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Conventional single-chamber pacemakers versus transcatheter pacing systems in a "real world" cohort of patients: A comparative prospective single-center study

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ABSTRACT

Purpose: Despite the developments in conventional transvenous pacemakers (VVI-PM), the procedure is still associated with significant complications. Although there are no prospective clinical trials that compared VVI-PM with transcatheter pacemaker systems (TPS).

Methods: This is a prospective, observational, single-center study that included all patients with an indication for a single-chamber pacemaker implant within a 4-year period. All clinical, ECG and echocardiographic characteristics at implant, electrical parameters, associated complications and mortality were analyzed. A Cox survival model and a Bayesian cohort analysis were performed for differences in complication rates between groups.

Results: There were 443 patients included (198 TPS and 245 VVI-PM). The mean age was 81.5 years (TPS group, 79.2 ± 6.6 years; VVI-PM group, 83.5 ± 8.9 years). There was a male predominance in TPS group (123, 62.1% vs. 67, 27.3%; $p < 0.001$). The presence of systolic dysfunction and renal insufficiency were more frequent in VVI-PM group than in TPS patients. Mean follow-up was 22.3 ± 15.9 months. In a multivariable paired data the TPS group presented fewer complications than VVI-PM group (HR = 0.39 [0.15–0.98], p-value 0.013), but major complications were not different (6, 3% vs 14, 5.6% respectively, $p = 0.1761$). There was no difference in the mortality rate between the groups. The TPS group had less risk than VVI-PM group to have a complication, with a 96% of probability.

Conclusions: TPS patients had a lower overall complication rate than VVI-PM patients including matched-pair samples using a Bayesian analysis. These results confirm the safety profile of TPS in clinical practice.

1. Introduction

Despite the advancements in conventional transvenous pacemakers, the procedure is still associated with significant complications, which are mostly related to the transvenous lead and the subcutaneous generator pocket, with short-term complication rates as high as 8%–12% [1–3]. Some of the most frequent complications are pneumothorax, cardiac tamponade, pocket hematoma, lead dislodgement, venous obstruction, tricuspid regurgitation, and endocarditis [4]. To address these issues, leadless transcatheter pacemaker systems (TPS) have been gradually developed. The two leadless systems that are currently available have demonstrated comparable performance and safety results [5], and although pneumothorax and pocket/lead infection did not occur, the leadless procedure is also associated with femoral vascular complications, the need to reposition the device intraoperatively, and a moderate risk of cardiac perforation resulting in pericardial effusion. The TPS MICRA (Medtronic Inc.®) has the same implant indications as single chamber pacemakers (VVI-PM), with similar functionality and features, including rate adaptive pacing,

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remote monitoring capabilities, and automated pacing capture threshold management [6]. Previous series have described a rate of 1.5% for short-term major complications [7] and up to 4% for mid-term follow-up [8]. The risk of major complications in TPS appears to be much lower (up to 48%) than with conventional transvenous pacemakers [9]. However there are no clinical trials comparing conventional pacemakers with TPS in a prospective fashion, TPS seems to have a lower rate of major complications [6] and a satisfactory performance at mid- and long-term follow-up [10] compared to historic cohorts of VVI-PM. In addition, there is little information about safety issues in middle-volume centers. The aim of this study was to prospectively compare the clinical characteristics, electrical performance, and related complications between TPS and a matched cohort of patients who were referred for VVI-PM implantation by the same operators and during the same period of time.

