

Pacemaker recovery after permanent pacemaker implantation post-transcatheter aortic valve implantation: A sub-study of the LANDMARK trial

Akihiro Tobe^{a,1}, Pieter C. Smits^{b,1}, Niels van Royen^c, Ignacio J. Amat-Santos^{d,e}, Martin Hudec^f, Matjaz Bunc^g, Ben J.L. Van den Branden^h, Peep Laanmetsⁱ, Daniel Unic^j, Bela Merkely^k, Renicus S. Hermanides^l, Vlasios Ninios^m, Marcin Protasiewicz^{n,o}, Benno J.W.M. Rensing^p, Pedro L. Martin^q, Fausto Feres^r, Manuel De Sousa Almeida^s, Eric van Belle^t, Axel Linke^u, Alfonso Ielasi^v, Matteo Montorfano^{w,x}, Mark Webster^y, Konstantinos Toutouzas^z, Emmanuel Teiger^{aa}, Francesco Bedogni^{ab}, Michiel Voskuil^{ac}, Manuel Pan^{ad}, Oskar Angerås^{ae,af}, Won-Keun Kim^{ag,ah}, Jürgen Rothe^{ai,aj}, Ivica Kristić^{ak}, Vicente Peral^{al}, Scot Garg^{am,an}, Geert A.A. Versteeg^c, Mario García-Gómez^{d,e}, Tsung-Ying Tsai^a, Ashokkumar Thakkar^{ao}, Udit Chandra^{ao}, Marie-Claude Morice^{b,ap}, Yoshinobu Onuma^a, Andreas Baumbach^{aq,ar}, Patrick W. Serruys^{a,*}

^a CORIB Research Centre for Advanced Imaging and Core laboratory, University of Galway, Galway, Ireland

^b Cardiovascular European Research Center (CERC), Massy, France

^c Department of Cardiology, Radboud University Hospital, Nijmegen, the Netherlands

^d Centro de Investigación Biomédica en Red - Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain

^e Department of Cardiology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

^f Department of Acute Cardiology, Middle-Slovak Institute of Cardiovascular Diseases, Banská Bystrica, Slovakia

^g Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

^h Department of Cardiology, Amphia Hospital, Breda, the Netherlands

ⁱ Department of Invasive Cardiology, North Estonia Medical Centre, Tallinn, Estonia

^j Department of Cardiac and Transplant Surgery, University Hospital Dubrava, Zagreb, Croatia

^k Heart and Vascular Center, Semmelweis University, Budapest, Hungary

^l Department of Cardiology, Isala Hospital, Zwolle, the Netherlands

^m Department of Cardiology, European Interbalkan Medical Center, Thessaloniki, Greece

ⁿ Department of Cardiology, Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland

^o Department of Non-Procedural Clinical Sciences, Faculty of Medicine, Wrocław University of Science and Technology, Wrocław, Poland

^p Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands

^q Department of Interventional Cardiology, University Hospital of Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain

^r Department of Invasive Cardiology, Instituto Dante Pazzanese, São Paulo, Brazil

^s CHRC, NOVA Medical School, NOVA University Lisbon, Lisbon, Portugal

^t Department of Interventional Cardiology, Lille University, Lille, France

^u Department of Internal Medicine and Cardiology, University Clinic, Heart Center Dresden, University of Technology Dresden, Dresden, Germany

^v Department of Interventional Cardiology, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milan, Italy

^w School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

^x Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

^y Department of Cardiology, Auckland City Hospital, Auckland, New Zealand

^z Department of Cardiology, Hippokraton Hospital, Athens, Greece

^{aa} Department of Interventional Cardiology, Henri Mondor University Hospital, Créteil, France

^{ab} Department of Clinical Cardiology, San Donato Hospital, Milan, Italy

^{ac} Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands

^{ad} Department of Cardiology, University Hospital Reina Sofía, University of Córdoba, IMIBIC, CIBERCV, Córdoba, Spain

^{ae} Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

^{af} Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

^{ag} Department of Cardiology & Angiology, University of Giessen and Marburg, Gießen, Germany

* Corresponding author at: Department of Cardiology, University of Galway, Galway, Ireland.

E-mail address: patrick.w.j.c.serruys@gmail.com (P.W. Serruys).

^{ah} Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany^{ai} Department of Cardiology and Angiology, Campus Bad Krozingen, University Heart Center-University of Freiburg, Bad Krozingen, Germany^{aj} Faculty of Medicine, University of Freiburg, Freiburg, Germany^{ak} Department of Cardiology, University Hospital of Split, Split, Croatia^{al} Department of Cardiology University Hospital Son Espases, Health Research Institute of the Balearic Islands (IdISBa), Palma, Balearic Islands, Spain^{am} Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom^{an} School of Medicine, University of Central Lancashire, Preston, United Kingdom^{ao} Department of Clinical Research, Meril Life Sciences Pvt. Ltd, Vapi, India^{ap} ICPS, Hôpital Privé Jacques Cartier, Massy, France^{aq} Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London and Barts Heart Centre, London, United Kingdom^{ar} Cleveland Clinic, London, United Kingdom

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ABSTRACT

Background: Conduction system disturbances resulting in permanent pacemaker implantation (PPI) are common complications after transcatheter aortic valve implantation (TAVI). In some patients, there is delayed recovery of the conduction system post-procedure. This study aims to report the incidence and predictors of ventricular pacing (VP) rate $\leq 1\%$ at 1 year after TAVI.

