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Indications and predictors for pacemaker implantation after isolated aortic valve replacement with bioprostheses: the CAREAVR study

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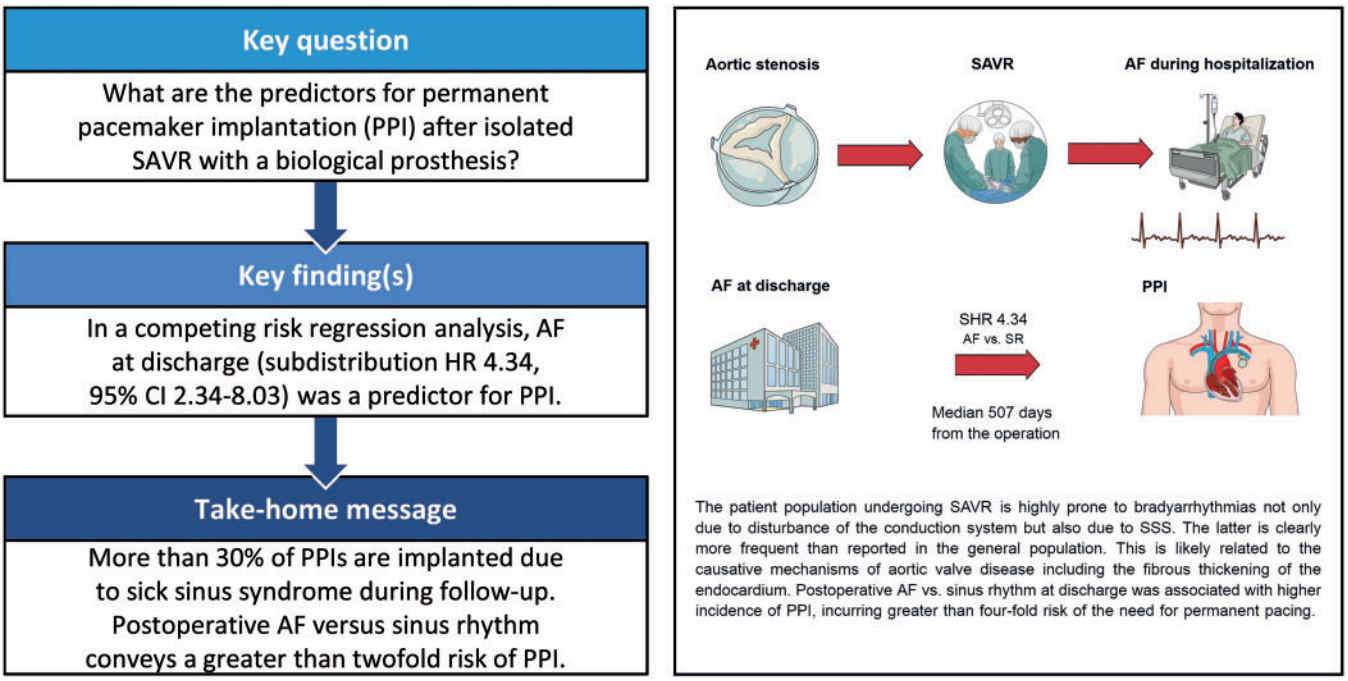

Abstract

OBJECTIVES: We sought to study the indications, long-term occurrence, and predictors of permanent pacemaker implantation (PPI) after isolated surgical aortic valve replacement with bioprostheses.

METHODS: The CAREAVR study included 704 patients (385 females, 54.7%) without a preoperative PPI (mean ± standard deviation age 75 ± 7 years) undergoing isolated surgical aortic valve replacement at 4 Finnish hospitals between 2002 and 2014. Data were extracted from electronic patient records.

