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Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing Transcatheter Aortic Valve Implantation: TAVI-NOR study

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ABSTRACT

Objective: To identify predictors of new permanent pacemaker implantation (PMI) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) and the impact on long-term prognosis.

Design: A prospective cohort study including patients who underwent TAVI due to severe AS from 2012 to 2019. Of the total 640 consecutive patients screened, 600 patients with severe AS treated with TAVI were included. 52 patients with PMI prior to TAVI were excluded.

Participants: Patients with severe AS undergoing TAVI.

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

Primary outcome measures: The need for a new PMI ≤30-days following TAVI, and all-cause death.

Results: The mean age was 80.6 years and 50% were males. Among the 548 eligible patients, 173 (31.6%) underwent PMI ≤30-days following TAVI, evenly distributed between in 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). Overall abnormal ECG (OR 1.73; 95% CI 1.14-2.63, p=0.010), RBBB (OR 2.23; 95% CI 1.09-4.59, p=0.028) and atrial fibrillation (OR 1.89 1.24-2.88, p=0.003) at baseline were strong predictors of PMI in the multivariable-adjusted analysis. The type of bioprosthesis, but not size, was associated with PMI (mechanically-expandable valves OR 3.48: 95% CI 2.16-5.59; Balloon-expandable valves OR 0.07: 95% CI 0.02-0.29, both p<0.001) - irrespective of age and sex. During a median follow-up of 60.4 months (range 3-131months), PMI after TAVI had no association with all-cause mortality (HR 0.89; 95% CI 0.69-1.16, p=0.403).

Conclusions: Our data from patients with severe AS show that an abnormal baseline ECG, the presence of RBBB, atrial fibrillation and bioprosthesis selection are associated with increased PMI rates following TAVI, regardless of sex. PMI following TAVI had no impact upon short or long-term survival.

Strengths and limitations of this study

- A large prospective cohort of patients with severe AS undergoing TAVI exploring predictors of PMI. As per study design, it was not possible to have a designated control group
- The study investigates relation of pre-existing atrial fibrillation with regards to PMI risk following TAVI. To date, few large-scale studies have investigated this.
- The grade of AV-block was not specifically addressed, given its established status as a strong predictor in previously published studies.
- The study explores prosthesis types and deployment mechanisms overall influence on the need for PMI following TAVI. The analysis did not factor for implantation depth, and CT LV-outflow tract perimeter was not available.

Introduction

In developed countries, the prevalence of moderate to severe degenerative aortic stenosis (AS) is approximately 3% in individuals ≥75 years (1). With aging of the 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 hospitalizations and ultimately death (2). Patients with AS >65 years and with comorbidities are at 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 improvement in quality of life and better prognosis (4-6). Although TAVI is less invasive compared to conventional surgery, it still carries the potential risk of procedure-related complications. In particular, permanent pacemaker implantation (PMI) remains a concern as TAVI is likely to be offered to lower risk patients. There is therefore a need for contemporary data in unselected cohorts in order to mitigate the risk of PMI, which in turn is associated with cardiovascular implantable electronic devices (CIED) related infective endocarditis, complications related to pacemaker implantation, need for regular device changes and longer duration of hospital stay (7, 8). Moreover, some patients who require chronic right ventricular (RV) pacing, may develop left ventricular (LV) dysfunction, with a higher risk of mortality (9).

Current guidelines indicate PMI in those patients who have persistent/recurrent high-grad AV block 24-48 hour post TAVI and patients with pre-existing RBBB developing new post procedure conduction disturbances (10). Furthermore, expert consensus recommends PMI in those with PR prolongation/axis change, or persistent new-onset left bundle-branch block (LBBB) with QRS duration >150 ms or PR >240 ms (11).

The primary aims of the current TAVI-NOR study including an unselected cohort of patients with AS were to determine the incidence and predictors of PMI following TAVI and assess the impact on all-cause mortality.

Methods

Study design

Between 2012 and 2019 a total of 640 patients who underwent TAVI at Haukeland University Hospital, Western Norway in collaboration with other regional hospitals, were screened for inclusion in the present study. The original design of the TAVI-NOR study was to investigate the impact of TAVI on LV function recovery, mass regression and outcome in patients with severe AS (12). 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 clinically severe symptomatic AS treated with TAVI were included in the TAVI-NOR study conducted. 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.

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 waved.

Cardiovascular risk factors and all-cause death

Information on cardiovascular risk factors and comorbidities including hypertension, diabetes, hyperlipidemia and coronary artery disease (defined by findings of conventional coronary angiography or cardiac computed tomography, history of myocardial infarction, previous coronary artery bypass surgery or percutaneous coronary intervention) at baseline were obtained from Norwegian Registry of Invasive Cardiology (NORIC) database and quality assured by the use of electronic patient records. Cardiovascular disease was defined as the presence of coronary artery disease, peripheral arterial disease or history of previous stroke or transient ischemic attack. Hypertension was defined as a history of hypertension, current or past use of antihypertensive medications, or repeated clinic blood pressure (BP) ≥140/90 mmHg. Hypercholesterolemia 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 30.12.2023 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, hospitalization for TAVI, and at each follow-up visit following TAVI. ECGs were carefully assessed for the presence of brady- or tachyarrhythmias such as atrio-ventricular blocks or atrial fibrillation (AF), or other conduction abnormalities including right or left bundle-branch block (RBBB and LBBB), bifascicular block, or intraventricular conduction

delay reflected by QRS widening without typical BBB morphology, or 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 ≥35mm, or R wave ≥11 in lead aVL (in the presence of left anterior fascicular block, R wave ≥13 mm) (13).

During the TAVI procedure, patients were secured by implanting a temporary 1-lead PM and monitored by 3-lead continuous ECG (telemetry) when transferred 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.

Echocardiogram

Standard transthoracic echocardiography was performed by certified sonographers or imaging Cardiologists according to the TAVI-NOR study protocol (12), using commercially available ultrasound machines (GE Vivid 5, 7, 9 and Philips 'Epiq 7) (12). All images were reanalyzed 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 4-

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 ± standard deviation, and categorical variables as frequencies with respective percentages. Student's t-test was used to compare difference in mean of continuous variables, and Chi-square test to compare difference in frequencies/proportions of categorical variables.

Univariate and multivariate binary logistic regression analyses were performed to identify predictors of PMI after TAVI. There was a collinearity between AF and abnormal ECG, thus the variables were not entered in the same model. 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 univariate 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 version 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 after the 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. In patients requiring PMI, the prevalence of AF (39% vs 26%, p=0.002) was significantly higher compared to those without need of PMI.

The prevalence of an overall abnormal ECG and RBBB at baseline was higher in those requiring PMI compared to 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 versus 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 to 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), stroke volume index (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 had 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 SEV were implanted in 64.6% 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 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 had implanted a mechanically-expandable valve (33.5% vs 10.7%, p<0.001) or first-generation SEV (31.2% vs 20.0%, p=0.004) during early low-volume phase compared to those who had implanted a second-/third-generation SEV, intra-annular SEV and/or BEV in the late high-volume phase (*Table 3*). The use of valve type did not predict all-cause mortality (*Supplementary Figure 1*).

