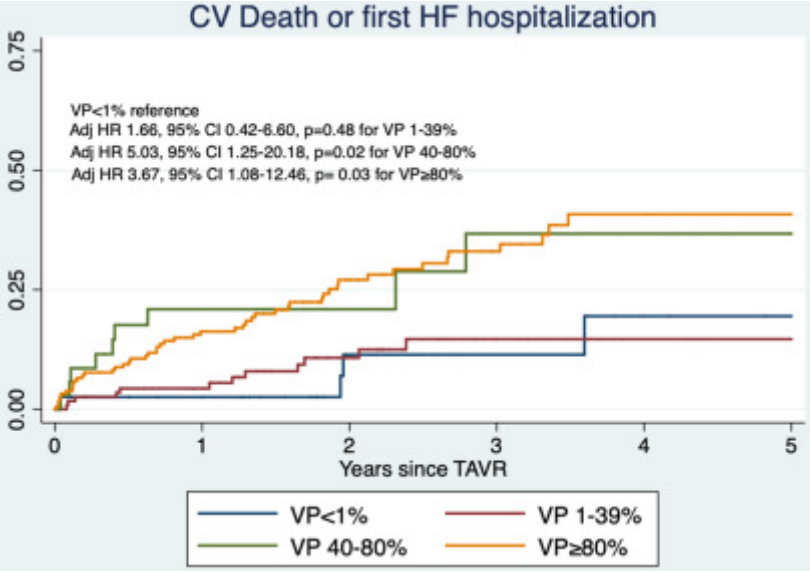
Values are n (%) or mean ± SD. *P* values in **bold** denote statistical significance.
AF = atrial fibrillation; AV = atrioventricular; AVB = atrioventricular block; BBB = bundle branch block; IV = intraventricular; LBBB = left bundle branch block; LAFB = left anterior fascicular block; PM = pacemaker; RBBB = right bundle branch block; RVAP = right ventricular apical pacing; VP = ventricular pacing.

Table 3. Predictors of Ventricular Pacing ≥40% at Follow-Up

	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)[a]	*P* Value	Multivariate OR (95% CI)[b]	*P* Value
Age	1.04 (1.01-1.08)	0.05	1.01 (0.94-1.06)	0.96	1.02 (0.96-1.10)	0.44
Female	0.66 (0.44-1.01)	0.05	0.49 (0.25-0.98)	**0.04**	0.49 (0.21-1.12)	0.09
NYHA functional class III or IV	1.67 (0.99-2.78)	0.05	1.30 (0.56-3.01)	0.54	0.74 (0.26-2.10)	0.57
Hb at admission	0.90 (0.79-1.02)	0.09	0.88 (0.72-1.06)	0.18	0.92 (0.73-1.17)	0.51
STS score	1.07 (0.99-1.16)	0.09	1.01 (0.89-1.16)	0.84	1.05 (0.89-1.23)	0.57
LVEF	0.98 (0.96-1.00)	0.06	0.96 (0.93-0.99)	**0.02**	0.95 (0.91-0.99)	**0.01**
RBBB	2.13 (1.11-4.07)	**0.02**	5.74 (1.51-21.8)	**0.01**	6.13 (1.30-28.87)	**0.02**
RBBB with LAFB	1.96 (1.04-3.66)	**0.04**	5.10 (1.26-20.66)	**0.02**	7.82 (1.30-46.95)	**0.02**
QRS duration	1.01 (1.00-1.02)	0.10	1.03 (1.01-1.05)	**0.02**	1.03 (1.01-1.07)	**0.04**
BE prostheses	0.61 (0.41-0.91)	**0.02**	0.46 (0.25-0.86)	**0.02**	0.43 (0.20-0.93)	**0.03**
Complete AVB as reason for PPI	4.80 (3.09-7.47)	**<0.001**	—		6.25 (2.81-13.90)	**<0.001**
AVM mode	0.36 (0.19-0.67)	**0.01**	—		0.55 (0.22-1.34)	0.19
Lower rate	1.03 (1.01-1.06)	**0.01**	1.03 (0.99-1.06)	0.09	1.01 (0.97-1.05)	0.65

ORs, 95% CIs, and *P* values were derived from univariate and multivariable logistic regression models and are expressed as the OR of having ventricular pacing ≥40% at follow-up.
AVM = atrioventricular delay management; BE = balloon-expandable; LVEF = left ventricular ejection fraction; PPI = permanent pacemaker implantation; other abbreviations as in Tables 1 and 2.
a. Adjusted model was fitted with backward stepwise logistic regression including all the covariables reported in the univariate analysis on the right excluding reason for PPI and AVM mode.
b. Fully adjusted model, adjusted for all variables from model 1 plus reason for PPI and AVM mode.