RESULTS: The follow-up was median 4.7 years (range 1 day to 12.3 years). Altogether 56 patients received PPI postoperatively, with the median 507 days from the operation (range 6 days to 10.0 years). The PPI indications were atrioventricular block (31 patients, 55%) and sick sinus syndrome (21 patients, 37.5%). For 4 patients, the PPI indication remained unknown. A competing risks regression analysis (Fine–Gray method), adjusted with age, sex, diabetes, coronary artery disease, preoperative atrial fibrillation (AF), left ventricular ejection fraction, New York Heart Association class, AF at discharge and urgency of operation, was used to assess risk factors for PPI. Only AF at discharge (subdistribution hazard ratio 4.34, 95% confidence interval 2.34–8.03) was a predictor for a PPI.

CONCLUSIONS: Though atrioventricular block is the major indication for PPI after surgical aortic valve replacement, >30% of PPIs are implanted due to sick sinus syndrome during both short-term follow-up and long-term follow-up. Postoperative AF versus sinus rhythm conveys >4-fold risk of PPI.

Clinical trial registration: clinicaltrials.gov Identifier: NCT02626871

Keywords: Aortic valve replacement • Conduction impairment • Permanent pacemaker implantation • Risk factor

ABBREVIATIONS

AF	Atrial fibrillation
AVB	Atrioventricular block
AVR	Aortic valve replacement
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PPI	Permanent pacemaker implantation
SAVR	Surgical aortic valve replacement
SSS	Sick sinus syndrome

INTRODUCTION

Aortic valve disease is the most common valvular defect requiring surgical or percutaneous treatment. Degenerative valve calcification increases as the population gets older. Fibrosis and calcification in stenotic aortic valves may extend into the annulus, interventricular septum and atrioventricular (AV) node [1]. Consequently defects in the AV conduction are relatively common in patients with aortic valve disease. Among these patients, a subsequent aortic valve replacement (AVR) may result in further AV conduction block necessitating implantation of a permanent pacemaker (PPI) [2–6].

With the advent of transcatheter AVR, increased risk for PPI shortly after procedure is well documented [7]. However, little is known about PPI occurrence and indications after isolated surgical AVR (SAVR) with bioprostheses due to a lack of long-term follow-up data after operation [8, 9]. Such data might be useful for assessing risks and benefits of treatment options as well as for patient counselling in patients undergoing SAVR or transcatheter AVR. Identification of patients at increased risk of PPI after SAVR is clinically meaningful to prevent arrhythmic complications such as syncope, exercise intolerance, heart failure and sudden death.

We sought to assess the incidence, timing, indications and predictors for PPI after isolated SAVR with a biological prosthesis.

PATIENTS AND METHODS

This study was conducted under the auspices of a multicentre retrospective registry, CAREAVR (ClinicalTrials.gov Identifier: NCT02626871), which includes patients who underwent isolated SAVR with a bioprosthesis at 4 University Hospitals in Finland (Turku, Oulu and Kuopio University Hospitals between 2002 and 2014 and Helsinki 2006–2014). For all the index patients, the indication for SAVR was aortic stenosis. The aim of CAREAVR is to assess the incidences of preoperative and postoperative atrial fibrillation (AF), strokes and systemic embolisms, PPIs, major bleeds, postpericardiotomy syndromes and mortality in patients undergoing isolated SAVR with a bioprosthesis.

Altogether 704 SAVR patients without preoperative PPI were included in the study. Patients who underwent any other major concomitant cardiac surgery procedure were excluded from this study. To obtain reliable and accurate follow-up data, only patients from the hospitals' catchment areas were included in this study. All the major adverse events including PPI, cerebrovascular events, bleeding and myocardial infarctions were treated in the same index hospitals, and therefore, the patient follow-up for adverse events can be considered reliable. The patient records were individually reviewed with a structured data-collection protocol for preoperative and perioperative data, discharge data and long-term follow-up events, including PPI, AF, stroke, bleeding and mortality. The information about preoperative rhythm was extracted from 12-lead preoperative EKG. The causes of death were retrieved from Statistics Finland. This governmental office monitors the time and causes of all deaths in Finland.

Data were entered in an electronic case-report form. An independent third-party data monitor checked the integrity of the data for each study site.