Predictors of PMI

Univariate predictors of PMI are presented in *Table 4.* Larger aortic root diameter was associated with a higher risk of new PMI (OR 2.07; 95% 1.30-3.29, 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 univariate (OR 1.91; 95% CI 1.31-2.80, p<0.001) and multivariable-adjusted models (OR 1.73; 95% CI 1.14-2.63, p=0.010). RBBB at baseline had a strong association with the need of a PMI after TAVI, in both univariate (OR 1.93; 95% 1.05-3.56, p= 0.034) and multivariable-adjusted analysis (OR

2.23; 95% 1.09-4.59, p=0.028). When an abnormal ECG was replaced by AF in the same multivariate model, it retained a strong association (OR 1.89; 95% CI 1.24-2.88, p=0.003) with the risk of PMI following TAVI. The use of mechanically-expandable valve was strongly associated with PMI following TAVI (OR 4.22; 95% CI 2.68-6.66, p<0.001), whereas BEV was not (OR 0.06; 95% CI 0.01-0.24, p<0.001). Among SEV, the first-generation valves were associated with PMI following TAVI, however second-, third-generation supra-annular and intra-annular valves were not (*Table 4*). These univariate associations between BEV and mechanically-expandable valve remained also significant in the multivariable-adjusted model (mechanically-expandable valve OR 3.48; 95% CI 2.16-5.59, p<0.001 and BEV OR 0.07; 95% CI 0.02-0.29, p<0.001). Adding age and sex to the same primary multivariable-adjusted model did not change our findings.

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 4Ai*). The results were consistent in early low and late high-volume phases (*Figure 4Aii-iii*). Kaplan-Meier curves showed significantly reduced event-free survival in patients with abnormal ECG compared to 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 0.69-1.16, p=0.403. In total, 38% (n=66) had PM dependency during the follow-up visits, and 7.5% (n=13) had RBBB, 34% (n=58) LBBB, and 0.6% (n=1) had bifascicular block (p<0.001).

Discussion

There are several key findings from the current study. First, the prevalence of new PMI following TAVI was 31.6%, which was particularly high in an 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. Fourth 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 center 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 comparisons, this difference is likely attributed to the selection of the valve type with some centers opting for

SEV with a higher rate of PMI compared to BEV with a reported lower rate 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 more comparable to the abovementioned high-volume TAVI centers. 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 categories) 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 and 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 individualized 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) as predictors of PMI following TAVI. In the current study, we did not observe an association between PMI following TAVI and sex. This is 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 indicated an overall 10% lower risk of PMI following TAVI in women compared to 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 regards to native annulus anatomy.

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 multivariate 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 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 to 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 upon ventricular rate or BBB, we did observe a significant association between pre-existing AF and need of PMI, and the multivariate 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 remodeling 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 hemodynamic 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 hospitalization 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 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 hospitalizations and mortality (43).

Limitation

As per study design, it was not possible to have a designated control group. 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 permanent pacemaker implantation. However, pacemaker rates declined with increasing procedural volumes and experience. An abnormal ECG, right bundle branch block and atrial fibrillation at baseline, and prosthesis type and deployment mechanisms, but not sex, influenced the need for new pacemaker implantation following TAVI. Permanent pacemaker implantation after TAVI was not associated with all-cause mortality.

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Availability of Data and Materials: Data is available by the corresponding author upon reasonable request.

CRediT authorship contribution statement

Daanyaal Wasim: Writing − review & editing, Writing − original draft, Methodology, Visualization, Conceptualization, Data curation, Formal analyses.

Abukar Mohamed Ali: Writing − review & editing, Methodology, Data curation, Formal analyses.

Øyvind Bleie: Writing − review & editing, Conceptualization, Methodology, Supervision.

Erik Jerome Stene Packer: Writing − review & editing.

Erlend Eriksen: Writing – review & editing.

Håvard Keilegavlen: Writing − review & editing, Validation.

Ronak Rajani: Writing − review & editing, Validation.

Svein Rotevatn: Writing − review & editing, Validation.

Sahrai Saeed: Writing − review & editing, Writing − original draft, Methodology, Supervision, Project administration.

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Tables

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[1]
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/m2)	26.3 ± 4.6	26.6 ± 4.8	26.2 ± 4.5	0.410
Body surface area (m2)	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 (beats/minute)	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%)	
Smokers	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
Antihypertensive medication	465 (85%)	149 (86%)	316 (84%)	0.572
Statin	401 (73%)	117 (68%)	284 (76%)	0.047

Anticoagulant	160 (29%)	67 (39%)	93 (25%)	0.001
Antiplatelet	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	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 (mmHg)	49.7 ± 15.1	48.9 ± 14.90	50.0 ± 15.3	0.407
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

[1]Two Sample t-test for continuous variables and χ^2 for categorical variables.
Mean ± std. deviation, or n (%).
NYHA, New York Heart Association.
LVH, Left ventricular hypertrophy.

Table 2. Comparison of patient characteristics according to the study phases.

	Study phases		
	Low-volume (n =192)	**High-volume (n = 356)**	**p-value**[1]
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/m2)	25.6 ± 4.3	26.7 ± 4.7	0.009
Body surface area (m2)	1.82 ± 0.20	1.86 ± 0.21	0.064
Pulse	70.0 ± 12.9	71.3 ± 13.2	0.253
Symptom Severity			0.585
Mild symptoms	87 (45%)	170 (48%)	
Moderate-severe	105 (55%)	186 (52%)	
Smokers	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
Anticoagulant	54 (28%)	106 (30%)	0.685
Death	119 (62%)	130 (37%)	<0.001
PMI ≤30-days post TAVI	88 (46%)	85 (24%)	<0.001

[1]Two Sample t-test for continuous variables and χ^2 for categorical variables.
Mean ± std. deviation, or n (%).

Table 3. Valve type distribution, size and access site.

Study phases				
Valve type	**Low-volume (n=192)**	**High-volume (n=356)**	**Total**	**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
Abbot 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**	**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%)	
Subclavian	14 (8.0%)	31 (8.0%)	8.0%)	0.724
Direct aorta	5 (3.0%)	17 (5.0%)	4.0%)	

Other	0	1 (0.3%)	1 (0.3%)	
Valve type	**PMI (n=173)**	**No PMI (n=375)**	**Total**	**p-value**
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
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

[1]Two Sample t-test for continuous variables and χ^2 for categorical variables.

Table 4. Univariate and multivariate predictors of new pacemaker implantation following TAVI.

	Univariate					Multivariate		
	N	**Events**	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**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/m2)	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	548	173	1.01	1.00, 1.02	0.063			
Right Bundle Branch Block (RBBB)	548	173	1.93	1.05, 3.56	0.034	2.23	1.09, 4.59	0.028

Left Bundle Branch Block (LBBB)	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/m2)	539	172	1.00	0.99, 1.02	0.61			
Mean pressure gradient	548	173	1.00	0.98, 1.01	0.41			
Aortic valve area	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	1.21-2.73	0.004			
- 2. Generation			0.62	0.41-0.94	0.024			
- 3. Generation			0.40	0.19-0.84	0.016			
- Intra-annular			0.73	0.36-1.48	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
Size (mm)	548	173	1.03	0.96, 1.09	0.41			

[1] OR = Odds Ratio, CI = Confidence Interval.
*Abnormal ECG was replaced by AF in the same model.

