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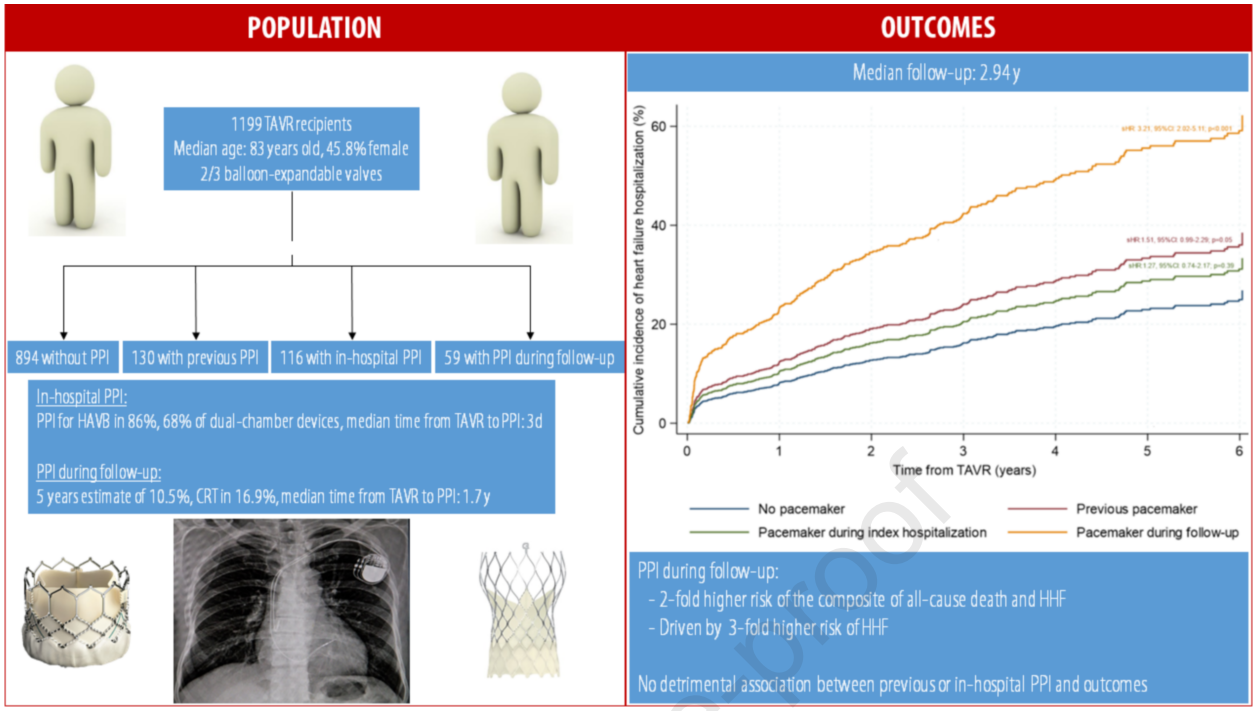

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Prognostic impact of permanent pacemaker implantation following transcatheter aortic valve replacement

Sam Sharobeem, MD[1], Dominique Boulmier, MD[1], Guillaume Leurent, MD[1], Marc Bedossa, MD[1], Christophe Leclercq, MD PhD[1], Philippe Mabo, MD[1], Raphael P. Martins, MD PhD[1], Jacques Tomasi, MD[2], Jean-Philippe Verhoye, MD,PhD[2], Erwan Donal, MD, PhD[1], Gwenaelle Sost, MD[3], Marielle Le Guellec, MSc[1], Hervé Le Breton, MD[1], and Vincent Auffret, MD, PhD[1].

Authors affiliations:

1. Université de Rennes 1, CHU Rennes Service de Cardiologie, Inserm LTSI U1099, F 35000 Rennes, France.
2. Université de Rennes 1, CHU Rennes Service de Chirurgie Cardiaque, Inserm LTSI U1099, F 35000 Rennes, France.
3. Université de Rennes 1, CHU Rennes Service de Gériatrie, F 35000 Rennes, France.

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Address for correspondence:

Vincent Auffret, MD, PhD

Service de Cardiologie

CHU Pontchaillou

2 rue Henri Le Guilloux, 35000 Rennes, France.

Email: vincent.auffret@chu-rennes.fr

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ABSTRACT

Background: Conduction disturbances requiring permanent pacemaker implantation (PPI) remain a common complication of transcatheter aortic valve replacement (TAVR).

Objectives: To determine the prognostic impact of PPI following TAVR, according to the timing of implantation relative to TAVR.

Methods: A total of 1199 patients (median age: 83 years old [78-86], 45.8% female) were included in the analysis, among whom 894 had no PPI, 130 had a previous PPI, 116 received in-hospital PPI, and 59 received PPI during follow-up. Median follow-up was 2.94 (1.42-4.32 years) years. The primary outcome was the composite of all-cause mortality and hospitalization for heart failure.

Results: PPI during follow-up was associated with a higher occurrence of the primary outcome (hazard ratio [HR]: 2.11, 95% confidence interval [CI]: 1.39-3.20) whereas previous and in-hospital PPI were not (HR: 0.96, 95%CI: 0.71-1.29, and HR:1.26, 95%CI: 0.88-1.81, respectively). PPI during follow-up associated with a higher risk of hospitalization for heart failure (sub HR: 3.21, 95%CI: 2.02-5.11) while this relation was only borderline significant for previous PPI (sub HR: 1.51, 95%CI: 0.99-2.29). In contrast, there was no relationship between in-hospital PPI and the subsequent risk of hospitalization for heart failure.

Conclusions: Previous PPI and in-hospital PPI had no long-term prognostic impact on the risk of all-cause mortality and hospitalization for heart failure, whereas PPI during follow-up associated with a higher risk of hospitalization for heart failure. The present study questions the deleterious influence of periprocedural post-TAVR PPI, which has previously been suggested by certain studies.