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. Because of the retrospective, registry-based nature of the study, informed consent was not required. The study conforms to the Declaration of Helsinki.

Statistical analysis

The statistical analyses were performed using SPSS, version 24 (IBM Corporation, Armonk, NY, USA), and STATA, version 15 (StataCorp LLC, College Station, TX, USA). Continuous variables were reported as mean ± standard deviation if normally distributed and as median (25th–75th percentiles) if they were skewed. The data were tested for normal distribution using Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables were described as counts and percentages. Pearson χ^2, Fisher's exact test, unpaired *t*-test and Mann–Whitney test were used for univariable analysis. Analyses were exploratory in nature. Competing risks regression analysis (Fine–Gray method) implemented with STATA, with all-cause mortality as a competing risk, adjusted with age, sex, diabetes, coronary artery disease, preoperative AF

Table 1: Preoperative data of 704 patients undergoing isolated aortic valve replacement divided into groups based on PPI

	PPI ($n = 56$)	No PPI ($n = 648$)	P-value
Preoperative data			
Age (years), mean ± SD	76 ± 7	75 ± 7	0.430
Females, *n* (%)	34 (60.7)	351 (54.2)	0.387
Weight (kg), mean ± SD	78 ± 23	78 ± 20	0.961
Height (cm), mean ± SD	164 ± 11	163 ± 20	0.947
BMI (kg/m^2), mean ± SD	27.6 ± 5.4	28.1 ± 10.6	0.704
NYHA class, *n* (%)			0.099[a]
I	6 (10.7)	98 (15.1)	
II	17 (30.4)	232 (35.)	
III	26 (46.4)	272 (42.0)	
IV	7 (12.5)	46 (7.1)	
Heart rate, mean ± SD	68 ± 10	70 ± 14	0.269
EKG preoperatively, *n* (%)			0.293[a]
Sinus rhythm	44 (78.6)	491 (75.8)	
Atrial fibrillation	5 (8.9)	87 (13.4)	
Treatment for dyslipidaemia, *n* (%)	38 (67.9)	373 (57.6)	0.178
Treatment for diabetes, *n* (%)	13 (23.2)	138 (21.3)	0.484
Treatment for hypertension, *n* (%)	43 (76.8)	483 (74.5)	0.512
Coronary artery disease, *n* (%)	16 (28.6)	193 (29.8)	0.956
Previous myocardial infarction, *n* (%)	4 (7.1)	51 (7.9)	0.722
Previous percutaneous coronary intervention, *n* (%)	5 (8.9)	62 (8.0)	0.947
Previous coronary bypass, *n* (%)	4 (7.1)	24 (3.7)	0.254
Previous aortic valve surgery, *n* (%)	1 (1.8)	15 (2.3)	0.742
Active endocarditis, *n* (%)	3 (5.4)	17 (2.6)	0.294
Previous endocarditis, *n* (%)	2 (3.6)	5 (0.8)	0.057
Recent myocardial infarction, *n* (%)	0	13 (2.0)	0.265
Chronic lung disease, *n* (%)	10 (17.9)	120 (18.5)	0.965
Occlusive arterial disease (ASO), *n* (%)	5 (8.9)	35 (5.4)	0.342
Active smoking, *n* (%)	5 (8.9)	44 (6.8)	0.676
Preoperative anti-arrhythmic medication, *n* (%)			
β-blocking agents	36 (64.3)	409 (63.6)	0.919
Verapamil	1 (1.8)	1 (0.2)	0.028
Amiodarone	2 (3.6)	8 (1.2)	0.160
Sotalol	0	1 (0.2)	0.768
Digoxin	3 (5.4)	45 (7.0)	0.643

Statistical tests: Pearson χ^2 test.

[a]Gamma test.

ASO: arteriosclerosis obliterans; BMI: body mass index; NYHA: New York Heart Association functional classification; PPI: permanent pacemaker implantation; SD: standard deviation.