SEV, self-expanding valve.
BEV, balloon-expandable valve.
BSH, Basal septal hypertrophy.
ASH, Asymmetrical hypertrophy.
EF, ejection fraction.

Supplementary tables

Supplementary table 1. Multivariate model adjusted for study phases

	Multivariate model	
	OR 95% CI	**P-value**
Age	1.01 (0.98-1.04)	0.461
Sex	0.88 (0.56-1.37)	0.581
Atrial fibrillation	1.98 (1.31-2.99)	0.001
Heart rate	0.99 (0.97-1.00)	0.061
RBBB	2.12 (1.10-4.10)	0.025
Aortic root diameter	1.94 (1.13-3.34)	0.017
Study Phases (High volume phase)	0.38 (0.26-0.56)	<0.001

Supplementary table 2. Adjusting for study phases and valve-types

	Multivariate model	
	OR 95% CI	**P-value**
Age	0.99 (0.96-1.03)	0.895
Sex	0.97 (0.61-1.53)	0.886
Atrial fibrillation	1.92 (1.24-2.98)	0.003
Heart rate	0.98 (0.97-1.00)	0.044
RBBB	2.87 (1.38-5.95)	0.005
Aortic root	1.44 (0.80-2.56)	0.221
Study phase	0.72 (0.38-1.34)	0.296
1.gen Corevalve®	1.44 (0.53-3.91)	0.478
Evolut R®	0.87 (0.39-1.95)	0.733
Evolut Pro®	0.59 (0.21-1.64)	0.313
Lotus®	3.49 (1.46-8.34)	0.005
Edward Sapien 3®	0.08 (0.02-0.38)	0.002

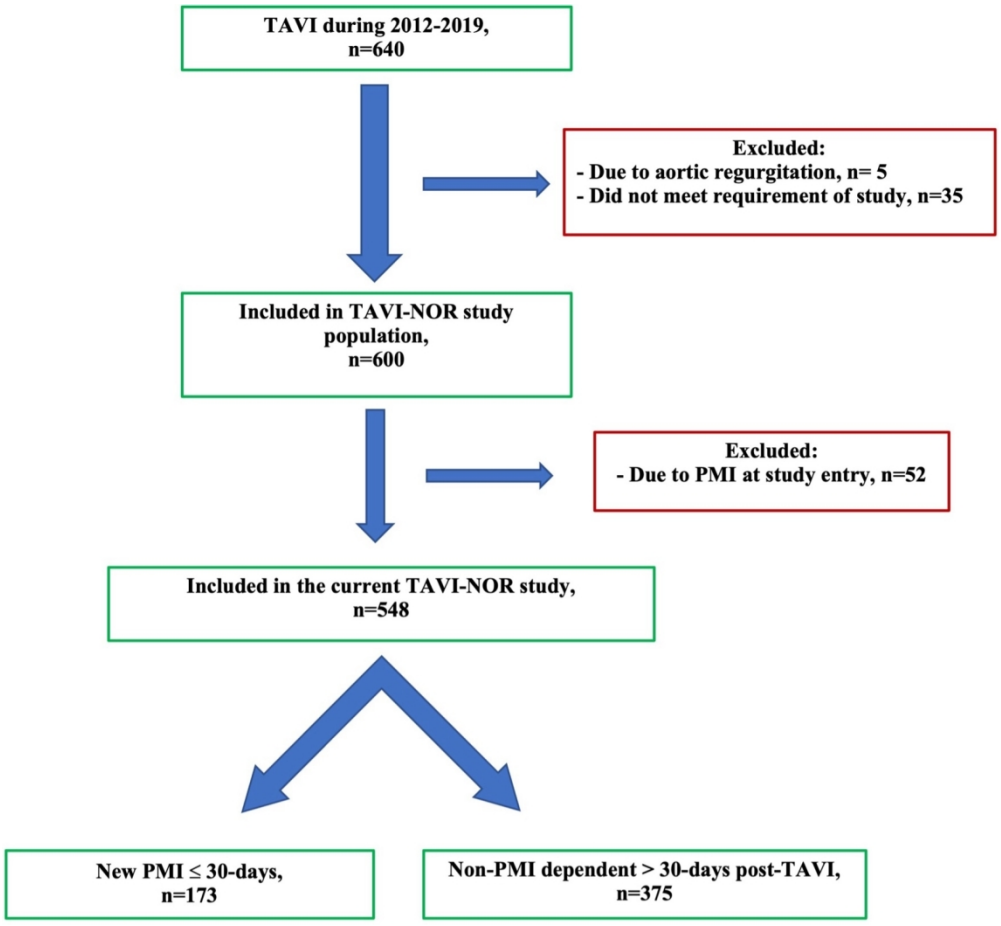


Figure 1. Inclusion flow-chart

203x187mm (220 x 220 DPI)

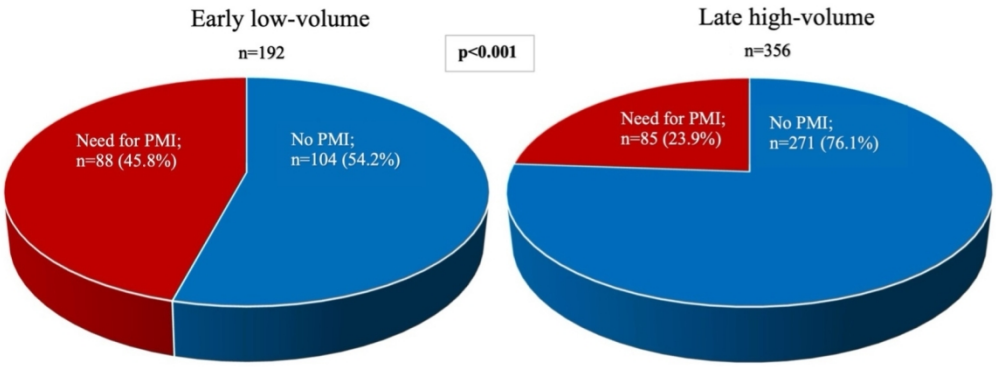


Figure 2. Distribution of permanent pacemaker implantation (PMI) in early low-volume phase to late high volume-phase.
In total 173 participants received PMI□30-days after TAVI. Out of 192 TAVI in low-volume phase, 88 (45.8%) received new PMI post TAVI, and out of 356 TAVI in high-volume phase, 85 (23.9%) received TAVI. □2 p value of <0.001.