KEYWORDS

Aortic stenosis ; TAVR ; Conduction disturbances ; Permanent Pacemaker Implantation ; Heart Failure ;

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INTRODUCTION

In patients with severe, symptomatic, aortic valve stenosis and an intermediate to high surgical risk, transcatheter aortic valve replacement (TAVR) progressively became the standard of care over surgical aortic valve replacement (SAVR)[1,2]. Following the demonstration of its non-inferiority compared with SAVR among patients at low-surgical risk in recent randomized trials[3,4], the extension of TAVR indications to younger, less comorbid patients with a longer life expectancy seems inevitable[1,2]. Therefore, it appears of paramount importance to prevent TAVR-related complications, which may have a deleterious long-term effect.

Among these complications, conduction disturbances, i.e. new-onset persistent left bundle branch block (LBBB) and permanent pacemaker implantation (PPI), remain the most common with rates which did not significantly decrease over time despite increased operators experience and refined newer-generation devices[5]. Although several reports have attempted to provide recommendations regarding the in-hospital management of these conduction disturbances[5-7], guidelines are mainly based upon experts' opinion considering the lack of reliable prospective data to inform their management. Moreover, long-term data on the prognostic impact of post-TAVR PPI, remain scarce and equivocal[5,8] even though the deleterious nature of right ventricular cardiac pacing has already been demonstrated in other clinical setting[9-12]. Nonetheless, peri-procedural conduction disturbances usually result from a direct injury to the conduction system, which may have different pathophysiological and prognostic implications than a degenerative impairment. Thus, delineating the long-term impact of PPI, according to its timing relative to TAVR, is crucial to allow an appropriate shared decision-making among patients suitable to TAVR and SAVR.

In this setting, the objectives of this study were to clarify the long-term prognostic impact of PPI, according to its timing relative to TAVR, upon the risk of mortality and hospitalization for heart failure (HHF).

METHODS

A full version of the methods can be found in the appendix.

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Study population

Patients who underwent TAVR at a single center from February 2009 to June 2018 were studied. Exclusion criteria were in-hospital death, surgical conversion or unsuccessful TAVR procedure. All patients gave written informed consent for the procedures and anonymous collection of their data, which were prospectively gathered in an electronic database as part of the national registries[13]. The research reported in this paper adhered to the Helsinki Declaration as revised in 2013.

PPI status

Patients were separated in the following four groups according to the occurrence and timing PPI: no PPI, previous PPI (P-PPI), in-hospital PPI (i.e. during the index hospitalization, IH-PPI) and PPI during follow-up (FU-PPI).

Indications for PPI

In accordance with international guidelines[14,15], IH-PPI was indicated for persistent high degree atrioventricular block (HAVB), defined as type 2 second degree AVB or third degree AVB, not expected to resolve or symptomatic sinus node dysfunction. Among patients with milder conduction disturbances such as new-onset LBBB with or without PR interval prolongation, the final indication of PPI was at the discretion of the senior electrophysiologist responsible for the patient, taking into account clinical data and the in-hospital ECG evolution. For such patients with conduction disturbances not representing absolute PPI indications, a local electrophysiological study-guided PPI strategy was implemented in our center in June 2017. Details regarding this strategy have been previously published[16].

During follow-up, the indication of PPI was at the discretion of the physician responsible for the patient.

Follow-up

Follow-up was performed by on-site clinical visit and/or telephone at 1-month post-TAVR, at 1 year and yearly thereafter.

Outcomes

The primary objective of the present study was to assess the long-term clinical impact of PPI, according to its timing relative to TAVR, on the composite of all-cause death and HHF.

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Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range) depending on their distribution, which was assessed using the Kolmogorov-Smirnov test, and were compared using the Kruskal-Wallis test. Categorical variables were summarized as numbers (percentages), and compared using chi-square tests or the Fisher exact test as appropriate. HHF was evaluated using competing-risk models with all-cause mortality as a competing event. Competing-risk models were used to determine the predictors of HHF by reporting adjusted sub-hazard ratios (sub HR) with their 95% confidence intervals (CI). All-cause mortality was analyzed using Cox proportional hazard models. Parametric multistate survival models, adjusted for the previously identified variables, were performed to predict the probability of transitioning from one state (post-TAVR status, post-TAVR PPI status, post-TAVR HHF status, death) to another over time. Generalised linear model for repeated measures with interaction was used to compare the changes in LVEF at different time points between groups. All tests were 2-sided at the 0.05 significance level. Statistical analyses were conducted using Stata Statistical Software Release 13 (StataCorp, College Station, TX) and the Statistical Package for Social Sciences version 25 (SPSS Inc., IBM, Armonk, New York).

RESULTS

Baseline and in-hospital characteristics

During the study period, 1250 patients underwent a TAVR procedure. Thirty-nine died during the subsequent hospitalization, 9 needed a surgical conversion, whereas the procedure was unsuccessful in 3 patients. A total of 1199 TAVR patients (median age: 83 years old, 45.8% female), discharged alive after a successful TAVR procedure, were included in the present analysis. Among them, 130 had a previous PPI, 116 were implanted during the index hospitalization and 59 during follow-up. Median follow-up was 2.94 years (1.42-4.32 years). Baseline characteristics of the study population are shown in **table 1**.

Procedural characteristics and in-hospital outcomes

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Procedural and in-hospital data are available in **supplementary table 1**. Briefly, balloon-expandable devices were implanted in 66.9% of patients whereas 32.1% received self-expandable valves. Rates of new-onset persistent left bundle branch block were 17.3%, 6.6%, 15.2%, and 25.0% in the no PPI, P-PPI, IH-PPI, and FU-PPI groups, respectively. Treatments at discharge are summarized in **supplementary table 2**.