Figure 1. Incidence of the Primary Endpoint According to VP Percentage at Follow-Up
CV = cardiovascular; TAVR = transcatheter aortic valve replacement; VP = ventricular pacing.



Central Illustration. The PACE TAVI International Multicenter Registry
Participating centers, incidence of primary endpoint **(left)**, and first heart failure (HF) hospitalization **(right)** according to ventricular pacing (VP) percentage. CV = cardiovascular; PM = pacemaker implantation; TAVR = transcatheter aortic valve replacement.

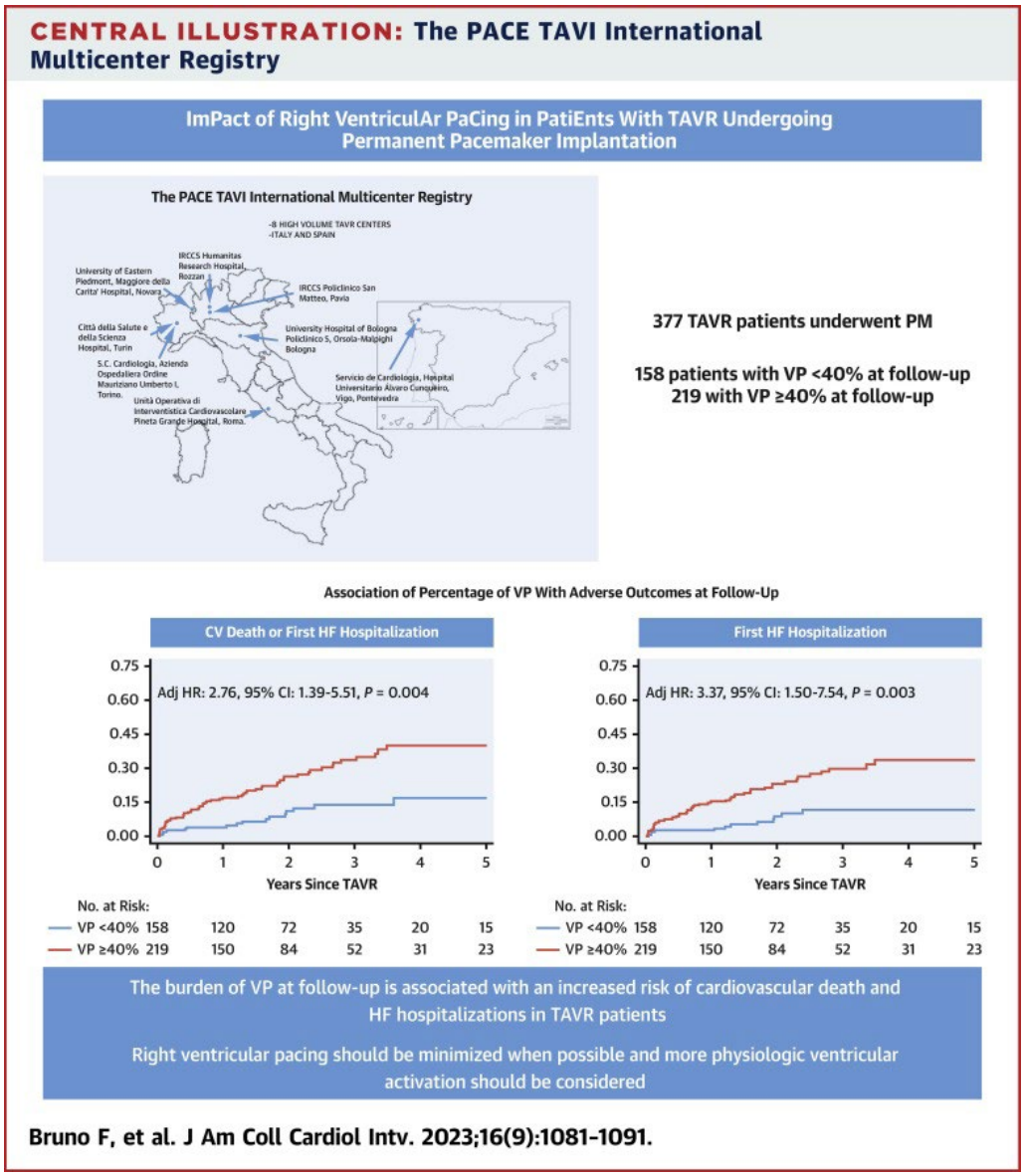


Figure 2. Incidence of Cardiovascular Death and All-Cause Death According to VP Percentage
(Left) Cardiovascular death. **(Right)** All-cause death. Abbreviations as in Figure 1.