Methods: This is a post-hoc sub-study of the LANDMARK multicentre trial, which randomized 768 patients in a 2:1:1 ratio to the Myval ($n = 384$) transcatheter heart valve (THV) series or contemporary THVs (Sapien [$n = 192$] and Evolut [$n = 192$] series) for the treatment of severe aortic stenosis. Overall, 122 (15.9%) patients underwent PPI within 30 days after TAVI, and 1-year pacemaker follow-up data were retrospectively collected in 99 patients. Pacemaker recovery (PMR) was defined as a VP rate $\leq 1\%$ at follow-up.

Results: PMR occurred in 18% (18/99) of patients. The PMR group was younger than the non-PMR group (78.6 ± 3.0 vs 81.1 ± 5.1 years, $p = 0.045$). Implantation depth under the non-coronary cusp did not differ between groups (5.7 ± 3.5 vs 5.8 ± 2.8 mm, $p = 0.94$). There were no significant differences in PMR rates based on THV type: Myval 25% (11/44), Sapien 19% (5/27), and Evolut 7% (2/28) ($p = 0.16$). In multivariable logistic regression, atrial fibrillation was associated with lower odds of PMR (odds ratio 0.09, 95% confidence interval 0.00–0.77, $p = 0.02$).

Conclusions: At 1 year, conduction system recovery (VP $\leq 1\%$) was observed in 18% of patients who underwent PPI after TAVI, with no significant difference among the Myval, Sapien and Evolut series. Atrial fibrillation was associated with lower odds of recovery.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established treatment option for patients with symptomatic severe aortic stenosis (AS). [1] It is less invasive than surgical aortic valve replacement (SAVR), leading to shorter hospital stays and faster recovery. The indications for TAVI are expected to expand further, particularly after its effectiveness was demonstrated compared to a surveillance strategy in asymptomatic patients with severe AS. [2]

Despite its advantages, conduction system disturbances resulting in permanent pacemaker implantation (PPI) remains a common complication after TAVI, with an overall incidence exceeding 10%. This is primarily due to mechanical compression of the conduction system by the stent frame, as well as edema, hematoma, inflammation and ischemia of the conduction system. [3] Some patients will remain pacemaker dependent; however, in others, conduction function recovers, albeit slowly, resulting in them no longer being pacemaker-dependent during follow-up. [4] However, data from randomized trials on pacemaker recovery rates during follow-up after TAVI are limited. [5]

In the recently reported randomized LANDMARK trial, PPI rates were 15.0%, 17.3% and 16.8% for Myval series, Sapien series and Evolut series, respectively. [6] Notably, concerns regarding these relatively high rates prompted the need for a more comprehensive analysis. This study aims to report the incidence and predictors of pacemaker recovery (PMR) in the randomized LANDMARK trial.

2. Methods

2.1. Design of the LANDMARK trial

The trial design and the main study results have been previously published. [6,7] In brief, LANDMARK is a prospective, multicentre, multinational, open-label, noninferiority trial conducted across 31 sites in 16 countries (Germany, France, Sweden, the Netherlands, Italy, Spain, Portugal, Greece, Hungary, Poland, Slovakia, Slovenia, Croatia, Estonia, New Zealand and Brazil). The trial was designed to demonstrate the noninferiority of the Myval transcatheter heart valve (THV) series compared to the contemporary standard THVs – Sapien and Evolut series – for the treatment of severe native AS. The study was approved by the ethics committees of all participating centres and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Eligible participants were adults aged ≥ 18 years with symptomatic severe native AS who were deemed suitable for transfemoral TAVI using all three study devices.

A total of 768 participants were enrolled and randomly assigned in a 1:1 ratio either to the Myval arm ($n = 384$) or the contemporary THV arm ($n = 384$), stratified according to the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) categories: low ($<4\%$), intermediate (4–8%), and high ($>8\%$) risk. Within the contemporary THV arm, participants were further randomized to receive either the Sapien ($n = 192$) or Evolut THV ($n = 192$). The trial demonstrated that the Myval THV series was noninferior to contemporary THVs for the 30-day early safety endpoint and the 1-year clinical efficacy endpoint. [6–8]

2.2. Study population and collection of pacemaker follow-up data

This post-hoc analysis of the LANDMARK trial aimed to examine the

¹ Equally contributed to the manuscript

1-year incidence of PMR in patients who received a PPI within 30 days following TAVI. Patients who did not undergo TAVI ($n = 12$), were converted to SAVR ($n = 1$), or had a pre-implant pacemaker ($n = 29$) were excluded. Among the remaining 726 patients, 122 received a PPI within 30 days of their TAVI. After excluding those who died within 1 year ($n = 10$), those without pacemaker follow-up data ($n = 10$), and

those who received cardiac resynchronization therapy (CRT, $n = 3$), 99 patients remained in the analysis cohort (**Supplementary Fig. 1**). Pacemaker follow-up data, including follow-up date, ventricular and atrial pacing rate, pacemaker mode, and lower rate setting, were collected retrospectively as part of routine clinical practice. [9] Pacemaker management was left to the discretion of each site. When 1-year

Table 1
Baseline and procedural characteristics.