Timing and characteristics of PPI

The clinical indications for PPI, device type and timing of PPI are available in **supplementary tables 3 and 4.** For IH-PPI, the most common indication was HAVB (86.2%) and most of the devices were dual chamber pacemakers (68.1%). For FU-PPI, only 6 patients (10.2%, 0.6% of patients at risk) underwent PPI within 30 days of TAVR while the median time to implantation was 1.7 (0.5-2.8) years. A significant proportion of patients (16.9%) received cardiac resynchronization therapy (CRT) among this sub-group. The Nelson-Aalen estimates of the rate of PPI during follow-up among the 953 patients discharged without a permanent pacemaker are represented in **supplementary Figure 1.**

Prognostic impact of permanent pacemaker status

During the study period, 275 patients (22.9%) experienced HHF and 447 (37.3%) died. Annual estimates of HHF within 5 years post-TAVR were: 11.0% (95% CI: 9.3-13.0%), 17.3% (95% CI: 15.3-19.7%), 22.4% (95% CI: 19.8-25.3%), 27.0% (95% CI: 24.0-30.3%), and 33.6% (29.7-37.7%). In the FU-PPI group, the first HHF occurred before PPI in 22 patients (37.3%) and after in 37 patients (62.7%). In the former subgroup, the first HHF occurred within a week of PPI in 7 patients (31.8%). In the latter subgroup the median delay between PPI and HHF was 1.3 (0.4-2.1) years. Annual survival estimates within 5 years post-TAVR were: 93.5% (95% CI: 91.9-94.8%), 87.3% (95% CI: 85.0-89.1%), 78.4% (95% CI: 75.6-80.9%), 66.2% (95% CI: 62.8-69.4%), and 54.5% (95% CI: 50.7-58.6%).

Figure 1 depicts the Kaplan-Meier estimates of the rate of the composite primary outcome over time according to PPI status. Variables associated with the composite of all-cause death and HHF in univariate and multivariable regressions are shown in **Table 2.** FU-PPI was associated with a higher occurrence of the primary outcome (HR: 2.11, 95%CI: 1.39-3.20, p<0.001) whereas P-PPI and IH-PPI

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were not (HR: 0.96, 95%CI: 0.71-1.29, p =0.77 and HR:1.26, 95%CI: 0.88-1.81, p=0.21, respectively).

The Kaplan-Meier estimates of the rate of all-cause mortality according to PPI status are provided in **Figure 2**. **Supplementary Table 5** reports the univariate and multivariable correlates of all-cause death. Only P-PPI demonstrated a protective association with all-cause mortality in multivariable analysis (HR: 0.61, 95%CI: 0.43-0.87, p=0.006) whereas other PPI groups were not significantly associated with survival.

Figure 3 reports the cumulative incidence functions of HHF according to PPI status. FU-PPI associated with a significantly higher risk of HHF (sub HR: 3.21, 95%CI: 2.02-5.11, p<0.001) while this relation was only borderline significant for P-PPI (sub HR: 1.51, 95%CI: 0.99-2.29, p=0.05). In contrast, there was no relationship between IH-PPI and the subsequent risk of HHF (**Supplementary Table 6**).

The adjusted probabilities of transitioning from post-TAVR status to post-TAVR HHF and death at each time point in the overall population and according to PPI status and timing, estimated by parametric multistate models, are represented in **supplementary Figures 2 and 3**, respectively. Regarding transition to HHF, there was an increasing probability from the no-PPI to P-PPI to IH-PPI and to FU-PPI within the first three years post-TAVR. Regarding transition to death, the probability steadily increased in all groups with a markedly higher probability at each time point in the FU-PPI group.

Changes in LVEF over time

An echocardiographic LVEF was available at a median follow-up of 408 days (361-961; mean 665 days) in 1089 patients. Changes in LVEF over time according to PPI status are shown in **Figure 4.**

DISCUSSION

The main findings of this large cohort of patients discharge alive after a TAVR procedure can be summarized as follows: 1- P-PPI patients showed evidence of a more evolved valvular heart disease at baseline. 2- IH-PPI was performed in 10.8% of patients, whereas FU-PPI occurred at a median timing of 1.7 years post-TAVR and involved a significant proportion of CRT (16.9%). 3- No detrimental

association was found between P-PPI or IH-PPI and the composite primary outcome of all-cause death or HHF. On the contrary, FU-PPI was independently associated with the primary outcome; a result driven by a 3-fold higher risk of HHF. 4- Despite an increased probability of transitioning to HHF and death among IH-PPI patients in multistate models, our multivariable regressions results suggest that the pacemaker implantation *per se* does not play a significant role in the long-term risk of these outcomes.

The rate of IH-PPI in the present study is in the lower range of previously published data[5,17], which may be explained by a restrictive implantation strategy. Indeed, the indication for pacing was persistent HAVB in 86.2% and symptomatic sinus node dysfunction in 0.9% of IH-PPI patients, which represent class I indications for pacing in recent guidelines[15]. In contrast, 71.4% and 5.6% of patients in a recent multicenter series investigating the long-term effect of 30-days PPI following TAVR received a permanent pacemaker for HAVB and sinus node dysfunction, respectively[8]. The indications for pacing was not reported in another recent single-center report of 816 patients focusing on the long-term impact of post-TAVR conduction disturbances[18]. Furthermore, in the present study, up to 31.3% of other indications were retained after an electrophysiological study-guided implantation strategy, which demonstrated its accuracy in identifying patients who can be safely discharged without PPI, thus avoiding unnecessary PPI[16]. The linear nature of FU-PPI**,** with only 0.6% of patients at risk undergoing PPI within 30 days of TAVR, also supports the appropriate selection of IH-PPI recipients in the present report.

