BMJ Open

Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing transcatheter aortic valve implantation: a prospective cohort study

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To cite: Wasim D, Ali AM, Bleie Ø, *et al*. Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing transcatheter aortic valve implantation: a prospective cohort study. *BMJ Open* 2025;**15**:e093073. doi:10.1136/bmjopen-2024-093073

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-093073).

Received 30 August 2024
Accepted 08 January 2025

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ABSTRACT

Objectives The primary objectives were to identify the predictors of new permanent pacemaker implantation in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). The secondary objectives were to investigate the temporal changes in permanent pacemaker implantation following TAVI and its impact on long-term prognosis.

Design Prospective observational cohort study of patients with AS undergoing TAVI.

Setting Single-centre study conducted at a tertiary hospital in Western Norway between 2012 and 2019.

Participants Among 600 consecutive patients with severe AS who were treated with TAVI, 52 patients with permanent pacemaker prior to TAVI were excluded. The remaining 548 patients were included in the present study.

Baseline measures An evaluation of baseline risk factors, 12-lead ECG and echocardiography.

Primary outcome measures The need for a new pacemaker implantation ≤30 days following TAVI and all-cause death.

Results The mean age was 80.6±6.7 years, and 50% were males. Among the 548 eligible patients, 173 (31.6%) underwent pacemaker implantation ≤30 days following TAVI, evenly distributed between females and males (29.6% vs 33.6%, p=0.317), with higher implant rates at low-volume phase (2012–2015) and lower implant rates at high-volume phase (2016–2019) (45.8% vs 23.9%, p<0.001). On multivariable analysis, an abnormal electrocardiogram (OR 1.73; 95% CI 1.14 to 2.63, p=0.010), right bundle branch block (OR 2.23; 95% CI 1.09 to 4.59, p=0.028) and atrial fibrillation (OR 1.89; 95% CI 1.24 to 2.88, p=0.003) at baseline were strong predictors of pacemaker implantation. The type of bioprosthesis, but not size, was associated with permanent pacemaker implantation (mechanically expandable valves OR 3.48, 95% CI 2.16 to 5.59; balloon-expandable valves OR 0.07, 95% CI 0.02 to 0.29, both p<0.001)—irrespective of age and sex. During a median follow-up of 60.4 months (range 3–131 months), permanent pacemaker implantation following TAVI was not associated with all-cause mortality (HR 0.89; 95% CI 0.69 to 1.16, p=0.403).

Conclusions In the current study, the rates of permanent pacemaker implantation following TAVI decreased substantially from the early low-volume phase to the late high-volume phase. An abnormal baseline ECG, right bundle branch block, atrial fibrillation and bioprosthesis selection remained important predictors of permanent pacemaker implantation. Permanent pacemaker implantation following TAVI had no impact on short or long-term survival.

Ethics and dissemination The Regional Committees for Medical and Health Research Ethics (approval number: REK vest 33814/2019) and the Institutional Data Protection Services approved the study protocol. The dissemination of study findings was through peer-reviewed publication, presentation at national and international scientific meetings and conferences.

Trial registration number NCT04417829.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study represents a large sample of unselected patients with aortic stenosis stratified by study phases, taking into account temporal changes in prosthesis types, operator experience and procedural planning.
⇒ The current study investigates the association between atrial fibrillation and the risk of permanent pacemaker implantation following transcatheter aortic valve implantation.
⇒ The atrioventricular block and its types were not specifically addressed, given its established status as a strong predictor of permanent pacemaker implantation in previous studies.
⇒ The study did not include a control group as per study design.

INTRODUCTION

In developed countries, the prevalence of moderate to severe degenerative aortic

stenosis (AS) is approximately 3% in individuals ≥75 years.[1] With an ageing population, the total number of patients with severe AS is anticipated to increase as overall life expectancy increases worldwide. Aortic valve replacement is the only available treatment to avoid heart failure, irreversible myocardial damage, repeated hospitalisations and ultimately death.[2] Patients with AS >65 years and with comorbidities are often at high risk of complications with conventional surgery[2 3] and are offered transcatheter aortic valve implantation (TAVI) as a relatively safe alternative to achieve an improvement in quality of life and prognosis.[4–6] Although TAVI is less invasive compared with conventional surgery, it still carries the risk of procedure-related complications. With TAVI gaining popularity in lower risk patients, there remains a concern as to the impact permanent pacemaker implantation (PMI) may have in younger cohorts of patients. Not only are pacemakers associated with a longer duration of hospital stay[7 8] and possible procedurally related complications, but they also carry a requirement for regular generator changes, an inherent risk of future infective endocarditis, and left ventricular (LV) dysfunction as a result of chronic right ventricular pacing with an associated higher risk of mortality.[9] There is therefore a need to better understand the predictors of PMI following TAVI and as to how this impacts on short and longer term mortality.

The primary aims of the current TAVI-NOR study were to determine the incidence and predictors of PMI following TAVI and how these have changed with operator experience and newer device iterations. The secondary aim was to evaluate the impact of PMI on short and long term all-cause mortality.

METHODS

Study design

Between 2012 and 2019, a total of 640 patients who underwent TAVI at Haukeland University Hospital, Western Norway, were screened for inclusion in the present study. The original design of the TAVI-NOR study (NCT04417829) was to investigate the impact of TAVI on LV function recovery, mass regression and outcome in patients with severe AS.[10] Patients who did not meet the study requirements of scheduled echocardiographic follow-up (n=35) or those who received TAVI for severe aortic regurgitation (n=5) were excluded. The remaining 600 patients with severe symptomatic AS treated with TAVI were included in the TAVI-NOR study. A further 52 patients were excluded owing to the presence of a pre-existing PMI, leaving 548 patients eligible for the purposes of the current study. A total of 207 TAVI procedures were performed in the early low-volume phase (2012–2015) and 393 in the late high-volume phase (2016–2019). Following the TAVI procedure, the patients were assessed at 1-month and 6–12-month follow-up. The indication for TAVI was decided by the multidisciplinary Heart Team.