Characteristics	Pacemaker recovery (VP $\leq 1\%$) ($n = 18$)	No pacemaker recovery (VP $> 1\%$) ($n = 81$)	P-value
Age (years)	78.6 $\pm$ 3.0	81.1 $\pm$ 5.1	0.045
Male, n (%)	8 (44.4)	52 (64.2)	0.20
Body mass index (kg/m ²)	26.4 $\pm$ 4.0	28.7 $\pm$ 5.6	0.10
STS score (%), median (Q1, Q3)	2.0 (1.6, 3.0)	2.3 (1.6, 3.8)	0.28
Low risk (<4%), n (%)	16 (88.9)	63 (77.8)	0.52
Intermediate risk (4–8%), n (%)	2 (11.1)	14 (17.3)	0.73
High risk (>8%), n (%)	0 (0)	4 (4.9)	1.00
Diabetes, n (%)	5 (27.8)	21 (25.9)	1.00
Dyslipidemia, n (%)	2 (11.1)	10 (12.4)	1.00
Hypertension, n (%)	11 (61.1)	49 (60.5)	1.00
eGFR <60 ml/min, n (%)	8 (44.4) ($n = 18$)	31 (40.3) ($n = 77$)	0.95
eGFR <30 ml/min, n (%)	2 (11.1) ($n = 18$)	8 (10.4) ($n = 77$)	1.00
Chronic obstructive pulmonary disease, n (%)	2 (11.1)	5 (6.2)	0.61
Previous stroke, n (%)	0 (0)	2 (2.5)	1.00
Previous MI, n (%)	2 (11.1)	7 (8.6)	0.67
Previous CABG, n (%)	1 (5.6)	4 (4.94)	1.00
Previous PCI, n (%)	3 (16.67)	6 (7.41)	0.36
NYHA III/IV, n (%)	6 (33.3)	40 (49.4)	0.33
Pre-procedural electrocardiogram			
PR interval, ms	183.5 $\pm$ 38.7 ($n = 17$)	202.9 $\pm$ 46.7 ($n = 56$)	0.13
AV conduction delay >200 msec, n (%)	5 (29.4) ($n = 17$)	22 (39.3) ($n = 56$)	0.65
QRS duration, ms,	104.2 $\pm$ 20.4 ($n = 18$)	116.4 $\pm$ 26.2 ($n = 81$)	0.07
LBBB, n (%)	0 (0)	7 (8.6)	0.34
RBBB, n (%)	3 (16.7)	22 (27.2)	0.55
LAFB, n (%)	2 (11.1)	15 (18.5)	0.73
LPFB, n (%)	0 (0)	3 (3.7)	1.00
RBBB + LAFB, n (%)	1 (5.6)	8 (9.9)	1.00
RBBB + LPFB, n (%)	0 (0)	3 (3.7)	1.00
Atrial fibrillation, n (%)	0 (0)	22 (27.2)	0.01
Bradycardia (< 60 bpm), n (%)	6 (33.3)	16 (19.8)	0.22
Pre-procedural echocardiogram			
LVEF (%)	62.1 $\pm$ 8.0 ($n = 17$)	58.0 $\pm$ 9.5 ($n = 74$)	0.10
Mean pressure gradient (mmHg)	35.8 $\pm$ 11.6 ($n = 17$)	39.2 $\pm$ 14.4 ($n = 79$)	0.35
Peak velocity (m/s)	3.8 $\pm$ 0.6 ($n = 17$)	4.0 $\pm$ 0.7 ($n = 79$)	0.38
Pre-procedural CT			
Annular area, mm ²	464.3 $\pm$ 90.2	485.7 $\pm$ 77.2	0.31
Annular perimeter, mm	77.4 $\pm$ 7.5	79.1 $\pm$ 6.2	0.29
Small annulus (≤ 430 mm ²), n (%)	7 (38.9)	21 (25.9)	0.41
Bicuspid valve, n (%)	1 (5.6)	6 (7.4)	1.00
Aortic valve calcification, mm ³	1122.0 $\pm$ 1119.5	1024.3 $\pm$ 699.9	0.64
None, n (%)	0 (0)	0 (0)	–
Mild, n (%)	5 (27.8)	11 (13.6)	0.16
Moderate, n (%)	6 (33.3)	28 (34.6)	1.00
Severe, n (%)	7 (38.9)	42 (51.9)	0.46
Procedural characteristics			
Valve type			0.16
Myval, n (%)	11 (61.1)	33 (40.7)	0.19
Sapien, n (%)	5 (27.8)	22 (27.2)	1.00
Evolut, n (%)	2 (11.1)	26 (32.1)	0.13
Balloon expandable (Myval + Sapien)	16 (88.9%)	55 (67.9%)	0.13
Pre-dilatation, n (%)	7 (38.9)	36 (44.4)	0.87
Post-dilatation, n (%)	1 (5.6)	15 (18.5)	0.29
Implantation depth analysed, n	16	73	
Implantation depth (NCC), mm	5.7 $\pm$ 3.5	5.8 $\pm$ 2.8	0.94
Implantation depth (LCC), mm	6.6 $\pm$ 2.8	5.9 $\pm$ 3.3	0.43
Implantation depth > 4 mm (NCC), n (%)	10 (62.5)	53 (72.6)	0.54
Implantation depth > 4 mm (LCC), n (%)	15 (93.8)	49 (67.1)	0.03

AV: Atrioventricular, CABG: Coronary artery bypass grafting, CT: Computed tomography, eGFR: Estimated glomerular filtration rate, LAFB: Left anterior fascicular block, LBBB: Left bundle branch block, LCC: Left coronary cusp, LPFB: Left posterior fascicular block, LVEF: Left ventricle ejection fraction, MI: Myocardial infarction, NCC: Noncoronary cusp, NYHA: New York heart association, PCI: Percutaneous coronary intervention, RBBB: Right bundle branch block, STS: Society of Thoracic Surgeons, VP: Ventricular pacing.

pacemaker follow-up data were unavailable, the closest follow-up data to the 1-year mark were collected.