207x81mm (220 x 220 DPI)

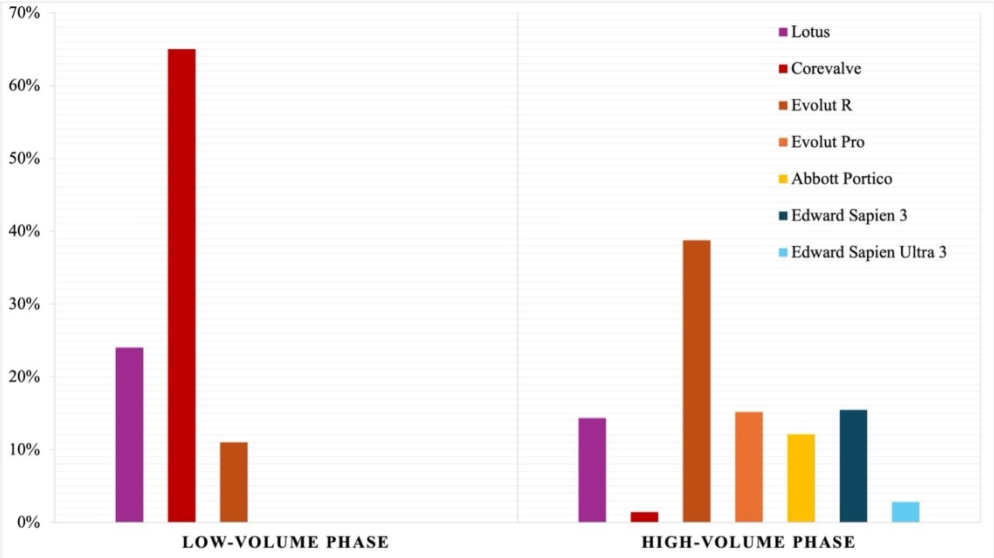


Figure 3. Distribution of valve type in the different study phases.
Illustration shows a significantly reduced use of mechanically-expandable valve Lotus® from 24% to 14% and first-generation self-expanding (SEV) Corevalve® from 65% to 1% from low-volume to high-volume phase. The use of second-generation SEV Evolut R® went 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%.

209x117mm (220 x 220 DPI)

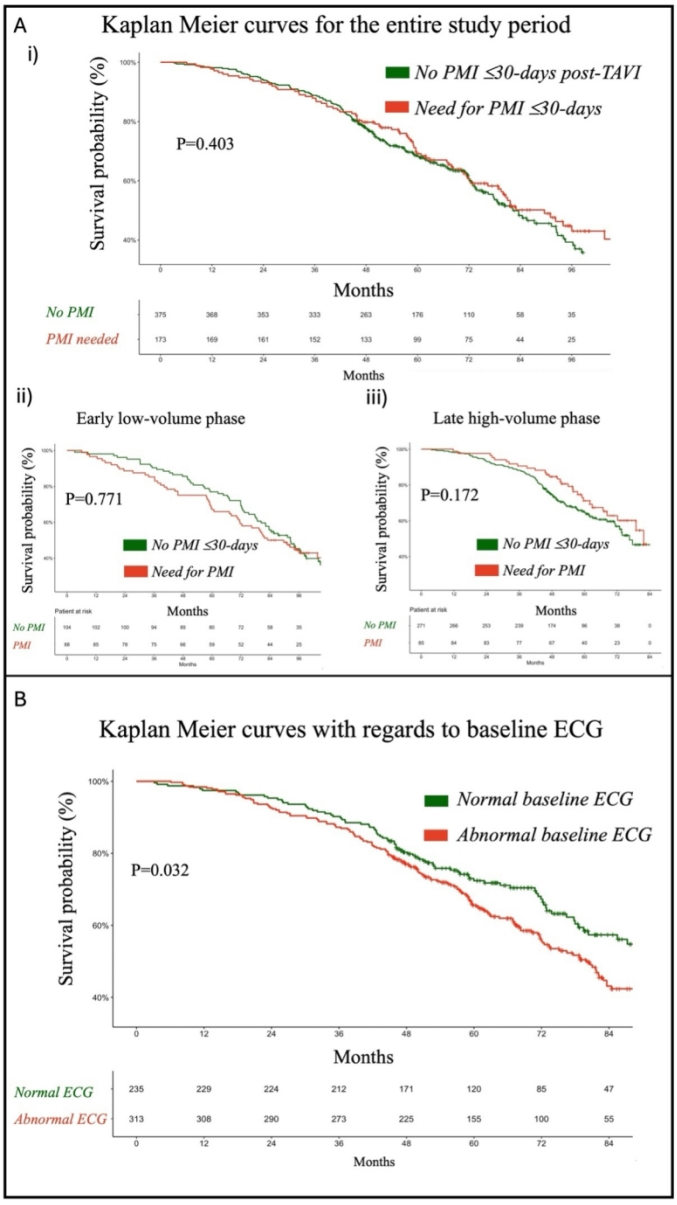
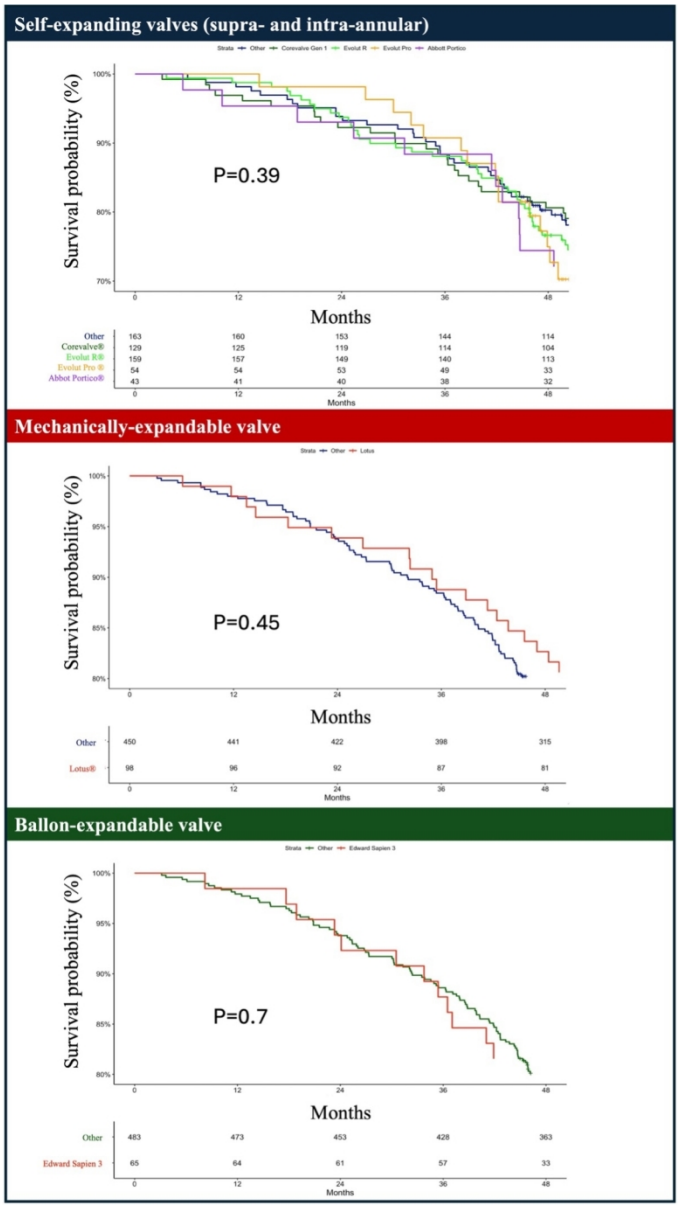


Figure 4. Kaplan-Meier (KM) curves.
Panel Ai shows that survival probability did not differ significantly in patient with and without need for new permanent pacemaker implantation (PMI) following TAVI in the entire study period. The same trend was also observed when patients were stratified for study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

144x246mm (220 x 220 DPI)



Kaplan-Meier curves for the different valve type.