Patient and public involvement

None.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (approval number: REK 33814/2019) and the Institutional Data Protection Services. Informed consent was waived.

Cardiovascular risk factors and all-cause death

Information on cardiovascular risk factors and comorbidities including hypertension, diabetes mellitus, hyperlipidaemia and coronary artery disease (defined by findings of conventional coronary angiography or cardiac CT, history of myocardial infarction, previous coronary artery bypass surgery or percutaneous coronary intervention) at baseline were obtained through the mandatory Norwegian Registry of Invasive Cardiology database. The data were prospectively collected and further quality assured through reviewing electronic patient records for the current TAVI-NOR study. Cardiovascular disease was defined as the presence of coronary artery disease, peripheral arterial disease or history of previous stroke or transient ischaemic attack. Hypertension was defined as a history of hypertension, current or past use of antihypertensive medications, or repeated clinic blood pressure ≥140/90 mm Hg. Hypercholesterolaemia was defined as previously established diagnosis or the use of statin.

Study endpoints

The primary endpoint was the need for a new PMI ≤30 days following TAVI and all-cause death. All-cause death was obtained by reviewing the electronic patient record or death certificates with 30 December 2022 as the censoring date.

ECG and pacemaker

Standard 12 lead ECGs with paper speed of 50 mm/s were obtained during the pre-TAVI work-up, hospitalisation for TAVI and at each follow-up visit following TAVI. ECGs were carefully assessed for the presence of brady- or tachyarrhythmias such as atrioventricular (AV) blocks or atrial fibrillation (AF), other conduction abnormalities (right bundle branch block (RBBB), left bundle branch block (LBBB), bifascicular and intraventricular conduction delays) and the presence of electronic pacing. The presence of any brady- or tachyarrhythmias, conduction abnormalities or signs of an ECG LV strain pattern was defined as an abnormal ECG. The presence of LV hypertrophy (LVH) was identified by Sokolow-Lyon product ≥35 mm or R wave ≥11 mm in augmented vector left (aVL) lead (in the presence of left anterior fascicular block, R wave ≥13 mm).[11]

During the TAVI procedure, patients were secured by implanting a temporary pacing wire and monitored by three-lead continuous ECG (telemetry) on transfer to the ward. Patients received a PMI if they developed high-degree AV block, pathological prolonged QRS duration

with either RBBB or LBBB following TAVI by the discretion of treating physician based on international guidelines.[12 13]

Echocardiogram

Standard transthoracic echocardiography was performed by certified sonographers or imaging cardiologists according to the TAVI-NOR study protocol,[10] using commercially available ultrasound machines (GE Vivid 5, 7 and 9 and Philips Epiq 7). All images were reanalysed offline in EchoPAC (GE Vingmed Ultrasound) according to guidelines.[14 15]

Aortic valve area (AVA) was calculated by continuity equation and AVA <1.0 cm^2 was defined as severe AS.[14 15] Transaortic flow was assessed by stroke volume index (SVi) or flow rate (unindexed stroke volume divided by systolic ejection time). A normal transaortic flow was defined by either SVi ≥35 mL/m^2 or flow rate ≥200 mL/s.[16] LV mass was calculated by the formula proposed by Devereux and indexed for body surface area, with a cut-off value of ≤95 g/m^2 for normal LV mass index in women and ≤115 g/m^2 in men. LV mass index values in combination with relative wall thickness (normal <0.43) was used to assess LV geometry types. The ratio of interventricular septum diameter/posterior wall diameter above 1.3 was defined as asymmetrical septal hypertrophy (ASH). Proximal or basal septal hypertrophy (BSH) was visually assessed in both parasternal long-axis and apical four-chamber views. The Simpson biplane method was applied to calculated LV ejection fraction.[17]

Statistics

Variables in the dataset were checked for normality by use of Kolmogorov-Smirnov or Shapiro-Wilk test. Continuous variables were presented as mean±SD and categorical variables as frequencies with respective percentages. Student's t-test was used to compare difference in mean of continuous variables and χ^2 to compare difference in frequencies/proportions of categorical variables.

Univariable and multivariable binary logistic regression analyses were performed to identify the predictors of PMI after TAVI. Multivariable models were adjusted for potential confounders and prognosticators based on univariable associations or clinical relevance. Furthermore, we assessed for multicollinearity with the use of variance inflation factor testing (threshold <5). Only variables with minimal correlation were included in the multivariable model presented. Specifically, AF and overall abnormal ECG were not entered in the same multivariable model due to their high collinearity. Although the collinearity between RBBB and abnormal ECG was low, an abnormal ECG was a composite variable including the component of RBBB. For this reason, RBBB and AF were tested in separate models. First-generation self-expanding valve (SEV) had a strong inverse correlation with mechanically expandable valve, and these two variables were tested in different models. The association of new PMI and overall abnormal ECG at baseline with all-cause mortality was tested in univariable Cox regression models. Kaplan-Meier curves were used to calculate event-free survival rates between patients with and without need for a new PMI and abnormal versus normal ECG at baseline. RStudio (POSIT, Boston, Massachusetts, USA) and SPSS V.28.0 (IBM corporation, Armonk, New York, USA) were used for data management and the statistical analyses.

RESULTS

Study population

The mean age in the entire study population was 80.6±6.6 years, and 50% were males. A total of 173 (31.6%) patients required PMI ≤30-days following their TAVI procedure (figure 1). There were no sex differences in the proportion of patients with new PMI (29.6% women vs 33.6% men, p=0.317).

The baseline characteristic of patients with versus without new PMI are presented in table 1. Both groups had a similar mean age (81.2±6.5 years vs 80.4±6.7 years, p=0.149), anthropometric measures and the prevalence of comorbidities such as hypertension, chronic kidney disease, cardiovascular disease, chronic lung disease and diabetes mellitus. In patients requiring PMI, the prevalence of AF was significantly higher compared with those without need of PMI (39% vs 26%, p=0.002).