Previous studies reached conflicting results regarding the impact of early PPI post-TAVRupon the risk of mortality and HHF at follow-up[8,19-23]. Most of these studies were of moderate size with a limited follow-up (<2 years). A recent study-level meta-analysis including >20000 patients with post-TAVR PPI suggested its deleterious influence on 1-year all-cause mortality as well as HHF, yet not cardiovascular death[24]. Chamandi et al. also reported a significant association between PPI within 30 days of TAVR and HHF among 1629 TAVR recipients at a median of 4 years of follow-up, without demonstrating a meaningful association either with cardiac or total mortality[8]. In their single-center series, Jørgensen et al. reported a higher risk of HHF and all-cause mortality among TAVR recipients with 30-days PPI at a median follow-up of 2.5 years. In the present study, P-PPI and IH-PPI had no

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detrimental association with survival or HHF, while only FU-PPI was significantly associated with HHF and the composite of all-cause death and HHF. Thereby, there are overall significant discrepancies in the literature regarding the true impact of pacing in TAVR recipients. A number of reasons may explain these differences. First, in studies by Chamandi et al. and Jørgensen et al. the PPI group included IH-PPI and FU-PPI patients implanted within 30 days of TAVR[8,18]. Nonetheless, it can be assumed that the majority of pacemakers were implanted during the index hospitalization given the median time from TAVR to PPI of 2 (1-4) days and the median length of hospital stay of 7 (5-9) days reported by Chamandi et al[8]. Therefore, it is unlikely that this difference in the definition of the PPI group played a significant role in the differing association of PPI with clinical outcomes. Second, the detrimental influence of a high burden (>40%) of right ventricular pacing has been previously highlighted[18,25]. These previous studies reported rates of approximately 50% of high pacing burden at follow-up among TAVR recipients who underwent early post-procedural PPI[8,18,25]. Unfortunately, the ventricular pacing percentage at follow-up was not routinely reported in our database. However, we demonstrated in a recent study including 78 TAVR recipients who benefited from our local electrophysiological study-guided PPI strategy, that 85% of patients had >1% of pacing, which is comparable to the data of Chamandi et al., nonetheless with only 25% of patients demonstrating a high pacing burden at follow-up[8,16]. Although a higher pacing burden may be expected among patients with unequivocal pacing indications such as HAVB, these data may also reflect a careful programming of devices to preserve the spontaneous conduction of patients. Of note, it has previously been demonstrated that up to 45% of TAVR patients who underwent PPI have sufficient atrioventricular conduction to avoid pacing at follow-up suggesting the importance of regular pacemaker interrogations and reprogramming in this population[26]. In keeping with this point, 68% of the IH-PPI patients received dual-chamber devices, which may offer the opportunity for a more physiologic pacing, compared with 57% in the study by Chamandi et al[8]. Third, it may also be hypothesize that significant residual confounding played a crucial role in previous studies, PPI being solely an innocent bystander of the worse outcomes observed. The fact that the association between PPI and increased 1-year mortality was independent of cardiac causes of death in the recent meta-analysis by Faroux et al supports this hypothesis[24]. The adjustment strategy performed in the present study, especially with the

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inclusion of echocardiographic parameters at discharge such as pulmonary hypertension, which we previously identified as a strong predictor of HHF post-TAVR[27], may have contributed to mitigate the association between IH-PPI and HHF. Overall, it should be stressed that our data do not support a lower threshold for IH-PPI. Rather, we believe that physicians should apply a careful selection strategy of PPI recipients post-TAVR based on class I indications in recent guidelines and rely on electrophysiological studies or ambulatory ECG monitoring, which are being further evaluated, to guide their management in equivocal cases[15].

From a pathophysiological standpoint, IH-PPI may affect patients with a direct injury to the conduction system with minimal or without significant structural heart damage whereas PPI remote from TAVR (either P-PPI or FU-PPI) may involve patients with a damage to their conduction pathways reflecting a more global degenerative impairment of their cardiac structure and function in the setting of more evolved valvular heart diseases[28]. Aside from the overall cardiac involvement of severe aortic stenosis, the former group is also more susceptible to experience a recovery of the atrioventricular conduction leading to low ventricular pacing rates unlikely to promote an asynchrony-induced left ventricular dysfunction and its subsequent complications[9-12,29]. Regarding FU-PPI, its exact role in the occurrence of HHF remains elusive despite the significant association evidenced in the present report (sub HR 3.21, 95% CI:2.02-5.11; $p<0.001$). Indeed the occurrence of HHF before PPI in a significant proportion of these patients and the high implantation rate of CRT (16.9%) among them, point towards an unfavorable evolution following TAVR independent of permanent pacing. Also, undiagnosed bradyarrhythmia may have precipitated these unfavorable events in some cases. Nevertheless, almost two-third of these patients had their first HHF after PPI, which may also suggest that they represent a cohort particularly sensitive to chronic right ventricular pacing. Overall, these data suggest we should raise our awareness regarding the myocardial involvement contributing to symptoms in severe aortic stenosis, provide patients with optimal guidelines-directed medical therapies, and ensure a close follow-up of TAVR recipients, especially those requiring pacing at follow-up.

This study represents a retrospective analysis of prospectively collected data and is subject to the inherent limitations of this study design. This was a single center report, which may limit the

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generalizability of our results. The lack of data regarding pacing percentage at follow-up precluded the analysis of its role in the long-term outcomes post-TAVR. We also acknowledge the lack of information regarding pacing indications prior to TAVR and at follow-up. Finally, although the follow-up of the present study is among the longest in studies focusing on the effect of pacing post-TAVR, it remains somewhat limited and we cannot exclude that it had some influence upon our results.

CONCLUSION

IH-PPI has no long-term detrimental influence on the composite of all-cause mortality and HHF, whereas FU-PPI increases its risk, mainly because of a higher risk of HHF. Provided an optimal patients selection for IH-PPI, these results are of major importance to inform TAVR candidates regarding the long-term risk of the procedure. Moreover, whether FU-PPI patients represent a cohort particularly sensitive to chronic right ventricular pacing should be evaluated in future studies. In the interim, physicians should pay the utmost attention to ensure a careful follow-up and optimize heart failure therapies (drug and/or device, i.e. CRT) among these patients.