2.3. Definition of pacemaker recovery

PMR was defined as a ventricular pacing (VP) rate $\leq 1\%$ as described in previous publications. [10–14] Since this was a post-hoc retrospective study, standardized pacemaker interrogation, such as verifying the patient's intrinsic heartbeat during pacing rate reduction, was not performed.

In addition to the VP threshold of 1%, we evaluated the distribution of other VP thresholds (20% and 40%) across the different THV types. These thresholds have been reported to be associated with pacemaker cardiomyopathy or clinical outcomes, or have been used in studies assessing pacemaker dependency after TAVI. [11,12,15–21]

2.4. Imaging analysis

Echocardiograms, 12-lead electrocardiograms (ECGs) and pre-procedural multislice computed tomography (CT) scans were analysed in core laboratories (echocardiogram: CORRIB core lab, University of Galway, Galway, Ireland; ECG: CERC, Massy, France; CT: TAVI core lab, India). Valve implantation depth was analysed by the CORRIB core lab using the final aortography at the index procedure. The depths were measured in the 3-cusp co-planar view as the distance from the nadir of the non-coronary cusp to the ventricular edge of the stent frame (NCC implantation depth) and the distance from the nadir of the left coronary cusp to the ventricular edge of the stent frame (LCC implantation depth).

2.5. Statistical analysis

Continuous variables are expressed as mean (standard deviation [SD]) or median (1st and 3rd quartiles) and compared using the *t*-test or Mann-Whitney *U* test. Categorical variables were reported as *n* (%), with differences assessed using chi-square or Fisher's exact tests. Univariable logistic regression analysis was performed to predict PMR (VP $\leq 1\%$) using baseline and procedural characteristics, with odds ratios and 95% confidence intervals (CIs). For variables exhibiting complete separation, Firth logistic regression method was used. Variables with a *p*-value < 0.10 in the univariable analysis were entered into the Firth multivariable logistic regression model. A two-sided *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed with R version 4.3.3.

3. Results

3.1. Baseline and procedural characteristics

Pacemaker follow-up data were available for 99 patients (Supplementary Fig. 1). The mean age was 80.7 (4.7) years, and 39% (*n* = 39) were women.

Table 1 presents baseline and procedural characteristics along with pacemaker follow-up data. PMR (VP $\leq 1\%$) occurred in 18 out of 99 (18%) patients, while 81/99 (82%) patients had no recovery (VP $> 1\%$). The PMR group was younger than the non-PMR group (78.6 [3.0] vs. 81.1 [5.1] years, *p* = 0.045). The rates of baseline right bundle branch block (RBBB; *n* = 3 [16.7%] vs. 22 [27.2%], *p* = 0.55) and left bundle branch block (LBBB, *n* = 0 vs. 7 [8.6%], *p* = 0.34) were numerically higher in the non-PMR group but the differences were not statistically significant. Atrial fibrillation was significantly more frequent in the non-recovery group based on the core lab reading of the baseline ECGs (*n* = 0 vs. *n* = 22 [27.2%], *p* = 0.01). The distribution of implanted valve type (*p* = 0.16) and the NCC (5.7 [3.5] vs. 5.8 [2.8] mm, *p* = 0.94) and LCC (6.6 [2.8] vs. 5.9 [3.3] mm, *p* = 0.43) implantation depths were also similar between the groups.

3.2. Pacemaker implantation

Complete atrioventricular block (AVB) was the most common indication for PPI in both groups (*n* = 15 [83%] vs 59 [73%], Table 2). PMR was observed in 15 (20%) of the 74 patients who underwent PPI for complete AVB, with similar PMR rates seen in those requiring a PPI for 2nd-degree AVB (13% [1/8]) or LBBB (18% [2/11]) (Fig. 1). The number of days between TAVI and PPI was non-significantly higher in the PMR group (5.5 [2.3, 7.0] vs 3.0 [2.0, 7.0] days, *p* = 0.16). Single-chamber pacemakers were more frequently implanted in the non-PMR group (*n* = 1 [6%] vs 29 [36%], *p* = 0.02), likely reflecting the higher prevalence of atrial fibrillation in that group.

3.3. Pacemaker follow-up data

The median time from PPI to pacemaker follow-up was 459 (401, 673) days in the PMR group and 388 (275, 583) days in the non-PMR group (*p* = 0.14, Table 2). The programmed lower rate limit did not differ (60 [50, 60] vs 60 [50, 60] bpm, *p* = 0.24). The VP rate was 0.3% (0.1, 1.0) in the PMR group and 52.4% (12.0, 98.1) in the non-PMR group (*p* < 0.001).

PMR was seen in 11 of 44 (25%) patients receiving the Myval series,

Table 2

Indication, device type, and follow-up data of permanent pacemaker implantation.