The prevalence of an overall abnormal ECG and RBBB at baseline was higher in those requiring PMI compared with those without, while the prevalence of LBBB did not differ between the groups (12% vs 8%, p=0.178). There was no statistically significant difference in the QRS duration or prevalence of LVH among the groups (table 1).

The prevalence of LVH on echocardiography and LV mass (unindexed 244.8±66.7 g vs 234.6±66.3 g, p=0.095; and indexed 131.5±32.7 g/m^2 vs 127.6±33.3 g/m^2, p=0.199) were comparable between those who required a PMI vs those who did not. The only significant difference in echocardiographic measures was the aortic root diameter at the level of sinus Valsalva, which was larger in those with PMI compared with those without (3.36 cm vs 3.25 cm, p=0.002). However, valve size per se was comparable in both groups (2.79±0.28 vs 2.76±0.28 cm, p=0.414).

The baseline LV ejection fraction (56.9%±9.3% vs 57.0±10.6%, p=0.880), SVi (42.8±10.1 mL/m^2 vs 42.3±12.2 mL/m^2, p=0.587) and AS severity evaluated by AVA (0.73±0.20 cm^2 vs 0.71±0.27 cm^2, p=0.426) were comparable between the groups.

The frequencies of PMI after TAVI decreased from 45.8% (88/192) in the early low-volume phase to 23.9% (85/356) in the late high-volume phase (p<0.001) (figure 2).

Patients enrolled in the early low-volume phase were older (81.8±6.2 years vs 80.0±6.8 years, p=0.002), had lower body mass index and a higher prevalence of hypertension and previous history of myocardial infarction (table 2).

The frequencies of valve types changed over the study phases. First-generation SEVs were implanted in 64.6%

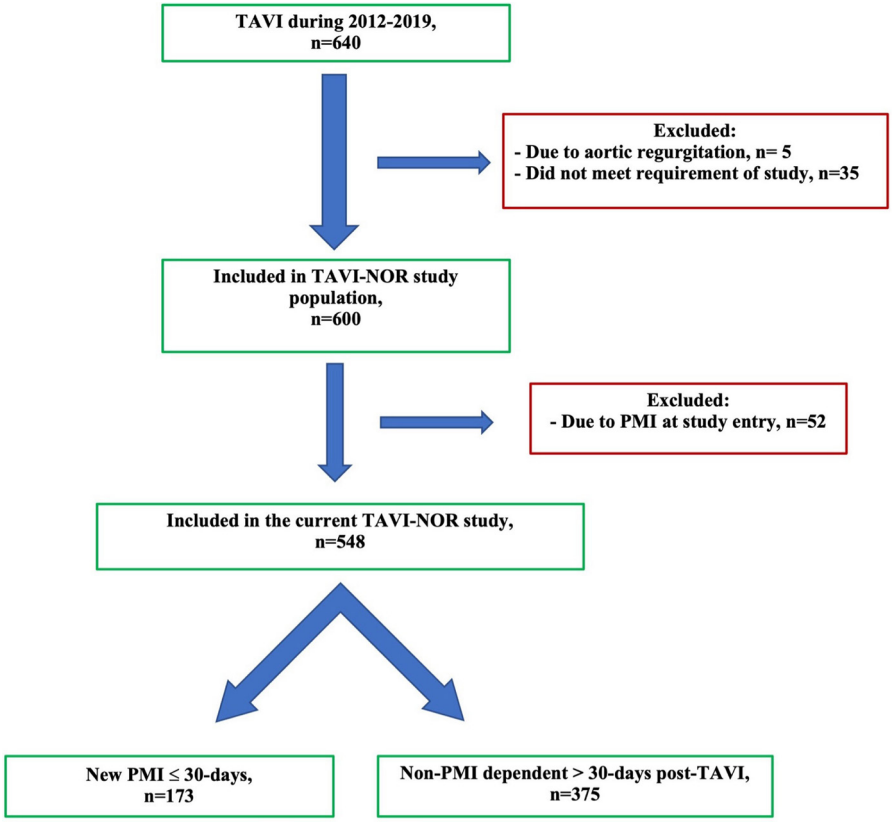

Figure 1 Inclusion flowchart. PMI, permanent pacemaker implantation; TAVI, transcatheter aortic valve implantation.

patients during low-volume phase and 1.4% in high-volume phase, while the use of second-generation SEV increased from 10.9% to 38.8% with the transition from early low-volume phase to late high-volume phase. Third-generation SEV (15.2%), intra-annular SEV (12.1%) and balloon-expandable valve (BEV) (18.3%) became available during high-volume phase. Mechanically expandable valve implant rates decreased from 24.5% to 14.3% (figure 3). There was also a difference in the distribution of valve types within patients requiring new PMI. The proportion of patient requiring PMI was higher in those who received a mechanically expandable valve (33.5% vs 10.7%, p<0.001) or first-generation SEV (31.2% vs 20.0%, p=0.004) in the early low-volume phase, compared with those who received a second-/third-generation SEV, intra-annular SEV and/or BEV in the late high-volume phase (table 3).

In total, 38% (n=66) had PM dependency during the follow-up visits, and 7.5% (n=13) had RBBB, 34% (n=58) had LBBB and 0.6% (n=1) had bifascicular block (p<0.001).

Predictors of permanent pacemaker implantation (PMI)

The univariable predictors of PMI are presented in table 4. A larger aortic root diameter was associated with a higher risk of PMI (OR 2.07; 95% 1.30 to 3.29, p=0.002) but was eliminated as predictor in the adjusted model (OR 1.65; 95% CI 0.99, 2.75, p=0.052). Overall, an abnormal baseline ECG was a predictor of PMI both in the univariable (OR 1.91; 95% CI 1.31 to 2.80, p<0.001) and multivariable-adjusted models (OR 1.73; 95% CI 1.14 to 2.63, p=0.010). The presence of RBBB at baseline had a strong association with the need of a PMI following TAVI, in both univariable (OR 1.93; 95% CI 1.05 to 3.56, p=0.034) and multivariable-adjusted analysis (OR 2.23; 95% CI 1.09 to 4.59, p=0.028). When an abnormal ECG was replaced by AF in the same multivariable model, it retained a strong association (OR 1.89; 95% CI 1.24 to 2.88, p=0.003) with the risk of PMI following TAVI.