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FIGURES LEGENDS

Figure 1 – Kaplan-Meier estimates of the composite of all-cause mortality and hospitalization for heart failure

CI: Confidence interval; HR: Hazard ratio, PPI: Permanent pacemaker implantation; TAVR: Transcatheter aortic valve replacement

Figure 2 – Kaplan-Meier estimates of all-cause death according to PPI status

Abbreviations as in Figure 1

Figure 3 – Cumulative incidence function of hospitalization for heart failure according to PPI status

sHR: Sub hazard ratio, other abbreviations as in Figure 1

Figure 4 – Changes in left ventricular ejection fraction over time according to PPI status

LVEF: left ventricular ejection fraction; PPI: Permanent pacemaker implantation

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Table 1 – Characteristics of the study population according to the presence and timing of implantation of a permanent pacemaker

	Patients without a permanent pacemaker (n=894)	Patients with a previous permanent pacemaker (n=130)	Patients with in-hospital permanent pacemaker implantation (n=116)	Patients with permanent pacemaker implantation during follow-up (n=59)	p-value
Baseline clinical characteristics					
Age, years	83.0 (78.75-86.0)	82.0 (77.75-85.0)	83.0 (78.0-86.0)	82.0 (78.0-86.0)	0.73
Female sex	441 (49.3)	44 (33.8)	44 (37.9)	20 (33.9)	<0.001
Body-mass index, kg/m²	26.1 (23.3-29.4)	26.65 (23.6-29.8)	25.90 (23.3-30.08)	26.4 (23.3-30.15)	0.84
Body Surface area, m²	1.78 ± 0.21	1.82 ± 0.20	1.78 ± 0.22	1.82 ± 0.23	0.19
NYHA class III or IV	365 (40.9)	69 (53.1)	55 (47.8)	30 (50.8)	0.02
Previous acute heart failure	315 (35.4)	56 (43.1)	34 (29.3)	26 (44.1)	0.08
NT-proBNP, pg/ml	1579 (704-3477)	2163 (1057-4405)	2141 (816-3951)	1637 (691-4787)	0.04
Medical history					
Diabetes mellitus					0.23
Oral antidiabetic drugs	130 (14.6)	19 (14.6)	20 (17.2)	8 (13.6)	
Insulin-treated	38 (4.3)	12 (9.2)	5 (4.3)	5 (8.5)	
Hypertension	624 (70.0)	82 (63.1)	79 (68.1)	41 (69.5)	0.45
Coronary artery disease					0.39
Single-vessel disease	176 (19.8)	23 (17.8)	22 (19.1)	14 (24.1)	
Two-vessel disease	104 (11.7)	20 (15.5)	17 (14.8)	12 (20.7)	
Three vessel disease	78 (8.8)	15 (11.6)	13 (11.3)	6 (10.3)	
Previous myocardial infarction	76 (8.5)	10 (7.7)	16 (13.8)	3 (5.1)	0.18
Previous CABG	93 (10.4)	13 (10.0)	16 (13.8)	12 (20.3)	0.09
Previous PCI	178 (19.9)	30 (23.1)	20 (17.2)	13 (22.0)	0.69
Previous balloon aortic valvuloplasty	78 (9.0)	18 (14.8)	5 (4.4)	7 (12.3)	0.04
Previous SAVR	37 (4.1)	8 (6.2)	1 (0.9)	2 (3.4)	0.20
Other cardiac surgery	22 (2.5)	3 (2.3)	4 (3.4)	4 (6.8)	0.25
Atrial fibrillation	309 (34.6)	73 (56.2)	54 (46.6)	20 (33.9)	<0.001
Previous pacemaker	-	130 (100)	-	-	
ICD	-	7 (5.5)	-	-	
CRT	-	9 (7.4)	-	-	

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Cerebrovascular disease	153 (17.2)	18 (13.8)	15 (12.9)	13 (22.0)	0.35
Previous stroke/TIA	104 (11.6)	22 (16.9)	13 (11.2)	4 (6.8)	0.19
Peripheral arterial disease	118 (13.2)	14 (10.8)	17 (14.7)	12 (20.3)	0.33
Previous chest radiotherapy	76 (8.6)	11 (8.5)	11 (9.5)	6 (10.2)	0.97
Chronic lung disease	298 (33.4)	46 (35.4)	35 (30.2)	24 (40.7)	0.54
Chronic kidney disease					0.15
Moderate	296 (33.3)	59 (45.7)	45 (39.8)	21 (35.6)	
Severe	37 (4.2)	6 (4.7)	2 (1.8)	3 (5.1)	
Dialysis	7 (0.8)	0 (0.0)	2 (1.8)	0 (0.0)	
Severe liver disease	10 (1.1)	2 (1.6)	0 (0.0)	1 (1.7)	0.63
Logistic EuroScore I	12.1 (8.6-19)	13.8 (9-20.8)	11.0 (8-20.8)	12.0 (8.5-17.9)	0.66
Logistic EuroScore II	2.7 (1.8-4.3)	2.9 (1.9-5.2)	2.6 (1.8-4.9)	2.9 (1.9-3.8)	0.77
Echocardiography					
LVEF (%)	60.0 (50-65)	59.0 (40.0-62.0)	60.0 (50.0-66.0)	55.0 (45.0-62.0)	<0.001
LVEF < 50%	204 (22.8)	48 (37.2)	28 (24.1)	21 (35.6)	0.001
LVEDD, mm	47.0 (42.0-52.0)	49.0 (45.0-56.0)	48.0 (43.7-53.5)	48.0 (44.0-52.0)	0.02
Aortic valve area (cm²)	0.70 (0.58-0.80)	0.70 (0.60-0.84)	0.70 (0.60-0.80)	0.77 (0.66-0.88)	0.03
Mean aortic gradient (mmHg)	51.0 (42.0-62.0)	44.5 (36.0-54.2)	51.0 (42.8-59.9)	49.0 (37.3-58.0)	<0.001
Mean aortic gradient <40 mmHg	153 (17.1)	42 (32.3)	15 (12.9)	15 (25.4)	<0.001
Aortic regurgitation grade III or IV	32 (3.9)	3 (2.5)	5 (4.7)	0 (0.0)	0.39
Mitral regurgitation grade III or IV	36 (4.1)	8 (6.5)	6 (5.4)	1 (1.8)	0.44
Moderate or severe mitral stenosis	65 (7.8)	8 (6.8)	10 (9.0)	5 (9.1)	0.92
sPAP, mmHg	40.0 (30.0-50.0)	45.0 (35.0-57.0)	43.0 (31.0-55.0)	42.5 (32.8-46.3)	0.08
Pulmonary hypertension					0.06
Moderate (sPAP:31-60 mmHg)	470 (54.0)	81 (62.3)	66 (57.4)	38 (66.7)	
Severe (sPAP: >60 mmHg)	79 (9.1)	17 (13.1)	13 (11.3)	4 (7.0)	
Right ventricular dysfunction	95 (11.5)	31 (27.4)	15 (13.4)	6 (10.9)	<0.001
Tricuspid regurgitation grade III or IV	33 (4.5)	10 (9.3)	6 (5.6)	1 (2.1)	0.14