2. Methods

This is a prospective, observational, single-center study that included all patients with an indication for a single-chamber pacemaker implant, according to the current guidelines [11], within a 4-year period (from June 1, 2015 to December 31, 2019) in an experienced center. The choice between a conventional transvenous pacemaker or TPS was made according to physician discretion after discussion with the Electrophysiologist Unit and considering the clinical characteristics and age of the patient. TPS was encouraged in those patients who were at a higher risk of infection or who had difficult vascular access or abandoned electrodes. TPS implantation was performed via femoral access according to the manufacturer's recommendations. VVI-PMs were implanted by cephalic dissection or subclavian puncture, and the choice of approach was based on the operator preference and all leads implanted were of active fixation. At implant, clinical characteristics, electrocardiographic, echocardiographic, and electrical parameters were collected in all patients. Follow-up in patients with TPS was performed systematically at 1, 3, 6, and 12 months and every year thereafter if uneventful. Patients with VVI-PM were scheduled for follow-up visits at 3 months after the procedure and yearly thereafter.

2.1. Complications

All complications and mortality were analyzed. Device-related complications were classified as minor or major. Major complications included the following: i) severe deterioration of clinical status; and/or ii) a life threatening event that required intervention that prolonged hospitalization or death; iii) vascular (aneurysm, pseudoaneurysm, arteriovenous fistula, hematoma and/or hemorrhage); iv) thoracic complications (pneumothorax); v) pericardial effusion and/or tamponade; vi) stimulation related failures (capture failure, electrode dislodgment); and vii) complications from the pacemaker pocket (infection or hematoma).

2.2. Statistical analysis

The statistical analysis was descriptive for categorical variables and included the frequency, percentage, mean, and standard deviation (SD) in numeric variables. The level of statistical significance was defined as $p < 0.05$. Complications data were paired by propensity score matching of age, left ventricular ejection fraction (LVEF), heart failure, anticoagulation, and renal failure. For the matched data, a Cox regression analysis was performed to analyze the complications. Multiple hypothesis testing was addressed with the Benjamini–Hochberg procedure. A Bayesian cohort analysis was used to estimate the probability of complications in both pacemaker groups with a binomial distribution. For prior probabilities, two possibilities were chosen. The first possibility was more skeptical (non-informative) prior (between −50% and +50%) for the risk difference between the TPS and VVI-PM groups. The second prior distribution was based on the difference found in the cohort of 1817 patients that was published by El-Chami [6] in 2018. Hence, the prior probability (between −27% and −52%) was the risk difference of the TPS group compared to the VVI-PM group. The risk followed a normal distribution, centered in −0.37 with a SD of 0.125. The baseline risk followed an uniform prior distribution (conservative, non-informative). The *posterior* distribution was calculated using the Metropolis–Hastings algorithm with 40,000 iterations and 2,000 burn-in iterations in two Markov chains. Statistical calculations were performed using the survival, MatchIt and rjags packages for R v.3.5 and SPSS v.19.

Table 1
Baseline patient characteristics.

	VVI-PM n = 245 (%)	TPS n = 198 (%)	P
Age	83.6	79.2	<0.00001
Men	67 (27.3)	123 (62.1)	<0.00001
Hypertension	155 (63.3)	160 (80.8)	<0.00001
Diabetes	63 (25.7	69 (34.8)	0.3662
COPD	33 (13.5)	34 (17.1)	0.2795
Renal disease	86 (35.1)	36 (18.2)	0.00007
Cardiomyopathy	68 (27.7)	95 (48)	0.00001
Ischemic cardiopathy	39 (15.9)	43 (21.7)	0.1181
Heart failure	67 (27.3)	46 (23.2)	0.3232
LVEF	56.9 (8.6)	59.8 (7.9)	0.000262
Peripheral arteriopathy	16 (6.5)	12 (6.1)	0.8398
Valvular disease	80 (32.6)	87 (43.9)	0.0148

COPD: chronic obstructive pulmonary disease, TAVI: transcatheter aortic valve implantation, LVEF: left ventricular ejection fraction.

Table 2
TPS and VVI-PM total complications.