The use of a mechanically expandable valve was strongly associated with PMI following TAVI (OR 4.22; 95% CI 2.68 to 6.66, p<0.001), whereas a BEV was not (OR 0.06; 95% CI 0.01 to 0.24, p<0.001). Among SEV, first-generation valves were associated with PMI following TAVI; however, second- and third-generation supra-annular and intra-annular valves were not (table 4). These univariable associations between BEV and mechanically expandable valve remained significant in the multivariable-adjusted model (mechanically expandable valve OR 3.48, 95% CI 2.16 to 5.59, p<0.001; and BEV OR 0.07, 95% CI 0.02 to 0.29, p<0.001).

When RBBB and AF were tested together in a separate supplementary model without including abnormal ECG in the model, both RBBB and AF were independent predictors of PMI, with other test variables remaining unchanged (online supplemental table 1). Adding age, sex and study phases to the same primary multivariable-adjusted model did not have any impact on our findings (online supplemental tables 2 and 3). Furthermore,

Table 1 Descriptive statistics of complete study population with comparison of participants with and without PMI ≤30 days following TAVI

	Overall (n=548)	PMI (n=173)	No PMI (n=375)	P value
Demographics, clinical characteristics and medications				
Age (year)	80.6±6.7	81.2±6.5	80.4±6.7	0.149
Male sex	271 (50%)	91 (53%)	180 (48%)	0.317
Body mass index (kg/m^2)	26.3±4.6	26.6±4.8	26.2±4.5	0.410
Body surface area (m^2)	1.85±0.21	1.86±0.21	1.84±0.21	0.259
Study phases				<0.001
Low volume	192 (35%)	88 (51%)	104 (28%)	
High volume	356 (65%)	85 (49%)	271 (72%)	
Heart rate (bpm)	71.0±13.0	70.0±15.0	72.0±12.0	0.124
NYHA functional class				0.694
I–II	257 (47%)	79 (46%)	178 (47%)	
III–IV	291 (53%)	94 (54%)	197 (53%)	
Smoking	248 (45%)	78 (45%)	170 (45%)	0.957
Chronic lung disease	107 (20%)	39 (23%)	68 (18%)	0.226
Diabetes mellitus type 2	99 (18%)	34 (20%)	65 (17%)	0.512
Hypertension	465 (85%)	149 (86%)	316 (84%)	0.572
Previous myocardial infarction	156 (29%)	53 (31%)	103 (28%)	0.445
Cardiovascular disease	388 (71%)	126 (73%)	262 (70%)	0.478
Chronic kidney disease	155 (28%)	48 (28%)	107 (29%)	0.849
Atrial fibrillation	163 (30%)	67 (39%)	96 (26%)	0.002
Anti-hypertensive medication	465 (85%)	149 (86%)	316 (84%)	0.572
Statin	401 (73%)	117 (68%)	284 (76%)	0.047
Anti-coagulant	160 (29%)	67 (39%)	93 (25%)	0.001
Anti-platelet	361 (66%)	109 (63%)	252 (67%)	0.315
ECG characteristics				
Abnormal ECG	313 (57%)	117 (68%)	196 (52%)	<0.001
Sokolow-Lyon product (mV)	2.9±1.0	2.8±1.1	2.9±1.0	0.320
ECG LVH by Sokolow-Lyon	146 (29%)	44 (28%)	102 (29%)	0.809
R amplitude in aVL (mm)	8.7±4.8	8.4±4.7	8.8±4.8	0.431
ECG LVH by R amplitude	174 (32%)	52 (30%)	122 (33%)	0.526
ECG LVH by either R or Sokolow-Lyon	250 (50%)	73 (47%)	177 (51%)	0.366
QRS complex duration (ms)	104±22	106±24	102±22	0.075
Right bundle branch block	46 (8.4%)	21 (12%)	25 (7%)	0.032
Left bundle branch block	50 (9.1%)	20 (12%)	30 (8.0%)	0.178
Bifascicular block	10 (1.8%)	2 (1.2%)	8 (2.1%)	0.427
Echocardiography characteristics				
Basal septal hypertrophy	227 (41%)	65 (38%)	162 (43%)	0.214
Asymmetric septal hypertrophy	113 (21%)	39 (23%)	74 (20%)	0.450
LVH by Echo	416 (76%)	135 (78%)	281 (75%)	0.430
LV mass (g)	237.8±66.5	244.8±66.7	234.6±66.3	0.095
LV mass indexed (g/m^2)	128.9±33.2	131.5±32.7	127.6±33.3	0.199
Aortic root diameter (cm)	3.28±0.39	3.36±0.39	3.25±0.39	0.002
Annulus diameter (cm)	2.08±0.18	2.09±0.16	2.08±0.18	0.435
Mean pressure gradient (mm Hg)	49.7±15.1	48.9±14.90	50.0±15.3	0.407

Continued

Table 1 Continued

	Overall (n=548)	PMI (n=173)	No PMI (n=375)	P value
Aortic valve area (cm^2)	0.72±0.25	0.73±0.20	0.71±0.27	0.426
Stroke volume indexed (ml/m^2)	42.4±11.6	42.8±10.1	42.3±12.2	0.587
EF biplane Simpson method (%)	57.0±10.0	56.9±9.3	57.0±10.6	0.880

Mean±SD or n (%).
ECG, electrocardiogram; EF, ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PMI, permanent pacemaker implantation; TAVI, transcatheter aortic valve implantation.

when multivariable logistic models were stratified by study phases, we identified the same predictors of PMI as in the primary model for the entire study population (online supplemental table 4).