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as number (percentage). CABG: Coronary artery bypass graft; CRT: Cardiac resynchronization therapy; EuroSCORE= European System for Cardiac Operative Risk Evaluation; HF: Heart failure; ICD: Implantable cardioverter-defibrillator; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New-York Heart Association; PCI: Percutaneous coronary intervention; sPAP: Systolic pulmonary artery pressure; TIA: Transient ischemic attack; SAVR: Surgical aortic valve replacement; STS-PROM= Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR: Transcatheter aortic valve replacement

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Table 2 - Univariate and multivariable predictors of the composite of all-cause death and heart failure hospitalization

Variable	Univariate HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
PPI				
Previous PPI	1.31 (1.00-1.72)	0.05	0.96 (0.71-1.29)	0.77
In-hospital PPI	1.45 (1.03-2.03)	0.03	1.26 (0.88-1.81)	0.21
PPI during follow-up	2.32 (1.55-3.49)	<0.001	**2.11 (1.39-3.20)**	**<0.001**
Age	1.02 (1.01-1.03)	0.004	**1.02 (1.00-1.03)**	**0.009**
Female sex	0.82 (0.70-0.97)	0.02	0.81 (0.66-1.00)	0.054
Body surface area	1.49 (1.01-2.18)	0.04	1.25 (0.72-2.19)	0.43
Previous aortic balloon valvuloplasty	1.29 (0.99-1.67)	0.056	0.97 (0.73-1.29)	0.86
Previous cerebrovascular disease	1.24 (1.01-1.53)	0.04	1.23 (0.98-1.54)	0.075
Chest radiotherapy	0.77 (0.58-1.04)	0.09	0.95 (0.69-1.30)	0.74
Atrial fibrillation	1.82 (1.54-2.15)	<0.001	**1.34 (1.11-1.62)**	**0.002**
NYHA III or IV	1.20 (1.01-1.41)	0.03	1.08 (0.90-1.29)	0.42
NTproBNP	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	0.075
Previous acute heart failure	1.69 (1.43-2.00)	<0.001	**1.30 (1.08-1.58)**	**0.007**
Chronic lung disease	1.39 (1.18-1.65)	<0.001	**1.30 (1.08-1.56)**	**0.005**
Previous diabetes mellitus				
Oral antidiabetic drugs	1.22 (0.98-1.54)	0.08	1.10 (0.86-1.40)	0.44
Insulin-treated	1.74 (1.24-2.43)	0.001	**1.58 (1.11-2.25)**	**0.012**
Chronic kidney disease				
Moderate	1.52 (1.28-1.80)	<0.001	**1.39 (1.14-1.69)**	**0.001**
Severe	1.32 (0.86-2.03)	0.21	1.09 (0.69-1.73)	0.71
Dialysis	1.93 (0.72-5.20)	0.19	0.79 (0.25-2.51)	0.69
Logistic EuroScore II	1.03 (1.01-1.06)	0.006	0.99 (0.96-1.02)	0.45
Mean aortic gradient prior to TAVR	0.991 (0.986-0.996)	0.002	**0.99 (0.99-1.00)**	**0.035**
Aortic regurgitation grade III or IV prior to TAVR	0.48 (0.25-0.93)	0.03	**0.49 (0.27-0.92)**	**0.026**
Moderate or severe mitral stenosis prior to TAVR	1.38 (1.02-1.86)	0.04	**1.38 (1.00-1.90)**	**0.047**
Approach				
Sub-clavian	1.02 (0.73-1.43)	0.91	0.95 (0.66-1.36)	0.77
Transaortic	1.11 (0.75-1.65)	0.61	0.89 (0.58-1.38)	0.62
Transapical	0.82 (0.57-1.17)	0.27	1.03 (0.69-1.53)	0.89
Transcarotid	1.58 (0.99-2.51)	0.05	1.17 (0.72-1.92)	0.52
Major vascular complications	1.50 (0.94-2.40)	0.09	**1.83 (1.13-2.99)**	**0.015**
Acute kidney injury stage 2 or 3	2.00 (1.03-3.91)	0.04	1.26 (0.62-2.57)	0.65
Percentage of optimal daily recommended dose of RAS inhibitor at discharge				
1% - < 25%	1.19 (0.80-1.76)	0.39	0.91 (0.60-1.39)	0.23
25% - < 50%	0.95 (0.75-1.21)	0.68	0.91 (0.71-1.18)	0.49
50% - < 75%	0.84 (0.66-1.06)	0.14	0.86 (0.67-1.10)	0.24
75% - 100%	0.77 (0.58-1.03)	0.08	0.92 (0.68-1.43)	0.57
Loop diuretics at discharge				
Dose < 40 mg/d	1.25 (1.04-1.51)	0.02	1.01 (0.82-1.25)	0.90
Dose > 40 mg/d	2.03 (1.62-2.56)	<0.001	1.27 (0.97-1.67)	0.08
LVEF at discharge	0.988 (0.982-0.994)	<0.001	0.99 (0.99-1.00)	0.23
LVEDD at discharge	1.01 (1.00-1.02)	0.02	1.00 (0.99-1.02)	0.91
Indexed aortic valve area at discharge	0.73 (0.55-0.98)	0.03	0.82 (0.58-1.15)	0.24
Aortic regurgitation grade III or IV at	1.80 (0.94-3.29)	0.08	1.57 (0.78-3.18)	0.21