Characteristics	Pacemaker recovery (VP $\leq 1\%$) (<i>n</i> = 18)	No pacemaker recovery (VP $> 1\%$) (<i>n</i> = 81)	P-value
Pacemaker implantation			
Indication for PPI			
Complete AV block, <i>n</i> (%)	15 (83.3)	59 (72.8)	0.55
2nd-degree AV block, <i>n</i> (%)	1 (5.6)	7 (8.6)	1.00
LBBB, <i>n</i> (%)	2 (11.1)	9 (11.1)	1.00
Bradycardia or sick sinus syndrome, <i>n</i> (%)	0 (0)	4 (4.9)	1.00
Alternating L-RBBB, <i>n</i> (%)	0 (0)	1 (1.2)	1.00
AF with significant pause, <i>n</i> (%)	0 (0)	1 (1.2)	1.00
Days from TAVI to PPI, days, median (Q1, Q3)	5.5 (2.3, 7.0)	3.0 (2.0, 7.0)	0.16
PPI within 2 days from TAVI, <i>n</i> (%)	5 (27.8%)	31 (38.3%)	0.57
Type of device			
Dual chamber, <i>n</i> (%)	17 (94.4)	50 (61.7)	0.02
Single chamber, <i>n</i> (%)	1 (5.6)	29 (35.8)	0.02
Leadless, <i>n</i> (%)	0 (0.00)	2 (2.5%)	1.00
Pacemaker follow-up data			
Days from PPI to pacemaker follow-up, days, median (Q1, Q3)	459 (401, 673)	388 (275, 583)	0.14
Mode of pacemaker at follow-up			
DDD(R), <i>n</i> (%)	11 (61.1)	43 (53.1)	0.72
VVI(R), <i>n</i> (%)	1 (5.6)	30 (37.0)	0.02
AAI(R), <i>n</i> (%)	1 (5.6)	0 (0.0)	0.18
AAI(R)-DDD(R), <i>n</i> (%)	5 (27.8)	6 (7.4)	0.03
Others, <i>n</i> (%)	0 (0.00)	2 (2.5)	1.00
Lower rate setting of ventricular pacing	60 (50, 60)	60 (50, 60)	0.24
Pacing rates at follow-up			
Ventricular pacing, %, median (Q1, Q3)	0.3 (0.1, 1.0)	52.4 (12.0, 98.1)	< 0.001
Atrial pacing, %, median (Q1, Q3)	22.0 (8.9, 53)	21.0 (8, 43.3)	0.85

AV: Atrioventricular, LBBB: Left bundle branch block, PPI: Permanent pacemaker implantation, RBBB: Right bundle branch block, TAVI: Transcatheter aortic valve implantation, VP: Ventricular pacing.

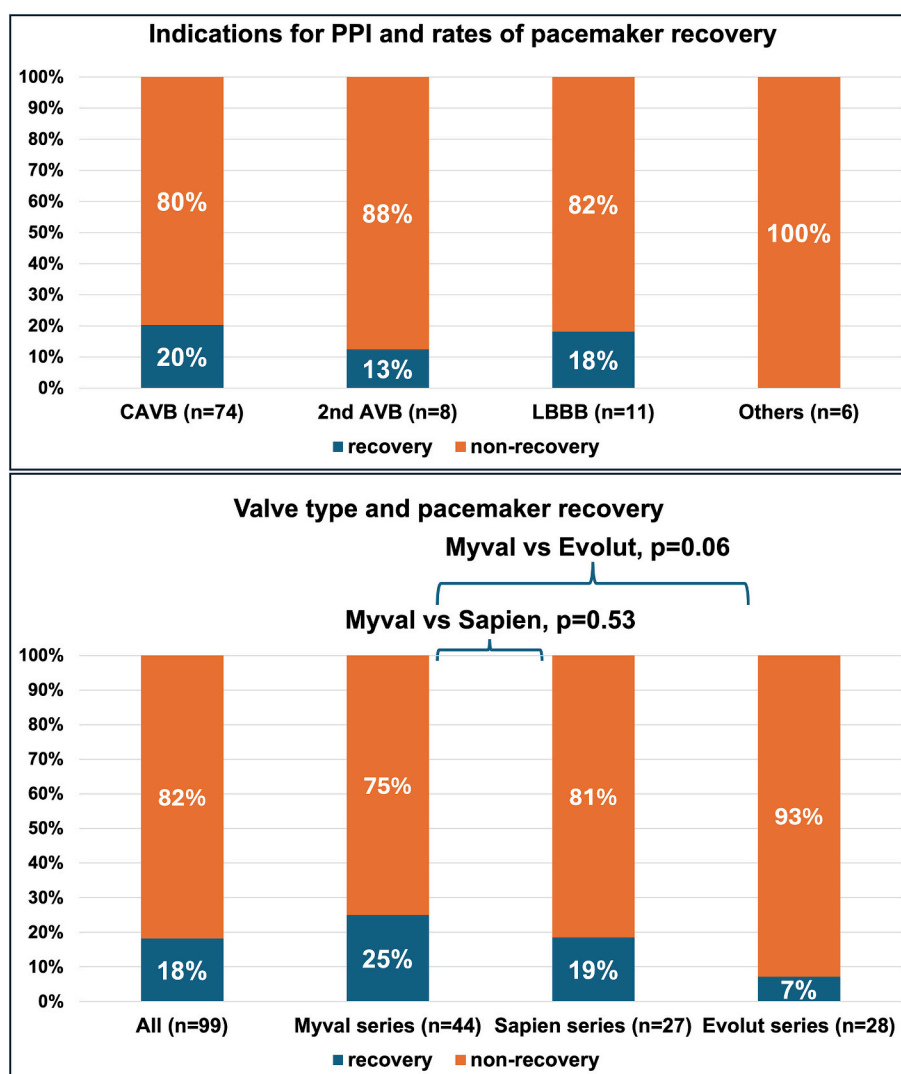


Fig. 1. Pacemaker recovery according to PPI indications and valve types.