139x246mm (220 x 220 DPI)

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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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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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 electrocardiogram 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±6.6 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). Upon multivariable analysis, an abnormal electrocardiogram (OR 1.73; 95% CI 1.14-2.63, p=0.010), right bundle branch block (OR 2.23; 95% CI 1.09-4.59, p=0.028) and atrial fibrillation (OR 1.89 1.24-2.88, 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

2.16-5.59; balloon-expandable valves OR 0.07: 95% CI 0.02-0.29, 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 0.69-1.16, 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 electrocardiogram, right bundle branch block, atrial fibrillation and bioprosthesis selection remained important predictors of permanent pacemaker implantation. Permanent pacemaker implantation following TAVI had no impact upon short or long-term survival.

Trial registration number: NCT04417829.

Strengths and Limitations of this study

- The current study investigates the association between atrial fibrillation and the risk of permanent pacemaker implantation following transcatheter aortic valve implantation.
- 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 AV-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 aging 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 hospitalizations and ultimately death [2]. Patients with AS >65 years and with comorbidities are at 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 to conventional surgery, it still carries the risk of procedure-related complications. With TAVI gaining popularity in lower risk patients, there remains 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 requirment for regular generator changes and 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 predcitors of PMI following TAVI and as to how this impacts upon 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, hyperlipidemia and coronary artery disease (defined by findings of conventional coronary angiography or cardiac computed tomography, 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 (NORIC) database. The data was 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 ischemic attack. Hypertension was defined as a history of hypertension, current or past use of antihypertensive medications, or repeated clinic blood pressure (BP) ≥140/90 mmHg. Hypercholesterolemia 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 30.12.2022 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, hospitalization 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 lead aVL (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 3-lead continuous ECG (telemetry) upon 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 upon 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, 9 and Philips 'Epiq 7). All images were reanalyzed 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 4-

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 ± standard deviation, and categorical variables as frequencies with respective percentages. Student's t-test was used to compare difference in mean of continuous variables, and Chi-square test 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 upon 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 version

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. In patients requiring PMI, the prevalence of AF was significantly higher compared to 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 to 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 versus 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 to 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), stroke volume index (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 SEV were implanted in 64.6% 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 to 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) LBBB, and 0.6% (n=1) had bifascicular block (p<0.001).

Predictors of 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% 1.30-3.29, 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 1.31-2.80, p<0.001) and multivariable-adjusted models (OR 1.73; 95% CI 1.14-2.63, 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% 1.05-3.56, p= 0.034) and multivariable-adjusted analysis (OR 2.23; 95% 1.09-4.59, 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 1.24-2.88, 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 2.68-6.66, p<0.001), whereas a BEV was not (OR 0.06; 95% CI 0.01-0.24, 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 2.16-5.59, p<0.001 and BEV OR 0.07; 95% CI 0.02-0.29, p<0.001).

When RBBB and AF was 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 (Supplementary Table 1). Adding age, sex and study phases to the same primary multivariable-adjusted model did not have any impact on our findings (Supplementary Table 2 and 3). Furthermore, 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 (Supplementary 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 4Ai). The results were consistent in early low and late high-volume phases (Figure 4Aii-iii). Kaplan-Meier curves showed significantly reduced event-free survival in patients with abnormal ECG compared to 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 0.69-1.16, p=0.403. The use of valve type did not predict all-cause mortality (Supplementary 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 center 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 centers opting for SEV with a higher rate of PMI compared to BEV with a reported lower rate 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 to the abovementioned high-volume TAVI centers. 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 categories) 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 and 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 individualized 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] as predictors of PMI following TAVI. In the current study, we did not observe an association between PMI following TAVI and sex. This is 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 indicated an overall 10% lower risk of PMI following TAVI in women compared to 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 regards to native annulus anatomy.

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 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 to 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 upon 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 remodeling 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 hemodynamic 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 hospitalization 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 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 hospitalizations 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 permanent pacemaker implantation. However, pacemaker implantation rates declined with increasing procedural volumes and experience. An abnormal ECG, right bundle branch block and atrial fibrillation at baseline, and 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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CRediT authorship contribution statement

Daanyaal Wasim is the guarantor of this study.

Daanyaal Wasim: Writing − review & editing, Writing − original draft, Methodology, Visualization, Conceptualization, Data curation, Formal analyses.

Abukar Mohamed Ali: Writing − review & editing, Methodology, Data curation, Formal analyses.

Øyvind Bleie: Writing − review & editing, Conceptualization, Methodology, Supervision.

Erik Jerome Stene Packer: Writing − review & editing.

Erlend Eriksen: Writing – review & editing.

Håvard Keilegavlen: Writing − review & editing, Validation.

Ronak Rajani: Writing − review & editing, Validation.

Svein Rotevatn: Writing − review & editing, Validation.

Sahrai Saeed: Writing − review & editing, Writing − original draft, Methodology, Supervision, Project administration.

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Figure legends

Figure 1. Inclusion flow-chart.

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 TAVI: 88 (45.8%) in early low-volume phase and 85 (23.9%) in late high-volume phase (Chi-square p-value of <0.001).

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 (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%.

Figure 4. Kaplan-Meier (KM) curves. Panel Ai shows that survival probability did not differ significantly in patient with and without need for new permanent pacemaker implantation (PMI) following 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). Panel B demonstrates survival probability according to baseline ECG. Overall survival was significantly better for patients with normal baseline ECG compared to those with abnormal baseline ECG.

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
Antihypertensive medication	465 (85%)	149 (86%)	316 (84%)	0.572
Statin	401 (73%)	117 (68%)	284 (76%)	0.047
Anticoagulant	160 (29%)	67 (39%)	93 (25%)	0.001
Antiplatelet	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	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 (mmHg)	49.7 ± 15.1	48.9 ± 14.90	50.0 ± 15.3	0.407
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 (%). bpm, beats per minute; EF, ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PMI, permanent pacemaker implantation.

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/m2)	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
Anticoagulant	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 (%). bpm, beats per minute; PMI, permanent pacemaker implantation

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

Valve type	Low-volume (n=192)	High-volume (n=356)	Total (n=548)	p-value
Study phases				
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
Abbot 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%)	
Subclavian	14 (8.0%)	31 (8.0%)	8.0%)	0.724
Direct aorta	5 (3.0%)	17 (5.0%)	4.0%)	

Other	0	1 (0.3%)	1 (0.3%)	
Valve types				
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
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.