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discharge				
Tricuspid regurgitation grade III or IV at discharge	2.15 (1.35-3.46)	0.001	0.99 (0.56-1.76)	0.96
Pulmonary hypertension at discharge				
Moderate (sPAP:31-60 mmHg)	1.70 (1.44-2.02)	<0.001	**1.61 (1.34-1.94)**	**<0.001**
Severe (sPAP: >60 mmHg)	4.19 (2.87-6.11)	<0.001	**3.44 (2.25-5.25)**	**<0.001**

CI: confidence interval; HR: hazard-ratio; PPI: permanent pacemaker implantation; RAS: renin-angiotensin system. Other abbreviations as in Table 1

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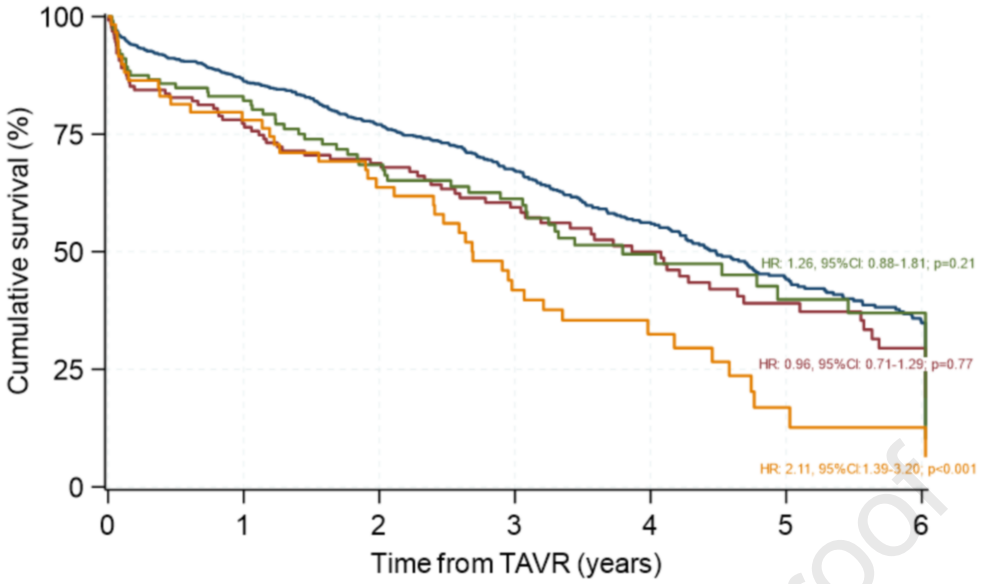

Number at risk

894	722	515	348	216	114	72
130	96	79	57	39	22	14
116	89	62	45	25	14	11
59	46	34	20	11	4	2

No pacemaker
Previous pacemaker
Pacemaker during index hospitalization
Pacemaker during follow-up

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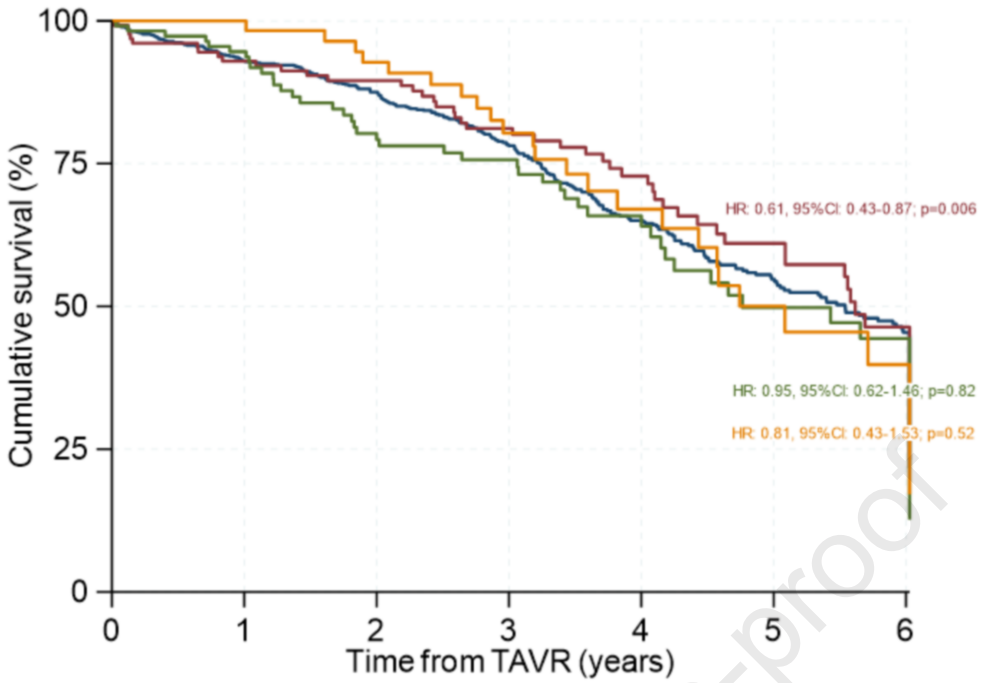

Number at risk

894	768	586	409	255	143	91
130	115	103	78	54	33	20
116	102	74	59	36	20	14
59	59	49	36	20	12	7

No pacemaker
Previous pacemaker
Pacemaker during index hospitalization
Pacemaker during follow-up