Upper panel: Indications for PPI and pacemaker recovery.

Lower panel: Valve types and pacemaker recovery.

Pacemaker recovery was defined as ventricular pacing rate at 1 year >1%. Pacemaker non-recovery was defined as ventricular pacing rate at 1 year >1%.

2nd AVB = 2nd degree atrioventricular block, CAVB = complete atrioventricular block, LBBB = left bundle branch block, PPI = permanent pacemaker implantation.

5 of 27 (19%) receiving the Sapien series, and 2 of 28 (7%) receiving the Evolut series. There were no statistically significant differences in recovery rates between Myval and Sapien ($p = 0.53$) or between Myval and Evolut ($p = 0.06$, Fig. 1). The distributions of patients stratified by other VP thresholds (20% and 40%) across THV types are shown in **Supplementary Figs. 2 A and 2B**. Overall, no significant differences were observed between Myval and Sapien or between Myval and Evolut groups across the different VP thresholds.

The results of univariable and multivariable logistic regression analyses are presented in **Table 3**. Multivariable logistic regression showed that atrial fibrillation was significantly associated with lower odds of PMR (OR 0.09, 95% CI 0.00–0.77, $P = 0.02$).

Sensitivity analysis was performed by excluding four patients without a clear guideline-based indication for pacemaker implantation (three LBBB and one bradycardia cases). [9] The overall PMR rates remained same as 18% in this sensitivity analysis (**Supplementary Figs. 3 A and 3B**).

4. Discussion

In this post-hoc sub-study of the LANDMARK randomized controlled trial, 18% of patients who underwent PPI within 30 days after TAVI demonstrated recovery from ventricular pacing ($VP \leq 1\%$) at the 1-year pacemaker follow-up. Recovery rates did not differ significantly between Myval and Sapien or between Myval and Evolut THV series. Atrial fibrillation was significantly inversely associated with recovery. Although numerous studies have examined PMR or pacemaker dependency using pacemaker follow-up data, our data are unique, as evidence from randomized trials is scarce and our data is core-lab assessed. [5] In addition, to our knowledge, this is the first report to present pacemaker follow-up outcomes for the Myval THV series.

The overall 30-day PPI rate in the LANDMARK trial was relatively high, especially the 17.3% rate seen with the Sapien THV series. These findings initially raised concerns and underscored the need for a more detailed evaluation; however, closer examination revealed that these rates were not disproportionately high compared to previous studies. In the CHOICE trial, the 30-day PPI rate in the balloon-expandable cohort was similarly 17.3%, while the more recent SOLVE-TAVI trial reported a

Table 3

Univariable and multivariable logistic regression analysis for predicting pacemaker recovery (VP $\leq 1\%$).

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.90 (0.80, 1.00)	0.050	0.92 (0.81, 1.03)	0.14
Male	0.45 (0.15, 1.25)	0.13		
Body mass index	0.91 (0.81, 1.01)	0.11		
STS score (%)	0.78 (0.52, 1.06)	0.18		
Diabetes	1.10 (0.32, 3.31)	0.87		
Hypertension	1.03 (0.36, 3.05)	0.96		
eGFR <60 ml/min	1.19 (0.41, 3.34)	0.75		
Chronic obstructive pulmonary disease	1.90 (0.26, 9.72)	0.47		
Pre-procedural electrocardiogram				
PR interval	0.99 (0.97, 1.00)	0.13		
QRS interval	0.98 (0.95, 1.00)	0.07	0.98 (0.96, 1.00)	0.11
LBBB	0.27 (0.00, 2.38)	0.29		
RBBB	0.54 (0.12, 1.82)	0.36		
LAFB	0.55 (0.08, 2.22)	0.46		
Bradycardia (< 60 bpm)	2.03 (0.63, 6.12)	0.22		
AF	0.07 (0.00, 0.57)	<0.01	0.09 (0.00, 0.77)	0.02
Pre-procedural echocardiogram				
LVEF	1.06 (0.99, 1.14)	0.10		
Mean pressure gradient	0.98 (0.94, 1.02)	0.35		
Pre-procedural CT				
Annular area, mm ²	1.00 (0.99, 1.00)	0.31		
Small annulus (≤ 430 mm ²)	0.98 (0.96, 1.01)	0.19		
Bicuspid valve	0.74 (0.04, 4.71)	0.78		
Valve calcification, mm ³	1.00 (1.00, 1.00)	0.63		
Valve calcification - categorical				
Mild	Reference	–		
Moderate	0.47 (0.12, 1.93)	0.28		
Severe	0.37 (0.10, 1.44)	0.14		
Procedural characteristics				
Valve type	–	–		
Myval, n (%)	Reference	–		
Sapien, n (%)	0.68 (0.19, 2.16)	0.53	1.16 (0.32, 4.11)	0.82
Evolut, n (%)	0.23 (0.03, 0.96)	0.07	0.40 (0.07, 1.65)	0.21
Valve type				
Balloon-expandable (Myval + Sapien)	Reference	–		
Self-expanding	0.26 (0.04, 1.02)	0.09		
Pre-dilatation, n (%)	0.80 (0.27, 2.23)	0.67		
Post-dilatation, n (%)	0.26 (0.01, 1.42)	0.21		