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	548	173	1.00	0.98, 1.01	0.41			
Aortic valve area	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	1.21-2.73	0.004			
- 2. Generation			0.62	0.41-0.94	0.024			
- 3. Generation			0.40	0.19-0.84	0.016			
- Intra-annular			0.73	0.36-1.48	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
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 hypertrophy; BEV, balloon-expandable valve; bpm, beats per minute; BMI, body mass index; BSH, Basal septal hypertrophy; CI, confidence interval; EF, ejection fraction; OR, odds ratio; SEV, self-expanding valve.

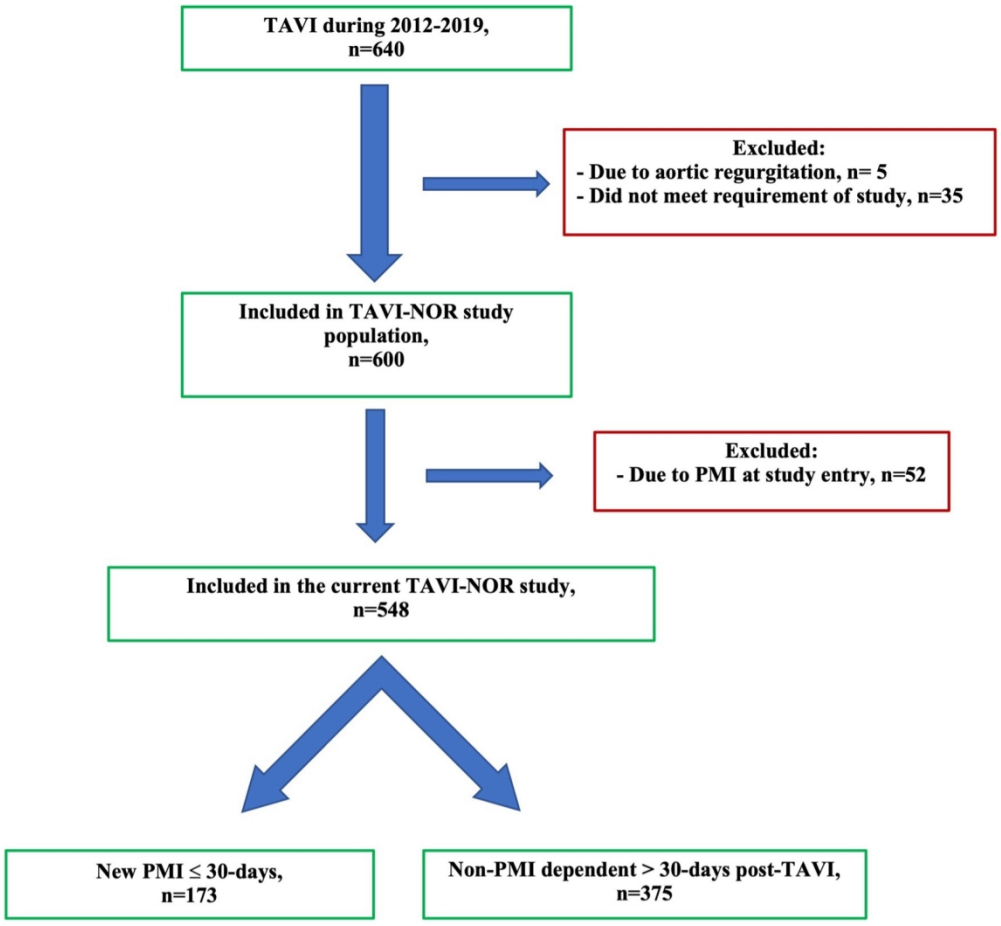

Figure 1. Inclusion flow-chart.

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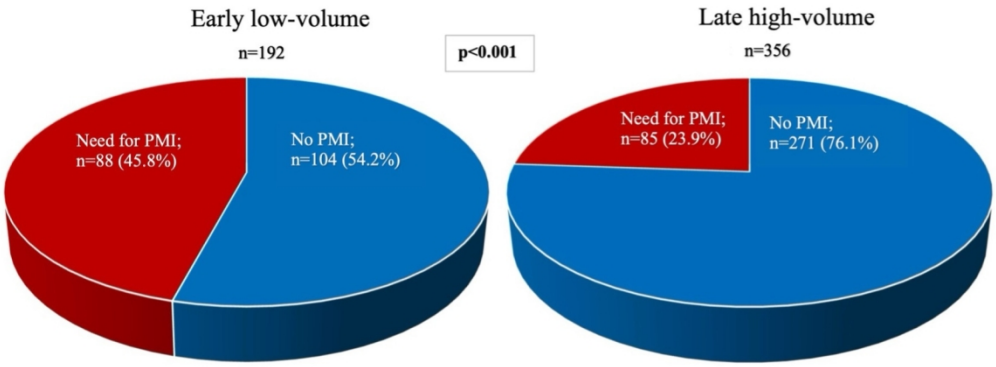

Figure 2. Distribution of permanent pacemaker implantation (PMI) in early low-volume phase to late high volume-phase. In total 173 (31.6%) participants received PMI ≤30-days after TAVI: 88 (45.8%) in early low-volume phase and 85 (23.9%) in late high-volume phase (Chi-square p-value of <0.001).

151x59mm (300 x 300 DPI)

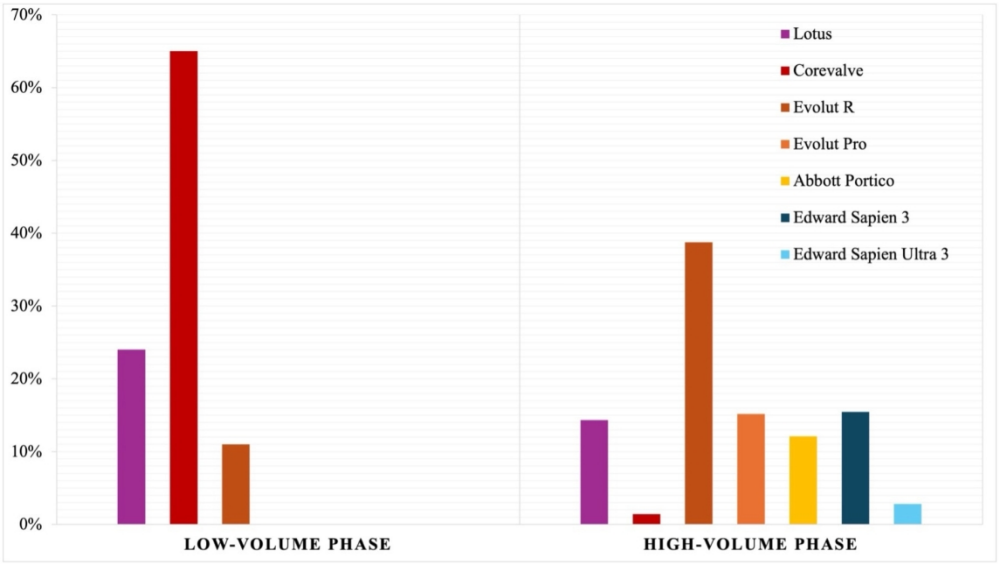

Figure 3. Distribution of valve types according to study phases. Illustration shows a significant reduction in the use of mechanically-expandable valve Lotus (from 24% to 14%) and first-generation self-expanding (SEV) Corevalve (from 65% to 1%) from low-volume to high-volume phase. The use of second-generation 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%.