	TPS (%)	VVI-PM (%)	P
TOTAL COMPLICATIONS	7 (3.5)	21 (8.6)	0.0303
Major complications	6 (3)	14 (5.6)	0.1761
Minor complications	1 (0.5)	7 (2.8)	0.0645
VASCULAR COMPLICATION	4 (2)	4 (1.6)	0.7607
Bleeding	0	0	
Puncture hematoma	0	0	
Arteriovenous fistula	3 (1.5)	0	
Pseudoaneurysm	1 (0.5)	0	
Hemothorax	0	1 (0.4)	
Pneumothorax	0	3 (1.2)	
CARDIAC PERFORATION	2 (1)	0	0.1992
Pericardial effusion	1 (0.5)	0	
Tamponade	1 (0.5)	0	
PACING	1 (0.5)	4 (1.6)	0.2639
Dislodgement	0	3 (1.2)	
Threshold elevation	1 (0.5)	0	
Pacemaker syndrome	0	1 (0.4)	
Electrode Fracture	0	0	
POCKET RELATED	0	12 (4.9)	NA
Hematoma	0	10 (4.1)	
Skin ulcer risk	0	2 (0.8)	
ENDOCARDITIS	0	1 (0.4)	1

NA, not analyzed.

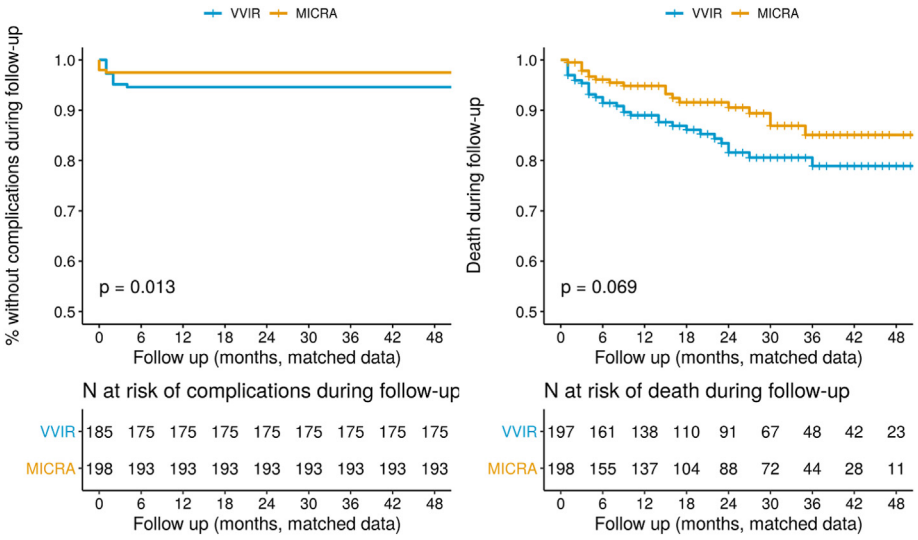

Fig. 1. Kaplan-Meier plots of time to event in matched data. A: risk of complications; B: risk of death.

Table 3
Total mortality and cause of death in people with VVI-PM and TPS. Data are number (%).

	VVI-PM (%)	TPS (%)	p
Total mortality	44 (17.9)	18 (9,1)	0.007476
Cardiac			
Heart failure	1 (0.4)	1 (0.5)	0.879791
Endocarditis	1 (0.4)	0	1
Non-cardiac			
Pneumonia	10 (4.1)	8 (4)	0.982566
Respiratory failure/respiratory arrest	5 (2)	2 (1)	0.387096
Stroke	5 (2)	2 (1)	0.387096
Chronic kidney disease	3 (1.2)	0	0.2568
Sepsis/Infected pressure ulcers	2 (0.8)	0	0.5045
Sepsis/Urinary tract infections	0	1 (0.5)	0.447
Lung cancer	2 (0.8)	0	0.5045
Prostate cancer	1 (0.4)	0	1
Epilepsy/Dementia	2 (0.8)	0	0.5045
Bleeding of digestive tract	2 (0.8)	0	0.5045
Volvulus	1 (0.4)	0	1
Intestinal ischemia	1 (0.4)	0	1
Bone fractures	1 (0.4)	1 (0.5)	0.879791
Unknown	7 (2.9)	3 (1.5)	0.344446