Survival analysis

During a median follow-up of 60.4 months (range 3–131 months), there were 167 (44.5%) deaths in patients without need of PMI ≤30 days and 82 (47.4%) in those with need of PMI (p=0.531). Survival was not significantly different between patients who required a PMI compared with those who did not in the entire study period (figure 4A (i)). The results were consistent in early low and late high-volume phases (figure 4A(ii, iii)). Kaplan-Meier curves showed significantly reduced event-free survival in patients with abnormal ECG compared with patients with normal ECG at baseline, and this difference was more apparent after 5 years (figure 4B). However, early PMI after TAVI (≤30 days) had no significant association with all-cause mortality (OR 0.89; 95% CI 0.69 to 1.16, p=0.403). The use of valve type did not predict all-cause mortality (online supplemental figure 1).

DISCUSSION

There are several key findings from the current study. First, the prevalence of new PMI following TAVI was 31.6%, and particularly high in early low-volume phase (45.8%) compared with the late high-volume phase (23.9%). Second, an abnormal ECG, AF and RBBB at baseline (pre-TAVI) were strong predictors of PMI ≤30 days following TAVI. Third, early generation TAVI valves were associated with a need for PMI. Finally, PMI ≤30-days was not associated with all-cause mortality.

The risk of overall new PMI due to development of high-grade AV block is reported to be 13% within 30 days, and 12% within 48 hours after TAVI.[18–20] This is largely related to the exertion of radial forces during deployment of the device to the native annulus resulting in contusion of the membranous septum,[21] where the His bundle passes. This may lead to the prolongation of His to ventricle interval.[22 23] Consequentially, high grade AV block may ensue requiring PMI.[22] Other factors that contribute to AV conduction damage related to the valve delivery mechanism are the height of deployment into the LV outflow tract, the magnitude of radial force applied,[21 24 25] the length of the membranous interventricular septum and the presence of pre-existing conducting tissue abnormalities.[24–27]

The 31.6% prevalence of new PMI following TAVI in our study is within the range reported in previous studies (2.3% to 36.1%).[21 28–30] Several important factors may account for this variability, including the valve type, volume of the procedures at the implanting centre and operator experience. This is exemplified by the data available from other regions during the same period as the low-volume phase in the current study, where the PMI rate following TAVI was 14% in Sweden (2008–2018), 23% in Ohio (USA) and 22% in Athens (Greece).[30–32] Although it is difficult to draw any firm conclusions, this difference is likely attributed to the selection of the valve type with some centres opting for SEV with a higher rate of PMI compared with BEV with a reported lower rate

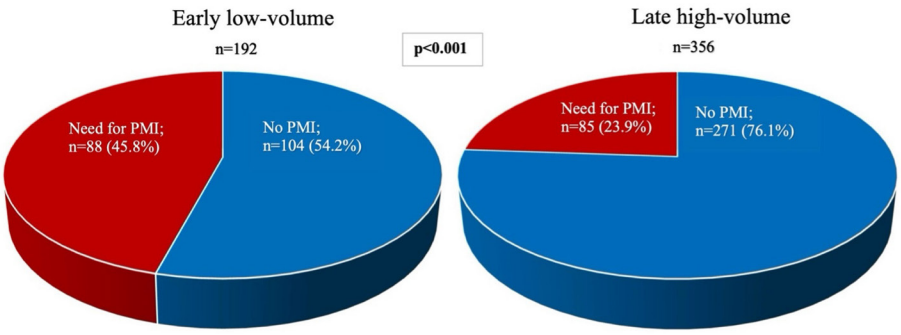

Figure 2 Distribution of permanent pacemaker implantation (PMI) in early low-volume phase to late high-volume phase. In total 173, (31.6%) participants received PMI ≤30 days after transcatheter aortic valve implantation: 88 (45.8%) in early low-volume phase and 85 (23.9%) in late high-volume phase (χ^2 p value of <0.001).

Table 2 Comparison of patient characteristics according to the study phases

Study phases	Low-volume (n=192)	High-volume (n=356)	P value
Age (year)	81.8±6.2	80.0±6.8	0.002
Sex			0.597
Female	100 (52%)	177 (50%)	
Male	92 (48%)	179 (50%)	
Body mass index (kg/m^2)	25.6±4.3	26.7±4.7	0.009
Body surface area (m^2)	1.82±0.20	1.86±0.21	0.064
Heart rate (bpm)	70±13	71±13	0.253
Symptom severity			0.585
Mild symptoms	87 (45%)	170 (48%)	
Moderate–severe	105 (55%)	186 (52%)	
Smoking	90 (47%)	158 (44%)	0.576
Chronic lung disease	35 (18%)	72 (20%)	0.574
Diabetes mellitus	43 (22%)	56 (16%)	0.053
Hypertension	176 (92%)	289 (81%)	0.001
Previous myocardial infarction	70 (36%)	86 (24%)	0.002
Cardiovascular disease	132 (69%)	256 (72%)	0.438
Chronic kidney disease	47 (24%)	108 (30%)	0.146
Atrial fibrillation	56 (29%)	107 (30%)	0.828
Statin	146 (76%)	255 (72%)	0.266
Anti-coagulant	54 (28%)	106 (30%)	0.685
Death	119 (62%)	130 (37%)	<0.001
PMI ≤30-days post-TAVI	88 (46%)	85 (24%)	<0.001

Mean±SD or n (%).
PMI, permanent pacemaker implantation; TAVI, transcatheter aortic valve implantation.