(preoperative EKG), left ventricular ejection fraction (LVEF), preoperative New York Heart Association (NYHA) class, rhythm at discharge (AF versus sinus rhythm) and urgency of the operation (elective, urgent and salvation), was used to assess risk factors for PPI. The putative predictors were chosen on the basis of plausible *a priori* biological link. Two-sided *P*-value <0.05 were considered statistically significant.

RESULTS

The mean age of the patients was 75 ± 7 years and 385/704 (54.7%) were females. The follow-up was median 4.7 years (range 1 day to 12.3 years). Baseline characteristics of patients with and without a forthcoming PPI are presented in Table 1. Patients with a PPI had a higher preoperative NYHA class than those without the need for a PPI and a larger proportion of them had verapamil as a preoperative antiarrhythmic medication (Table 1). These were the sole baseline differences observed between the groups. Data pertaining to perioperative and postoperative characteristics of interest are presented in Table 2, and data pertaining to aortic valve disease and conduction abnormalities are presented in Table 3.

A total of 179 patients (25.4%) had preoperative AF, almost half of these being permanent AF (Table 1). The groups with and without postoperative PPI had a similar prevalence of preoperative AF. Altogether 479 (68.0%) patients had postoperative AF. Fifty-six patients (8.0%) received PPI postoperatively, with the median 507 days from the operation (range 6 days to 10.0 years). Both groups (PPI versus no PPI) had similar late mortality rates (19.6% vs 19.1%). The recorded reasons for death within these groups included cancer-related death [1 vs 13 cases (1.8% vs 2.0%)], fatal bleed [0 vs 4 cases (0% vs 0.6%)], ischaemic heart disease (ICD–10 (International Classification of Diseases) I20.0–25.9) [1 vs 17 cases (1.8% vs 2.6%)], stroke (ICD–10 I60.0–69.8) [0 vs 11 cases (0% vs 1.7%)] and other unspecified causes [4 vs 27 cases (7.1% vs 4.2%)].

A Kaplan–Meier curve of PPI-free survival and the number of index persons at risk are shown in Fig. 1. The PPI indications were AV block (AVB) (31 patients, 55%) and sick sinus syndrome (SSS) (21 patients, 37.5%). The PPI indication was unknown in 4 cases.

In a competing risks regression analysis (Fine–Gray method) adjusted with age, sex, diabetes, coronary artery disease, preoperative AF (preoperative EKG), LVEF, NYHA class, AF at discharge and urgency of operation, only AF at discharge (subdistribution hazard ratio 4.34, 95% confidence interval 2.34–8.03) was a

Table 2: Perioperative and postoperative data of 704 patients undergoing isolated aortic valve replacement divided into groups based on PPI

	PPI ($n = 56$)	No PPI ($n = 648$)	*P*-value
Operative data			
Operation status, *n* (%)			0.635[a]
Elective	53 (94.6)	603 (93.1)	
Urgent	3 (5.4)	40 (6.2)	
Salvage	0	1 (0.2)	
Reoperation within 7 days, *n* (%)	3 (5.4)	21 (3.2)	0.530
In-hospital data			
Elevated CK-MB (>100), *n* (%)	2 (3.6)	22 (3.4)	0.973
Length of hospital stay (days), mean ± SD	12 ± 7	11 ± 8	0.347
Postoperative data, *n* (%)			
Cardioversion within 30 days	8 (14.3)	89 (13.7)	0.917
In-hospital AF paroxysm	32 (58.2)	297 (45.8)	0.078
AF at discharge	27 (48.2)	163 (25.2)	<0.001
AF after discharge	16 (28.6)	243 (37.5)	0.184
Mortality (late)	11 (19.6)	124 (19.1)	0.926
30 Days	0	25 (3.9)	0.134
1 Year	2 (3.6)	43 (6.6)	0.368
5 Years	6 (10.7)	93 (14.4)	0.453

Statistical tests: Pearson χ^2 test.

[a]Gamma test.

AF: atrial fibrillation; CK-MB: creatine kinase-MB; PPI: permanent pacemaker implantation; SD: standard deviation.