3. Results

3.1. Baseline characteristics

There were 443 patients who underwent a pacemaker implantation from June 1, 2015 to December 31, 2019 who were included, and 198 patients were in the TPS group while 245 patients were in the VVI-PM group. Mean age was 81.5 years (TPS group, 79.2 ± 6.6 years; VVI-PM group, 83.5 ± 8.9 years). There was a male predominance in the TPS group (123, 62.1%) and a female predominance in the VVI-PM group (178, 72.6% and $p < 0.0001$). There were also statistically significant differences regarding the presence of LV systolic dysfunction, renal insufficiency, and oral anticoagulation prescriptions between VVI-PM and TPS patients (Table 1). At the time of the procedure, the vast majority of patients were in atrial fibrillation (388, 87.6%; slow ventricular response 253, 57.2%; atrioventricular block 101, 22.8%; or fast ventricular response 34, 7.7%) or left atrial flutter (15, 3.4%). Ninety one (37.1%) pacemakers in the VVI-PM group were implanted by cephalic venodissection and 154 (62.8%) were implanted by subclavian puncture. In both groups, three patients had a previous pacemaker extraction, three patients with VVI-PM and four patients in the TPS group presented with a history of an infection. Average fluoroscopy time was significantly different between the groups: 6.09 ± 5.1 min in the TPS group versus 4.04 ± 7.02 min in the VVI-PM group ($p < 0.001$). The median time of fluoroscopy in between the groups was of 5.13 min in the TPS group versus 3.3 min in the VVI-PM group.

3.2. Outcomes

The mean follow-up was 22.3 ± 15.9 months. The TPS were located as follows: 51 in apex, 122 in mid-septum and 25 in the outflow tract and the VVI-PM ventricular leads: 239 in apex, 5 in mid-septum and 1 in outflow tract. The TPS group reported significantly lower total complications than the VVI-PM group (7, 3.5% vs. 21, 8.6% respectively, $p = 0.0303$). However, there were no differences in major complications between the groups (6, 3% vs. 14, 5.6% respectively, $p = 0.1761$) (Table 2). In a multivariable analysis of data matched by age, LVEF, chronic heart failure, anticoagulation status, and chronic kidney disease, the TPS group presented fewer complications than the VVI-PM group (Hazard ratio (HR) = 0.39, confidence interval (CI) 95%: 0.15–0.98; $p = 0.013$) (Fig. 1A). The most frequent complications in patients with TPS were vascular (4, 2%), and associated with heart effusion (2, 1%). In patients with VVI-PM, the most frequent complications were pocket generator-related (12, 4.9%), pneumothorax (3, 1.2%), and electrode dislodgement (3, 1.2%) (Table 2). During the follow-up, 62 patients died (14%), including 18 in the TPS group (9.1%) and 44 in the VVI-PM group (17.9%) with significant difference between the groups (Table 3). Only one of the deaths was pacemaker related in the TPS group, even though there was no statistically significant difference in the paired analysis (Fig. 1B).

3.3. Non-informative prior in terms of differences in complications

After the Bayesian analysis, the mean posterior probability of complications for the VVI-PM group was 9.8% (credible interval [CrI] at 95%: 5.6–15%), while that in the TPS group was 4.6% (CrI at 95%: 1.9–8.5%). The *posterior* probability of having fewer complications in the TPS group than in the VVI-PM group was of 96.4% (Fig. 2A).