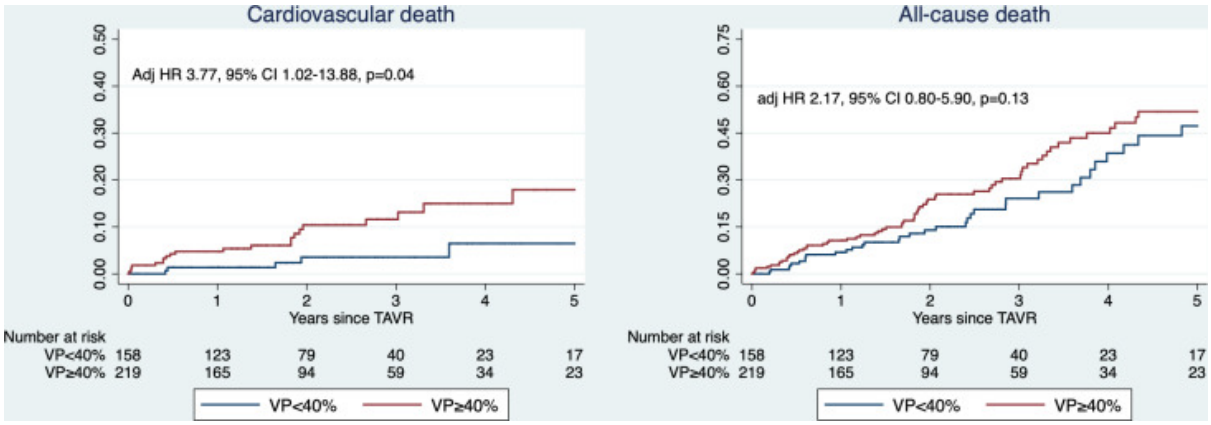


Figure 3. Changes of Left Ventricular Ejection Fraction Over Time in the Whole Population and in Patients With LVEF ≤40% According to VP Percentage
LVEF = left ventricular ejection fraction; VP = ventricular pacing.

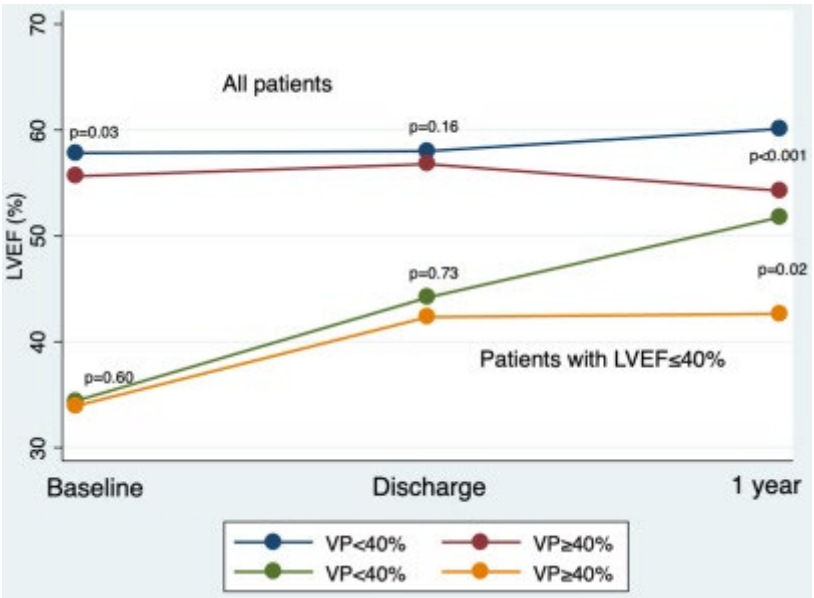


Figure 4. Symptom Status Over Time According to VP Percentage
FU = follow-up; NYHA = New York Heart Association; VP = ventricular pacing.