Table 3: Characteristics pertaining to aortic valve disease and conduction abnormalities in 704 patients undergoing isolated aortic valve replacement divided into groups based on PPI

Characteristics	PPI ($n = 56$)	No PPI ($n = 648$)	*P*-value
Preoperative AF, *n* (%)	16 (28.6)	163 (25.2)	0.877[a]
Permanent	6 (10.7)	79 (12.2)	0.835
Paroxysmal	10 (17.9)	83 (12.8)	0.424
Aortic valve max pressure gradient ($n = 639$), mean ± SD	74 ± 25	79 ± 22	0.087
Aortic valve mean gradient ($n = 542$), mean ± SD	43 ± 13	48 ± 14	0.012
Aortic regurgitation ($n = 673$), *n* (%)	29 (51.8)	353 (54.5)	0.402[a]
Aortic regurgitation degree, *n* (%)			
1	49 (81.7)	517 (79.8)	
2	9 (16.1)	75 (11.6)	
3	1 (1.8)	38 (5.9)	
4	1 (1.8)	14 (2.2)	
Mitral valve regurgitation ($n = 681$), *n* (%)	39 (69.6)	343 (53.4)	0.074[a]
Mitral valve regurgitation degree, *n* (%)			
2	10 (17.9)	75 (11.6)	
3	1 (1.8)	15 (2.3)	
Prosthetic AV diameter (mm), mean ± SD	23.1 ± 1.87	22.9 ± 2.31	0.496

Statistical tests: Pearson χ^2 test.

[a]Gamma test.

AF: atrial fibrillation; AV: aortic valve; PPI: permanent pacemaker implantation; SD: standard deviation.

predictor for a PPI. The analysis summary is shown in Table 4. A total of 19 (34% of all PPIs) patients had the PPI within 30 days of the AVR; of them, 11 (58%) had AVB and 6 (32%) had SSS, and for 2 patients, the indication was unknown. Cumulative incidence function for PPI (AF versus sinus rhythm at discharge) is shown in Fig. 2.

DISCUSSION

The main findings of the present study are: (i) one-third of PPIs were due to SSS; (ii) timing of PPI is relatively uniform over the first operative month; and (iii) AF at discharge was the only significant predictor of PPI.

To the best of our knowledge, the significance of AF rhythm at discharge has not been similarly associated with the indication of PPI in prior SAVR studies.

Previous studies on PPI after isolated SAVR show that pre-existing conduction system abnormalities are associated with an increased risk of PPI [10, 11]. However, a more robust predictive factor is an advanced aortic valve disease with severe calcification and the consequent damage to the conduction system [12]. This may be a marker of more diffuse atrial involvement in patients

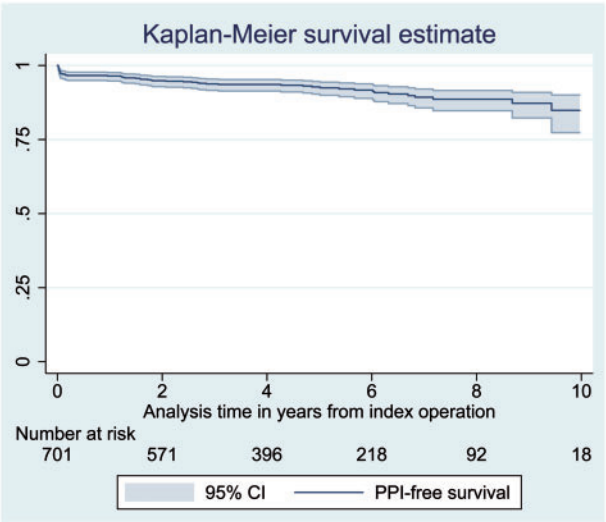

Figure 1: PPI-free survival displayed as a function of years from the index operation. Numbers at risk are indicated for each 2-year interval. CI: confidence interval; PPI: permanent pacemaker implantation.