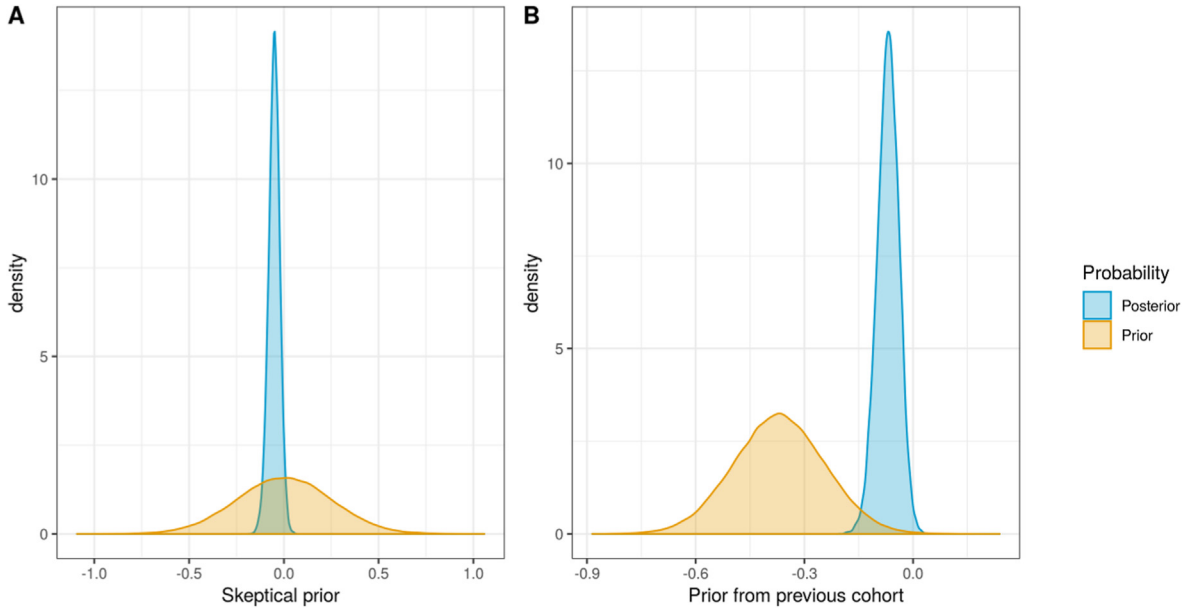

Fig. 2. Bayesian cohort analysis. Probability distribution for risk differences based on two a priori probabilities.

3.4. Optimistic prior for TPS based on a previous study

The mean posterior probability of complications for the VVI-PM group was 11% (CrI at 95%: 6.5–16.6%), while that in the TPS group was 4.1% (CrI at 95%: 1.7–7.5%). Considering the data from a previous cohort, the *posterior* probability of having fewer complications in the TPS group than in the VVI-PM group was of 99.3% (Fig. 2B).

Electrical parameters in patients with TPS were stable at the short and mid-term follow-up visits, with an average threshold at implant of 0.55 ± 0.26 V/0.24 ms (n = 198), and it was 0.56 ± 0.31 V/0.24 ms (n = 119), 0.56 ± 0.32 V/0.24 ms (n = 73), and 0.61 ± 0.47 V/0.24 ms (n = 42) at 12, 24 and 36 months. The average impedance at implant was 779.8 ± 211 Ω, and it was 584 ± 102 Ω, 580.5 ± 91 Ω, and 538.8 ± 91 Ω at 12, 24, and 36 months. The average R amplitude at implant was 10.7 mV ± 4.6, and it was 13.5 mV ± 4.6, 14.5 mV ± 4.9, and 12.9 mV ± 5.2 at 12, 24, and 36 months (Fig. 3).

The stimulated QRS duration in conventional VVI pacing were of: 175.9 ms (±19.3) and in LPS-PM of: 153.1 ms (±14), with a significant difference between the groups ($p < 0.00001$). LV function at follow-up in the VVI-PM group was of 56.4 (±5.9) and in LPS-PM of 58 (±5), with only one case of cardiomyopathy in the VVI group (0.4%).