Table 3 (continued)

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Implantation depth, mm (NCC)	0.99 (0.82, 1.19)	0.94		
Implantation depth, mm (LCC)	1.07 (0.90, 1.26)	0.43		
Implantation depth > 4 mm (NCC)	1.16 (0.87, 1.52)	0.29		
Implantation depth > 4 mm (LCC)	0.92 (0.71, 1.13)	0.46		
Days from TAVI to PPI	1.04 (0.91, 1.16)	0.54		

CT: Computed tomography, eGFR: Estimated glomerular filtration rate, LAFB: Left anterior fascicular block, LBBB: Left bundle branch block, LCC: Left coronary cusp, LVEF: Left ventricle ejection fraction, NCC: Noncoronary cusp, RBBB: Right bundle branch block, STS: Society of Thoracic Surgeons, TAVI: Transcatheter aortic valve implantation, VP: Ventricular pacing.

rate of 19.2% and the Swiss-TAVI registry documented 14.2%. [22–24] Taken together, the PPI rate observed in LANDMARK falls within the expected range for balloon- or self-expandable valves. Consequently, the initial concern was eventually withdrawn.

The definitions of pacemaker recovery or pacemaker dependency, as well as the timing of assessment, vary across studies. Among studies using a VP rate of <1%, and reporting results between approximately 1 month and 1 year post-TAVI, the incidence of PMR ranges widely from 2.4% to 66%. [10–14,21,25–27] The study population greatly influences the VP burden: for example, in cohorts restricted to patients with pre-existing RBBB, the incidence of VP < 1% was as low as 2.4–7.1%, indicating that recovery is less likely in the presence of pre-existing RBBB. [11,12] In contrast, a study evaluating prophylactic PPI in patients with pre-existing RBBB reported a VP < 1% rate of 29% (23/79). [26] Moreover, in the PROMOTE trial, prophylactic PPI was performed according to a prespecified algorithm for patients with either pre-existing conduction system disturbances or new conduction system disturbances after TAVI. [27] At 30 days, the proportion of patients with VP < 1% was 42.6% (26/61) in the prophylactic PPI group compared with 14.5% (22/152) in the non-prophylactic PPI group. These findings suggest that the frequency of PMR is higher when PPI is performed prophylactically. One study reported a relatively high PMR rate of 65% (19/29). [21] In that study, the PMR rate was 17% (2/12) among patients who underwent PPI for high-degree AV block, whereas PMR was observed in 100% (17/17) of patients who received PPI for LBBB. In our study, 18% (2/11) of patients who underwent PPI for LBBB demonstrated PMR. Given the variability in indications for PPI in the setting of LBBB, including whether electrophysiological studies were performed and whether concomitant PR prolongation was present, further evaluation in a larger population is needed. In the sensitivity analysis excluding three LBBB patients without a clear guideline-based indication for PPI, the PMR rate was 13% (1/8, **Supplementary Fig. 3**). Overall, the recovery rate of 18% in the present study lies within the spectrum reported previously.

This study did not demonstrate a statistically significant difference in PMR rates among different THV types; however, PMR rates were numerically higher in the Myval group compared with the Evolut group (25% vs 7%, $p = 0.06$). This finding may be explained by the generally higher PPI rate with Evolut series compared with balloon-expandable valves, related to the deeper implantation depth, direct contact and stress below the membranous septum and overstretching of aortic annulus, which may affect the conduction system. [3] Such mechanical stress may also influence recovery from conduction disturbances. These observations require validation in larger populations.

Although the clinical impact of new PPI after TAVI remains debated, several studies have reported associations between PPI and increased

long-term mortality or rehospitalization. [24,28] It is well established that a higher right ventricular pacing burden is associated with pacemaker myocardiopathy or adverse clinical outcomes. [15–17,21] This also appears to be applicable to patients requiring PPI after TAVI and a higher right ventricular pacing burden has consistently been linked to worse clinical outcomes; for instance, a pacing rate > 40% has been associated with increased mortality, [19,20,29] while other studies have also shown adverse associations at lower thresholds of >30%, >20% or even >10%. [30–32]

From this standpoint, both unnecessary PPI and high rate of ventricular pacing should be avoided. Chang et al. evaluated a “temporary-permanent” pacemaker as a 1-month bridging strategy. [33] In 70 patients with new high-degree AVB, complete AVB, or first-degree AVB plus LBBB, a single-chamber pacemaker lead was fixed to the right ventricular septum, sutured to the skin, and externally connected to a generator secured with an adhesive dressing. Freedom from indications for PPI was strictly defined as the absence of pacing in both a 12-lead ECG and a 24-h Holter monitor at 1 month, together with a 0% ventricular pacing rate during the preceding week. At 1 month, 75.7% (53/70) of patients no longer required a PPI, supporting the use of a temporary-permanent pacemaker to allow for a 1-month buffer period. Furthermore, appropriate pacemaker programming and structured follow-up after PPI are crucial in minimizing unnecessary ventricular pacing. [34]