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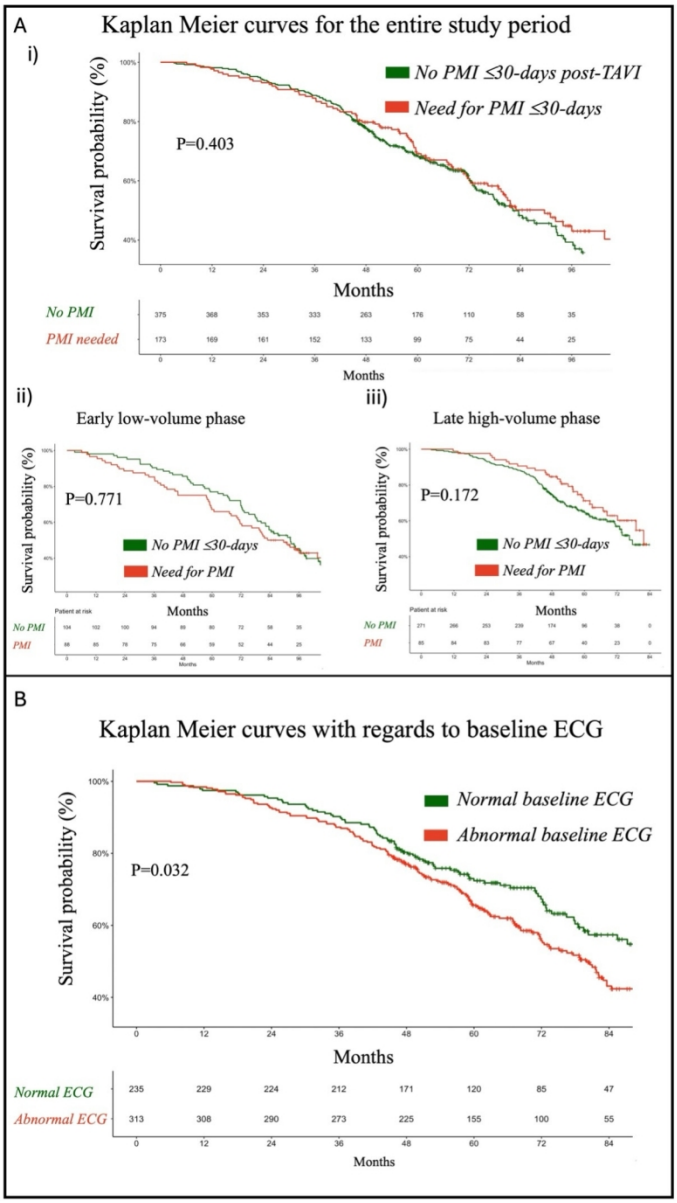

Figure 4. Kaplan-Meier (KM) curves. Panel Ai shows that survival probability did not differ significantly in patient with and without need for new permanent pacemaker implantation (PMI) following TAVI in the entire study period. The same trend was also observed when patients were stratified for study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

106x180mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

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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Supplemental Tables and Figures

Supplementary Table 1

Supplementary Table 2

Supplementary Table 3

Supplementary Table 4

Supplementary Figure 1

Supplementary Table 1. Multivariable-adjusted model with right bundle branch block and atrial fibrillation tested together.

		Univariable			Multivariable	
	N	Events	OR	95% CI	p-value	OR	95% CI	p-value
General predictors								
Atrial fibrillation	548	173	1.84	1.25, 2.70	0.002	1.8	1.23, 2.87	0.003
Heart rate (bpm)	548	173	0.99	0.97, 1.00	0.098	0.9	0.97, 1.00	0.029
ECG predictors								
Abnormal ECG	548	173	1.91	1.31, 2.80	<0.001	1.9	1.28, 2.88	0.002*
Right bundle branch block	548	173	1.93	1.05, 3.56	0.034	2.9	1.45, 5.98	0.003
Echocardiographic predictors								
Aortic root diameter (cm)	547	173	2.07	1.30, 3.29	0.002	1.6	0.98, 2.71	0.061
SEV	548	173	0.70	0.48, 1.04	0.075			
- 1. Generation			1.82	1.21, 2.73	0.004			
- 2. Generation			0.62	0.41, 0.94	0.024			
- 3. Generation			0.40	0.19, 0.84	0.016			
- Intra-annular			0.73	0.36, 1.48	0.381			
Mechanically-expandable valve	548	173	4.22	2.68, 6.66	<0.001	3.4	2.14, 5.52	<0.001
BEV	548	173	0.06	0.01, 0.24	<0.001	0.07	0.02, 0.29	<0.001

*Abnormal ECG was replaced by atrial fibrillation and right bundle branch block in the same model.

BEV, balloon-expandable valve; bpm, beats per minute; CI, confidence interval; OR, odds ratio; SEV, self-expanding valve.

Supplementary Table 2. Multivariable model adjusted for study phases.

	Multivariable model	
	OR (95% CI)	**p-value**
Age	1.01 (0.98-1.04)	0.461
Sex	0.88 (0.56-1.37)	0.581
Atrial fibrillation	1.98 (1.31-2.99)	0.001
Heart rate (bpm)	0.99 (0.97-1.00)	0.061
Right bundle branch block	2.12 (1.10-4.10)	0.025
Aortic root diameter (cm)	1.94 (1.13-3.34)	0.017
Study Phase (high volume phase)	0.38 (0.26-0.56)	<0.001

bpm, beat per minute.

Supplementary Table 3. Multivariable model adjusted for study phases and valve-types.

	Multivariable **model**	
	OR (95% CI)	**p-value**
Age	0.99 (0.96-1.03)	0.895
Sex	0.97 (0.61-1.53)	0.886
Atrial fibrillation	1.92 (1.24-2.98)	0.003
Heart rate (bpm)	0.98 (0.97-1.00)	0.044
Right bundle branch block	2.87 (1.38-5.95)	0.005
Aortic root diameter (cm)	1.44 (0.80-2.56)	0.221
Study phase (high volume phase)	0.72 (0.38-1.34)	0.296
1. Generation Corevalve	1.44 (0.53-3.91)	0.478
Evolut R	0.87 (0.39-1.95)	0.733
Evolut Pro	0.59 (0.21-1.64)	0.313
Lotus	3.49 (1.46-8.34)	0.005
Edward Sapien 3	0.08 (0.02-0.38)	0.002

bpm, beats per minute.