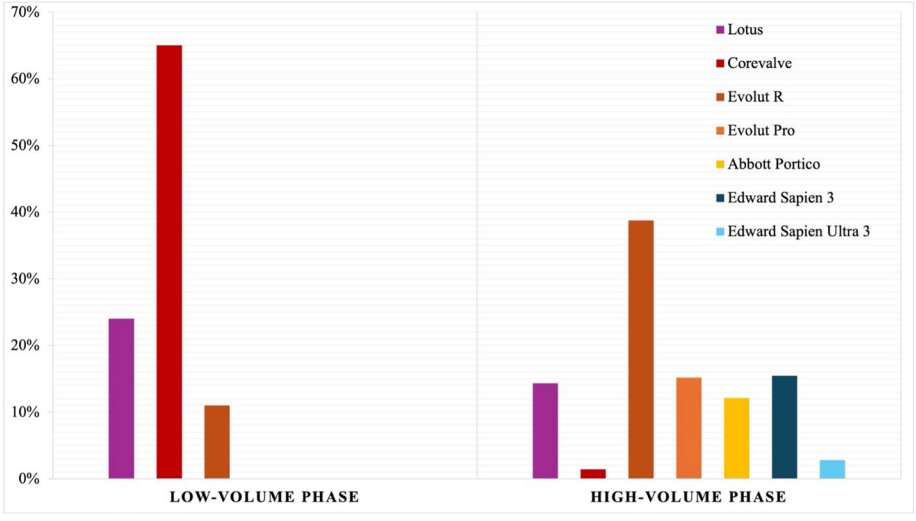

Figure 3 Distribution of valve types according to study phases. Illustration shows a significant reduction in the use of mechanically expandable valve Lotus (from 24% to 14%) and first-generation self-expanding valve (SEV) corevalve (from 65% to 1%) from low-volume to high-volume phase. The use of second-generation SEV Evolut R increased from 11% to 39% in the high-volume phase, and a variety of newer valve types were implanted, such as third-generation SEV Evolut Pro 15%, intra-annular SEV Abbott Portico 12%, balloon-expandable valves Edward Sapien 3 15% and Edward Sapien Ultra 3 3%.

Table 3 Valve types, size and access site according to study phases and need for PMI

Study phases	Low-volume (n=192)	High-volume (n=356)	Total (n=548)	P value
Mechanically expandable valve				
Lotus	47 (24.5%)	51 (14.3%)	98 (17.9%)	p=0.003
Self-expanding valve				
Corevalve	124 (64.6%)	5 (1.4%)	129 (23.5%)	p<0.001
Evolut R	21 (10.9%)	138 (38.8%)	159 (29.0%)	p<0.001
Evolut Pro	0 (0.0%)	54 (15.2%)	54 (9.9%)	p<0.001
Abbott Portico	0 (0.0%)	43 (12.1%)	43 (7.8%)	p<0.001
Balloon-expandable valve				
Edward Sapien 3	0 (0.0%)	55 (15.4%)	55 (10.0%)	p<0.001
Edward Sapien 3 Ultra	0 (0.0%)	10 (2.8%)	10 (1.8%)	p<0.001
PMI ≤30 days after TAVI	**PMI (n=173)**	**No PMI (n=375)**	**Total (n=548)**	**p-value**
Valve size (mm)	27.7±2.8	27.9±2.8	27.6±2.8	0.414
Valve in valve	15 (2.7%)	1 (0.6%)	14 (3.7%)	0.035
Access site				
Femoral	154 (89.0%)	326 (87.0%)	480 (87.6%)	0.724
Subclavian	14 (8.0%)	31 (8.0%)	8.0%)	
Direct aorta	5 (3.0%)	17 (5.0%)	4.0%)	
Other	0	1 (0.3%)	1 (0.3%)	
Mechanically expandable valve				
Lotus	58 (33.5%)	40 (10.7%)	98 (17.9%)	p<0.001
Self-expanding valve				
Corevalve	54 (31.2%)	75 (20.0%)	129 (23.5%)	p=0.004
Evolut R	39 (22.5%)	120 (32%)	159 (29.0%)	p=0.023
Evolut Pro	9 (5.2%)	45 (12%)	54 (9.9%)	p=0.013
Abbott Portico	11 (6.4%)	32 (8.5%)	43 (7.8%)	p=0.379
Balloon expandable valve				
Edward Sapien 3	2 (1.2%)	53 (14.1%)	55 (10.0%)	p<0.001
Edward Sapien 3 Ultra	0 (0.0%)	10 (2.7%)	10 (1.8%)	p=0.030

PMI, permanent pacemaker implantation.

of PMI. Additionally, the lower prevalence might also be in part due to procedural volume, as the prevalence of PMI in our study population fell to 24% in the late high-volume phase, which is comparable with the abovementioned high-volume TAVI centres. Another factor could be the overall cohort size and patient selection. Patients recruited in the early phase of our study were older, had lower body mass index (probably reflecting poorer health in this age category) and a higher burden of comorbidities compared to the late phase with younger patients. The change in population characteristics between the transition of study phases also reflects an improvement in patient selection over time, better procedural planning, operator experience, implantation technique and choice of valve type. These all may have influenced the observed decline in new PMI rates in the late high-volume phase. Of note, in our study, the choice of valve type changed significantly over time. The use of mechanically expandable valve declined to 14% from 25%, while the use of BEV increased to 18% from 0% from low- to high-volume phase. Furthermore, although SEV remained the prevailing valve of choice, there was a gradual reduction in its use over time as individualised valve selection per patient anatomy became more prevalent. Similar findings have been previously reported in a smaller cohort of 338 AS patients undergoing TAVI in which a decline in the prevalence of PMI rates was observed (31.7% in 2008–2013 to 19.3% in 2014–2017).[29]

Previous studies have identified that male sex and baseline conduction abnormalities (AV block, left anterior fascicular block and RBBB)[26 27] are predictors of PMI following TAVI. In the current study, we did not observe an association between PMI following TAVI and sex. This is in line with the findings of Costa *et al*[18] who neither find any difference in new PMI between men and women (p=0.528). A recent systematic review and meta-analysis

Table 4 Univariable and multivariable predictors of new pacemaker implantation following TAVI