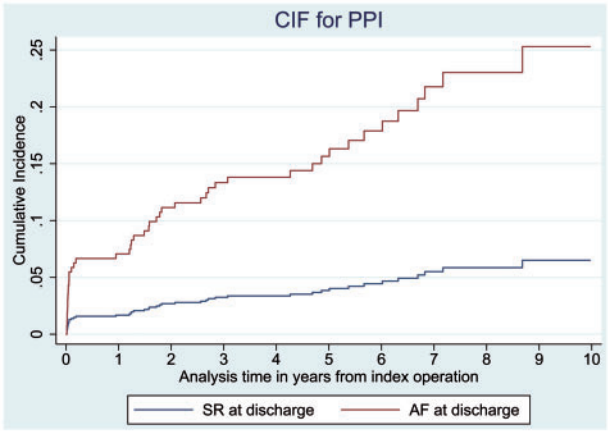

Figure 2: The CIF for PPI with SR/AF at discharge as covariates. AF: atrial fibrillation; CIF: cumulative incidence function; PPI: permanent pacemaker implantation; SR: sinus rhythm.

undergoing SAVR. Indeed, only recently atrial cardiomyopathy has been defined as a factor that may be present with aortic stenosis [13].

Histological changes in the conduction system often develop in patients with aortic valve disease. Yeo *et al.* [14] observed that fibrosis and sclerosis of the conduction system account for about half of the cases with AVB, but involvement of the mitral ring or central fibrous body (i.e. right fibrous trigone) may be the most common cause of complete heart block with a narrow QRS complex in the elderly. Putative causes in the literature have ranged from purely mechanical (e.g. elevated left ventricular pressure) and ischaemic factors to more general, age-related processes, such as exaggerated degenerative changes and primary degenerative disease of the conduction system [15, 16]. A possible molecular mechanism might involve a homeodomain-only protein, which is highly expressed in the adult murine cardiac conduction system [17]. Aortic valve disease and aortic regurgitation, in particular, exacerbate the pathological process, resulting in fibrous thickening of the endocardium of the ventricular septum. This thickening process is likely to cause an impingement on the underlying conducting tissue, which in the long run may contribute to the deceleration and eventually block the AV conduction in patients with aortic stenosis. However, the most important factors leading to AVB among SAVR patients relate to the irritation of tissues and mechanical injury caused by the surgery (among others, surgical sutures).

We hypothesize that the late appearance of AVB in our data is due to the combined effects of mechanical irritation of tissues during surgery as well as the consequent tissue damage that subsists, despite careful decalcification and cautious suturing. Age-related processes gradually cause further degenerative changes in the tissues, ultimately crossing the threshold of sufficient damage for AVB to develop.

However, the observational and retrospective nature of the study is a limitation that prevents us to draw any definite conclusions about the causes of AVB.

Prevalence of PPI after bioprosthetic SAVR was higher in the present data than in previous studies [11, 12, 18–21]. Van Mieghem *et al.* [11] reported a rate of PPI of 2.0% in a series of 734 patients within 30 days after SAVR, while 4.0% required PPI >30 days after SAVR. Robich *et al.* [21] reported an incidence of 4.8% of PPI after SAVR alone in their data of 659 692 patients from the Nationwide Inpatient Sample database. A pooled analysis reported on PPI in 3.3% of patients after isolated aortic valve replacement and of 5.9% after aortic valve replacement with or without coronary artery bypass grafting [22]. Moreover, in older studies conducted in the 1970s and 1980s, the prevalence of AVR-related PPI ranged 1–6%, but the median age of patients in these studies was lower compared to our study [18, 23].

Quite surprisingly, the first postoperative month is a period of relatively uniform incidence of PPI, while the transcatheter AVR experience emphasizes the first operative week. This difference may be due to larger trauma caused by the open surgery. Evidently, very few PPIs are made within the very first days as recuperation of the conduction is still possible.