4. Discussion

In the present study, we analyzed the clinical characteristics and mid-term follow-up complications between TPS and a cohort of VVI-PM patients. Our results revealed an elderly population with a high rate of co-morbidities in both groups. Overall, there were fewer complications in the TPS group than in the VVI-PM group. In a matched patient analysis, the TPS group also had a lower complications rate. Additionally, Bayesian analysis in our sample showed that the TPS group had fewer complications than the VVI-PM group. Even based on *prior* probability that assigns the same probability of complications to one or the other group, the *posterior* probability of lower complications in the TPS group was 96%. Short-term related complications occurred frequently in both groups, and they were associated with the implant procedure. As observed in other studies of conventional endovascular pacemakers, the incidence of complication is still substantial, and most complications occurred early after pacemaker implantation [12]. The most common cause was lead-related re-intervention, especially for vascular access and lead dislodgment [13]. In our study, the rate of dislodgment was 1.2% in the VVI-PM group. These data seem consistent with the series of single-lead pacemakers in the Danish Registry, in which the dislodgment rate was 1.2% [14], and the FOLLOWPACE study, which showed dislodgement rate of 3.3% [12] (this study also included dual-chamber pacemakers). No patients in the TPS group had device dislodgment, the IDE Registry reported two cases of device dislodgement out of 1817 TPS patients (0.12%), and one of them had embolization. Both devices were successfully retrieved [6]. In the TPS group, the vascular access complication rate was 2%, while that in the VVI-PM was 1.6%. The vascular complication rate in the IDE Registry was lower (0.61%) compared with our results [6]. These data emphasize the importance of a careful vascular access and consideration of ultrasound guidance or venography for venous puncture, especially in an elderly population. In the VVI-PM group, pocket-related adverse events were the most frequent complication (4.9%), although the incidence of reoperation was low, especially for hematomas that were mostly managed conservatively. This finding was consistent with the conservative management of hematoma in other series (rate of hematoma, 2.97%; required surgical drainage, 0.07%) [12]. Many patients were taking oral anticoagulation agents during pacemaker implantation (80.1%). This was not surprising because our cohort consisted of elderly patients with atrial fibrillation and multiple comorbidities. However, anticoagulation was not an independent factor for complications. There was a high rate of overall mortality (62 patients, 14%), and one case was related to pacemaker endocarditis in the TPS group, which was similar to other TPS series with a procedure-related death rate of up to 0.28% [6]. The mortality rate at follow-up was attributed to the characteristics of the population in which age and multiple co-morbidities played an important role [15–17].

However, our study had the expected limitation that was not a randomized trial, and the choice of each pacemaker was based on the patients' clinical conditions. Furthermore, the number of