Numerous factors have been reported to be associated with PMR or pacemaker dependency, including pre-existing RBBB, first-degree AVB, left anterior hemiblock, implantation depth, membranous septum length, the difference between membranous septum length and implantation depth, use of self-expanding valves, prosthesis oversizing, calcification of the aortic valve or left ventricular outflow tract. [5,10,13,14,21,25,30,35,36] In the present study, multivariable logistic regression analysis identified atrial fibrillation as independently associated with lower odds of PMR. Atrial fibrillation and conduction system disturbances shares common risk factors such as aging, hypertension, heart failure and ischemic heart disease. It has been reported that patients with a prolonged PR interval or first-degree AVB have a higher risk of developing atrial fibrillation, [37] whereas patients with atrial fibrillation have an annual PPI rate of 1–2% or more. [38,39] Recent study also reported that atrial fibrillation was an independent predictor of VP > 20% among patients who received PPI after TAVI. [31] The absence of other statistically significant predictors besides atrial fibrillation may be attributed to the limited number of patients included in the analysis and small number of patients who experienced PMR. Another reason may be the limited availability of the membranous septum length, which is a known risk factor. Because its measurement was not mandated by the trial protocol and the number of analysable cases were limited, it was not included in the present analysis.

4.1. Limitations

This study has several limitations. First, it is a post-hoc sub-study of a randomized controlled trial, and 1-year pacemaker follow-up data were collected retrospectively. Pacemaker follow-up was not standardized across centres; the timing, pacemaker mode, and lower-rate limit were all left to each site's discretion. When 1-year checks were not performed, data from the closest available time point from 1 year were used. Since the median lower rate setting was 60 beats per minute, some patients may have received pacing due to non-pathological or nocturnal bradycardia or due to prolongation of RR intervals in atrial fibrillation, potentially influencing the incidence of PMR. The information on hysteresis time and AV delay was not collected. Second, the definition of conduction system recovery relied solely on VP, without assessing the intrinsic heartbeat. Third, the number of patients who received a PPI and experienced PMR was limited, resulting in insufficient statistical power to identify predictors of PMR other than atrial fibrillation (e.g. RBBB, LBBB, etc). This limited sample size also reduced the ability to detect

potential differences in PMR rates across THV types. Fourth, the implantation depth was measured by aortography, and the association between implantation depth at the LCC and PMR may be spurious. Fifth, temporal changes in VP could not be evaluated because only the 1-year pacemaker follow-up data were collected. In addition, the dates of the preceding pacemaker interrogation were not obtained; therefore, the exact duration over which the reported VP burden was recorded is unknown. Sixth, the impact of VP at 1 year on subsequent clinical outcomes was not evaluated. The LANDMARK trial plans to follow patients for up to 10 years, and therefore, the prognostic implications of VP beyond 1 year will be assessed in future analyses.

5. Conclusions

At 1 year, pacemaker recovery ($VP \leq 1\%$) was observed in 18% of patients who underwent PPI after TAVI in the randomized LANDMARK trial, with no significant differences across the Myval, Sapien and Evolut series, which needs further confirmation with larger population. Atrial fibrillation was independently associated with lower odds of recovery.

CRedit authorship contribution statement

Akihiro Tobe: Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Pieter C. Smits:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Niels van Royen:** Writing – review & editing, Investigation. **Ignacio J. Amat-Santos:** Writing – review & editing, Investigation. **Martin Hudec:** Writing – review & editing, Investigation. **Matjaz Bunc:** Writing – review & editing, Investigation. **Ben J.L. Van den Branden:** Writing – review & editing, Investigation. **Peep Laanmets:** Writing – review & editing, Investigation. **Daniel Unic:** Writing – review & editing, Investigation. **Bela Merkely:** Writing – review & editing, Investigation. **Renicus S. Hermanides:** Writing – review & editing, Investigation. **Vlasis Ninios:** Writing – review & editing, Investigation. **Marcin Protasiewicz:** Writing – review & editing, Investigation. **Benno J.W.M. Rensing:** Writing – review & editing, Investigation. **Pedro L. Martin:** Writing – review & editing, Investigation. **Fausto Feres:** Writing – review & editing, Investigation. **Manuel De Sousa Almeida:** Writing – review & editing, Investigation. **Eric van Belle:** Writing – review & editing, Investigation. **Axel Linke:** Writing – review & editing, Investigation. **Alfonso Ielasi:** Writing – review & editing, Investigation. **Matteo Montorfano:** Writing – review & editing, Investigation. **Mark Webster:** Writing – review & editing, Investigation. **Konstantinos Toutouzas:** Writing – review & editing, Investigation. **Emmanuel Teiger:** Writing – review & editing, Investigation. **Francesco Bedogni:** Writing – review & editing, Investigation. **Michiel Voskuil:** Writing – review & editing, Investigation. **Manuel Pan:** Writing – review & editing, Investigation. **Oskar Angerås:** Writing – review & editing, Investigation. **Won-Keun Kim:** Writing – review & editing, Investigation. **Jürgen Rothe:** Writing – review & editing, Investigation. **Ivica Kristić:** Writing – review & editing, Investigation. **Vicente Peral:** Writing – review & editing, Investigation. **Scot Garg:** Writing – review & editing. **Geert A.A. Versteeg:** Writing – review & editing, Investigation. **Mario García Gómez:** Writing – review & editing, Investigation. **Tsung-Ying Tsai:** Writing – review & editing, Investigation. **Ashokkumar Thakkar:** Project administration, Data curation. **Udita Chandra:** Project administration, Data curation. **Marie-Claude Morice:** Writing – review & editing, Formal analysis. **Yoshinobu Onuma:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Andreas Baumbach:** Writing – review & editing, Investigation. **Patrick W. Serruys:** Writing – review & editing, Supervision, Conceptualization.

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Appendix A. Supplementary data

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