	Univariable					Multivariable		
	N	Events	OR	95% CI	P value	OR	95% CI	P value
General predictors								
Age (year)	548	173	1.02	0.99, 1.05	0.15			
Male sex	548	173	1.20	0.84, 1.72	0.32			
BMI (kg/m^2)	548	173	1.02	0.98, 1.06	0.41			
Hypertension	548	173	1.16	0.69, 1.94	0.57			
Chronic kidney disease	548	173	0.96	0.64, 1.44	0.85			
Diabetes mellitus	548	173	1.17	0.74, 1.85	0.51			
Cardiovascular disease	548	173	1.16	0.77, 1.73	0.48			
Atrial fibrillation	548	173	1.84	1.25, 2.70	0.002	1.89	1.24, 2.88	0.003*
Heart rate (bpm)	548	173	0.99	0.97, 1.00	0.098	0.99	0.97, 1.00	0.056
ECG predictors								
Abnormal ECG	548	173	1.91	1.31, 2.80	<0.001	1.73	1.14, 2.63	0.010
Sokolow-Lyon product (mv)	548	173	0.92	0.77, 1.09	0.32			
ECG LVH by Sokolow-Lyon	548	173	0.92	0.62, 1.38	0.69			
R amplitude (mm)	548	173	0.99	0.95, 1.02	0.43			
ECG LVH by R amplitude	548	173	0.89	0.60, 1.32	0.56			
ECG LVH by R or Sokolow	548	173	0.89	0.60, 1.32	0.39			
QRS complex duration (ms)	548	173	1.01	1.00, 1.02	0.063			
Right bundle branch block	548	173	1.93	1.05, 3.56	0.034	2.23	1.09, 4.59	0.028
Left bundle branch block	548	173	1.50	0.83, 2.73	0.18			
Bifascicular block	548	173	0.54	0.11, 2.55	0.43			
Echocardiographic predictors								
BSH	548	173	0.79	0.55, 1.15	0.21			
ASH	548	173	1.18	0.76, 1.83	0.45			
Aortic root (cm)	547	173	2.07	1.30, 3.29	0.002	1.65	0.99, 2.75	0.052
Annulus (cm)	547	173	1.50	0.54, 4.16	0.44			
Stroke volume index (ml/m^2)	539	172	1.00	0.99, 1.02	0.61			
Mean pressure gradient (mmHg)	548	173	1.00	0.98, 1.01	0.41			
Aortic valve area (cm^2)	541	172	1.29	0.64, 2.62	0.48			
EF Simpson (%)	548	173	1.00	0.98, 1.02	0.88			
SEV	548	173	0.70	0.48, 1.04	0.075			
1. Generation			1.82	1.21 to 2.73	0.004			
2. Generation			0.62	0.41 to 0.94	0.024			
3. Generation			0.40	0.19 to 0.84	0.016			
Intra-annular			0.73	0.36 to 1.48	0.381			
Mechanically expandable valve	548	173	4.22	2.68, 6.66	<0.001	3.48	2.16, 5.59	<0.001
BEV	548	173	0.06	0.01, 0.24	<0.001	0.07	0.02, 0.29	<0.001
Valve size (mm)	548	173	1.03	0.96, 1.09	0.41			

*Abnormal ECG was replaced by atrial fibrillation in the same model.
ASH, asymmetrical septal hypertrophy; BEV, balloon-expandable valve; BMI, body mass index; BSH, Basal septal hypertrophy; EF, ejection fraction; SEV, self-expanding valve; TAVI, transcatheter aortic valve implantation.

indicated an overall 10% lower risk of PMI following TAVI in women compared with men.[33] However, we were unable to reaffirm this observation and attribute this to potential differences in valve-type strategy used in men and women to ensure best fit with regard to native annulus anatomy.

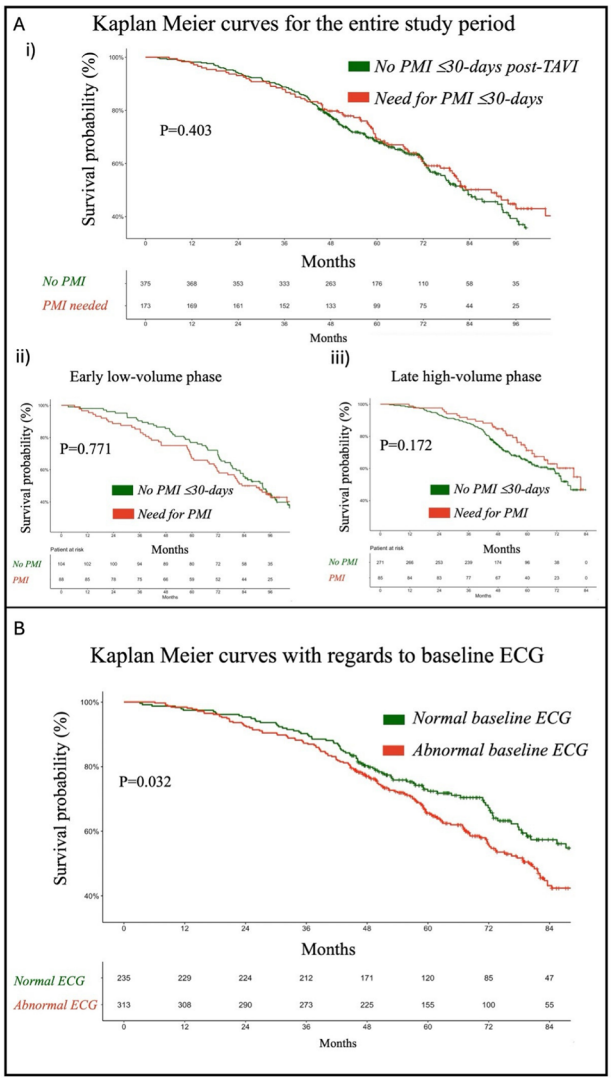

Figure 4 Kaplan-Meier curves. (**Ai**) The survival probability did not differ significantly in patient with and without need for new permanent pacemaker implantation (PMI) following transcatheter aortic valve implantation (TAVI) in the entire study period. The same trend was also observed when patients were stratified for study phases ((**Aii**) early low-volume phase, (**Aiii**) late high-volume phase). (**B**) Survival probability according to baseline ECG. Overall survival was significantly better for patients with normal baseline ECG compared with those with abnormal baseline ECG.