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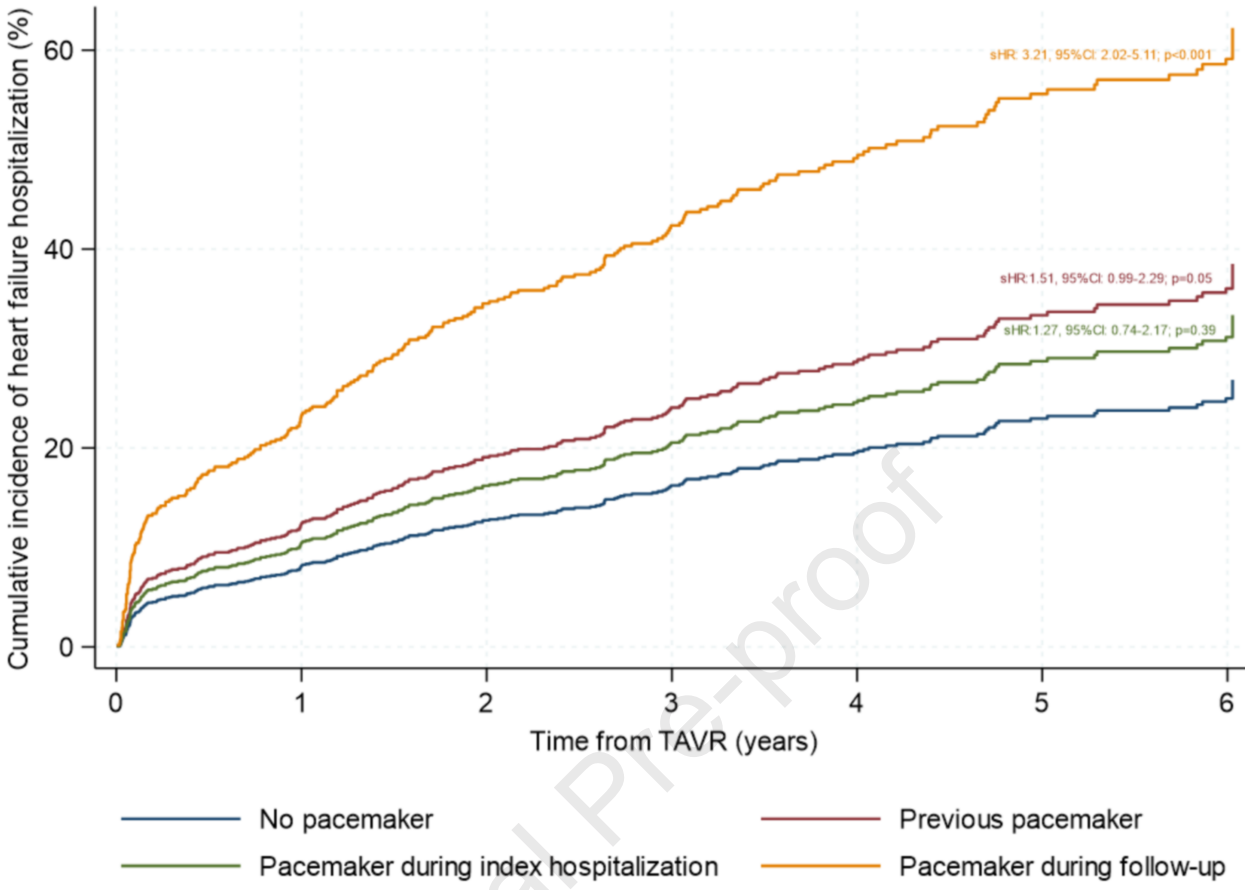

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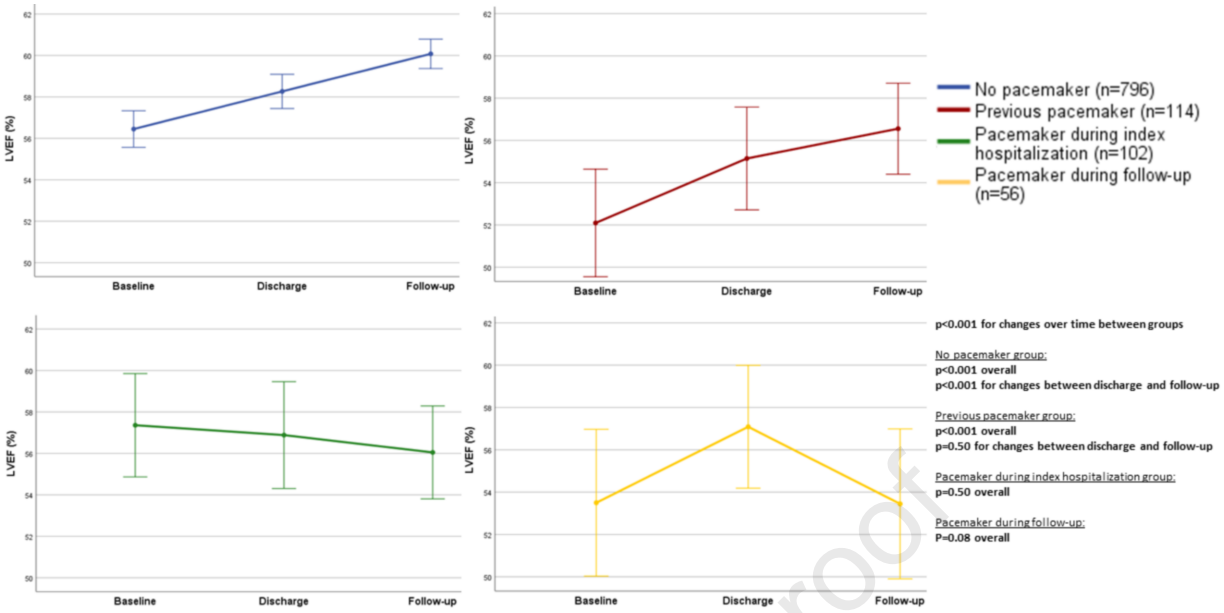

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