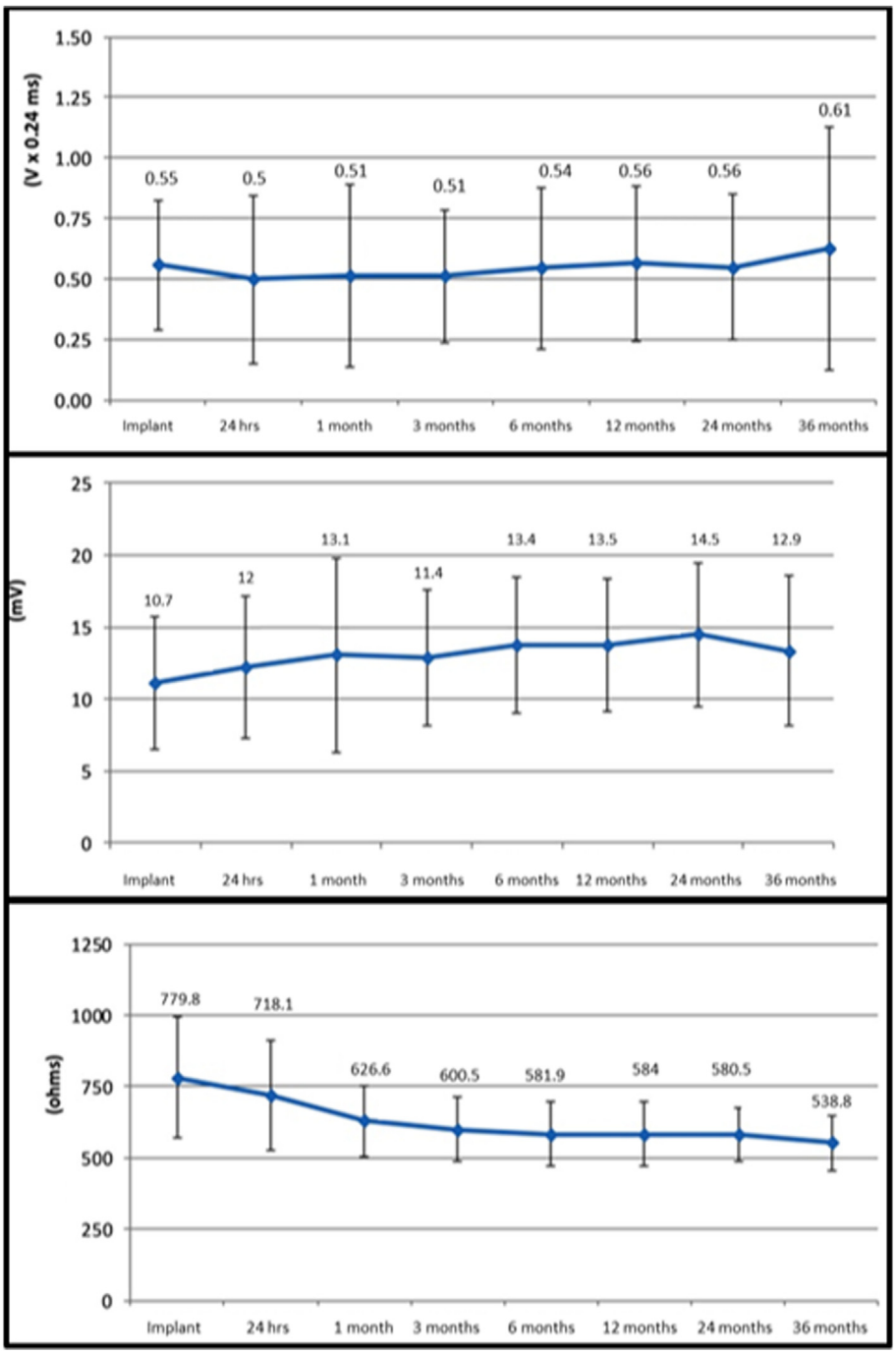

Fig. 3. Transcatheter pacing system electrical performance. A: Pacing capture thresholds. B: Sensing. C: Impedance. The vertical solid lines represent the SD. SD, standard deviation; n, the number of patients with data that were available at each time point.

patients included and the follow-up probably underestimates the infectious complications, particularly in VVI-PM group, according to other published studies [18]. Additionally, pocket-related complications that are more likely to be presented in mid- and long-term follow-up were not well represented in this study.

Finally, as published by Gupta and cols, as well as other studies, the stimulated QRS duration difference between the groups, could be related to the different location predominant in each type of PM, considering that RV mid-septal and RVOT septal pacing were associated with significantly lower QRS duration as compared with apical pacing [19,20].

5. Conclusions

TPS patients had a lower overall complication rate than VVI-PM patients including matched-pair samples using a Bayesian analysis. These results confirm the good safety profile of TPS in daily clinical practice.

CRediT authorship contribution statement

Jose Luis Martinez-Sande: Conceptualization, Investigation, Visualization, Writing - original draft. **Javier Garcia-Seara:**

Investigation, Writing - review & editing. **Laila Gonzalez-Melchor:** Data curation, Formal analysis, Investigation, Writing - review & editing. **Moises Rodriguez-Mañero:** Writing - review & editing. **Aurora Baluja:** Methodology, Formal analysis. **Xesus Alberte Fernandez-Lopez:** Writing - review & editing. **Jose Ramon Gonzalez Juanatey:** Conceptualization, Supervision, Validation.

Declaration of competing interest

The authors whose names are listed certify that they have NO conflict of interest and NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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