This study has important clinical implications. The patient population in question is highly prone to bradyarrhythmias not only due to the disturbance of the conduction system but also due to SSS. The latter is clearly more frequent than reported in the general population [24, 25]. This is likely related to the causative mechanisms of aortic valve disease including the fibrous thickening of the endocardium. It has been suggested that cannulation of the right atrium for cardiopulmonary bypass could be a possible cause of a relatively late occurrence of SSS [26, 27]. In our study, no detailed information about this or other operative incidents could be obtained. However, according to our data, during the first 30 postoperative days, the cumulative hazard rates of PPI after SAVR for AVB and SSS, respectively, possibly reflect the relatively slow development of SSS due to the mechanism proposed above.

The relatively high incidence for the need of PPI and the significantly increased risk of PPI in conjunction with AF suggest that some patients who have undergone bioprosthetic AVR and are diagnosed with AF at discharge may need more careful monitoring to alleviate symptoms as well as to minimize morbidity associated with conduction anomalies.

Limitations

Methodologically, this study has several strengths. A validated, structured case-report form was used at all study sites. As a

Table 4: The competing risks regression model SHRs of postoperative pacemaker implantation with all-cause mortality as a competing risk

Variables	Model 0		Model 1		Model 2	
	SHR	95% CI	SHR	95% CI	SHR	95% CI
Age (years)	1.03	0.99–1.08	1.02	0.98–1.07	1.01	0.96–1.06
Male gender	0.85	0.50–1.43	0.79	0.42–1.47	0.76	0.40–1.46
Treatment for diabetes			1.27	0.64–2.51	1.14	0.57–2.30
Coronary artery disease			0.94	0.46–1.91	0.97	0.46–2.04
Preoperative AF (preoperative EKG)			0.61	0.24–1.56	0.27[a]	0.10–0.72
NYHA (III–IV vs I–II)			1.26	0.69–2.31	1.37	0.74–2.50
LVEF (LVEF <40% vs ≥40%)			1.26	0.37–4.31	1.14	0.31–4.25
Rhythm at discharge (AF versus SR)					4.34[a]	2.34–8.03
Operation status (urgent versus elective)					0.32	0.03–3.10

[a]Statistically significant.

AF: atrial fibrillation; CI: confidence interval; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association functional classification; PPI: permanent pacemaker implantation; SHR: subdistribution hazard ratio; SR: sinus rhythm.

quality control, a professional third party monitored the data and found only minor issues. The main limitation of this study is the retrospective nature of data. However, the data contain relatively detailed information about the baseline characteristics, operative procedures and parameters as well as the chosen outcome variables. The indications of PPI for each individual patient, the implantation procedure and the consequent monitoring for clinical outcomes were in general well reported at each hospital. The impact of preoperative conduction disorders in EKG on PPI probability could not be reliably estimated with the data.

CONCLUSIONS

In conclusion, the incidence of PPI after bioprosthetic SAVR is higher than previously documented. The difference was most evident in the early postoperative period, i.e. the first 30 days after operation. Though AVB is the major indication for PPI after SAVR, >30% of PPIs are implanted due to SSS during both short-term follow-up and long-term follow-up. Postoperative AF versus sinus rhythm at discharge was associated with higher incidence of PPI, incurring >4-fold risk of the need for permanent pacing. These findings highlight the need for better monitoring of patients after hospital discharge and the significance of well-delineated criteria to screen patients in a high risk for developing cardiac arrhythmias after SAVR.

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Author contributions

Samuli J. Salmi: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing—review & editing. **Tuomo Nieminen:** Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Supervision; Writing—review & editing. **Juha Hartikainen:** Conceptualization; Writing—review & editing. **Fausto Biancari:** Conceptualization; Writing—review & editing. **Joonas Lehto:** Data curation; Writing—review & editing. **Maunu Nissinen:** Data curation; Writing—review & editing. **Markus Malmberg:** Writing—review & editing. **Fredrik Yannopoulos:** Writing—review & editing. **Jyri Savolainen:** Data curation; Writing—review & editing. **Juhani Airaksinen:** Conceptualization; Writing—review & editing. **Tuomas Kiviniemi:** Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Supervision; Writing—review & editing.

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