We showed that an abnormal ECG at baseline was a strong determinant of PMI. Interestingly, an abnormal ECG, but not PMI per se, was a predictor of poor prognosis.

The presence of RBBB at baseline remained a strong predictor of PMI regardless of the improvement in the procedural planning, device deployment/implantation techniques and access to newer generations of devices. This is consistent with the findings of prior studies.[29 34] Although the presence of RBBB is an electrocardiographic risk marker of PMI following TAVI, it lacks sensitivity and should be used in conjunction with careful electrocardiographic monitoring and documentation of interval change following device deployment.[19]

We found that pre-existing AF was associated with a 1.5-fold increased rate of PMI following TAVI on multivariable analysis. This is consistent with the data presented by other studies identifying pre- and post-TAVI AF as a predictor of PMI. The PARTNER trials also identified post-TAVI AF as a predictor of PMI.[35] Furthermore, a smaller study conducted on patients with AS receiving Edward Sapien 3 valve reported that patients requiring PMI had significantly higher prevalence of pre-existing AF.[36] Finally, a recent study from Korea, comparing patients with pre-existing AF, new onset AF or sinus rhythm at baseline, reported that 1-year risk of PMI or mortality was significantly higher in patients with AF compared with sinus rhythm.[37]

Uncertainty, however, remains as to the importance of AF as a meta-analysis of 41 studies up to January 2014 on PMI following TAVI found no association with pre-TAVI AF or LBBB, regardless of the valve-type used.[26] Similarly, in a more recent report from STS/ACC TVT registry, prior conduction abnormalities significantly predicted the need for PMI, but AF was equally present in both groups and did not predict the need for PMI.[25] Given the potential discrepancies in these findings, it is plausible that the role of AF in earlier studies was attenuated by more potent variables such as pre-existing age-related conduction system degeneration, coronary ischemia or AS-related myocardial damage and fibrosis. As TAVI now emerges as a treatment option for lower-risk and younger patients, the role of pre-existing AF may become more apparent as a predictor of PMI. Certainly, studies on patients with severe AS document existence of intranodal disease in some patients with AF (with a slow intrinsic ventricular rate <100 beat per minute) and LBBB.[38] Although, in our study, we did not stratify AF patients based on ventricular rate or bundle branch block, we did observe a significant association between pre-existing AF and need of PMI, and the multivariable model was adjusted for heart rate. Taking our results in context, we would advocate a careful and extended monitoring patients with a pre-existing abnormal ECG, AF or RBBB undergoing TAVI with close follow-up in the early phase following discharge. Nonetheless, further prospective studies are indicated to ratify this recommendation.

Long-term right ventricular pacing per se may induce electromechanical asynchrony and LV remodelling and increase the risk of AF and heart failure.[39 40] Hence, patients who receive new PMI after TAVI warrant careful echocardiographic assessment, not only to evaluate the haemodynamic performance of the prosthetic valve, but also to evaluate LV function on serial echocardiograms.

Finally, in TAVI-NOR, new PMI after TAVI was not associated with all-cause mortality. This is in contrast to some prior studies. In a large study of 1116 patients (mean age of 80.9±5.3 years) undergoing TAVI without prior PM, Costa *et al*[18] reported that new PMI after TAVI was associated with an increased risk of mortality at

6 years. Importantly, patients in need of PMI had poor prognosis at 1-year follow-up mainly due to heart failure and increased risk of hospitalisation in the PARTNER trial[9] and in the TVT registry study.[25] Conversely, other studies reported no difference in mortality within 30 days,[30 41 42] 2 years[42] and at 10 years[30] between patients in need of PMI versus those without. A recent report from the SWEDEHEART TAVR study found no difference in mortality, heart failure or prevalence of endocarditis with a 10-year follow-up time and suggested this to be a result of including a more homogenous study population using transfemoral access.[30] In contrast to this abovementioned study, our study population was unselected with the use of different access sites, and even though mortality was similar between the two groups, we did find a higher prevalence of an abnormal ECG (reflecting underlying cardiac disease and a marker of poor long-term prognosis) in those requiring PMI after TAVI. Given the fact that new onset LBBB and PMI after TAVI are strongly associated with poor long-term outcome,[41] close monitoring of LV function on echocardiography is recommended to enable early initiation of medical therapy where appropriate to reduce heart failure hospitalisations and mortality.[43]

Limitation

As per study design, it was not possible to have a designated control group. Another limitation was that information on changes in medical therapy before and after PMI was unavailable. In our study, we did not factor for valve implantation depth, and CT LV-outflow tract perimeter was not available. However, the primary aim was not to explore anatomical predictors by CT for PMI as these have been documented elsewhere in detail and was not available in the registry database. The role of computer modelling was also not factored into predicting PMI implantation, which may enable PMI rates to fall further. In future studies, implantation height should be considered, as the mechanics involved can contribute to reduced risk.[20 44] In our study, we did not specifically address the grade of AV block, given its established status as a strong predictor in previously published studies. Hospitalisations and development of heart failure during follow-up were not recorded.

Conclusions

In an unselected cohort of patients with AS undergoing TAVI, approximately one-third of patients required early pacemaker implantation. However, pacemaker implantation rates declined with increasing procedural volumes and experience. An abnormal ECG, RBBB and AF at baseline, and the prosthesis type and deployment mechanisms, but not sex, influenced the need for new pacemaker implantation following TAVI. Although pacemaker implantation after TAVI was not associated with all-cause mortality in this study, it should be interpreted with caution since pacemaker implantation has been suggested as a marker of poor long-term outcome in some other cohorts.

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Funding This study was funded by Western Norway Health Trust.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. Data is available by the corresponding author upon reasonable request.

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