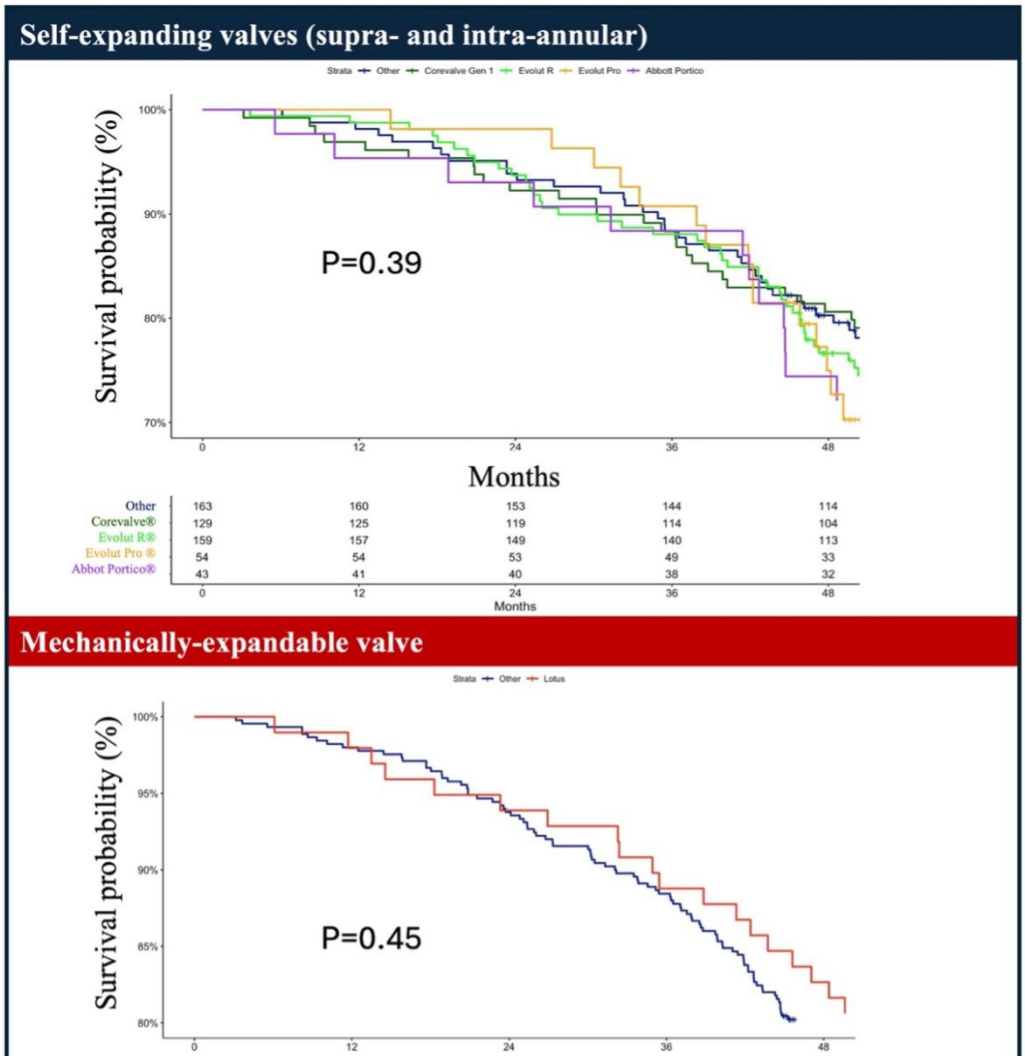
Supplementary Table 4. Multivariable-adjusted model stratified by study phase (early low-volume phase and late high-volume phase).

	Low-volume phase				High-volume phase			
	N	**OR**	**95% CI**	**p-value**	**N**	**OR**	**95% CI**	**p-value**
General predictors								
Atrial fibrillation	192	1.96	1.01, 3.86	0.049	356	1.96	1.12, 3.45	0.019
Heart rate (bpm)	192	0.99	0.97, 1.01	0.415	356	0.98	0.96, 1.00	0.046
ECG predictors								
Abnormal ECG	192	1.96	1.04, 3.70	0.039	356	1.64	1.08, 3,12	0.025
Right bundle branch block	192	1.58	0.57, 4.52	0.378	356	5.12	1.82, 13.2	0.002
Echocardiographic predictors								
Aortic root diameter (cm)	191	2.22	0.96, 5.32	0.066	356	1.29	0.66, 2.51	0.451
Mechanically-expandable valve	192	2.90	1.44, 6.01	0.003	356	3.72	1.94, 7.22	<0.001
BEV					356	0.08	0.01, 0.28	<0.001

*Abnormal ECG was replaced by atrial fibrillation and right bundle branch block in the same model.

BEV, balloon-expandable valve; bpm, beats per minute; OR, odds ratio; CI, confidence interval.

Supplementary Figure 1: Kaplan-Meier curves showing survival for different valve types.



Open access Protocol

BMJ Open

Impact of transcatheter aortic valve implantation on left ventricular function recovery, mass regression and outcome in patients with aortic stenosis: protocol of the TAVI-NOR prospective study

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ABSTRACT

Introduction Transcatheter aortic valve implantation (TAVI) is a widely used treatment option as an alternative to surgical aortic valve replacement in patients with severe aortic stenosis (AS) at high or intermediate surgical risk. TAVI improves symptoms, induces reverse left ventricular (LV) remodelling and increases overall survival. However, a careful patient selection is essential to achieve better outcome. Evidence on LV functional recovery and LV mass regression after TAVI based on contemporary registry data is scarce. The impact of TAVI on the arterial vasculature is also less explored.

Method and analyses This is a study of 600 consecutive patients with AS who underwent a TAVI at Haukeland University Hospital, Bergen, Norway. Demographics, clinical data, arterial haemodynamics and echocardiographic parameters were prospectively collected. In the present paper, we describe the design, major scientific objectives and echocardiography imaging protocol of the TAVI-NOR (TAVI in western NORway) study. The main objectives are: To explore the impact of TAVI on cardiac structure and function in patients with severe AS, identify the echocardiographic predictors of reverse LV remodelling, assess survival benefits according to baseline risk profile, evaluate long-term therapeutic success as reflected by reduction in valvular-arterial impedance and to investigate the impact of various types of blood pressure response immediately after TAVI on clinical outcome.

Ethics and dissemination The study was approved by the Regional Committees forMedical and Health Research Ethics (REK vest, ref. number 33814) and theInstitutional Data Protection Services. Patients' consent was waived. The study findings will be disseminated via peer-reviewed publications and presentation in national and international scientific meetings and conferences.

Trail registration number The study was registered in the international database: ClinicalTrials.gov, Identifier: NCT04417829.

Strengths and limitations of this study

- This is a large prospective study of patients with severe aortic stenosis who underwent transcatheter aortic valve implantation in western Norway.
- Clinical and echocardiographic assessment will be performed at 6–12 months follow-up visit in a real-world context.
- Long-term outcome data in terms of cardiovascular and all-cause mortality will be available.
- The limitations are that there is no control arm for comparison and this is a single-centre registry study.

INTRODUCTION

Degenerative aortic stenosis (AS) is the most common heart valve disease requiring valve intervention, and the prevalence is increasing in developed countries as a result of the ageing population. The development of symptoms (angina, syncope or dyspnoea) or a drop in left ventricular ejection fraction (LVEF) <50% are class I indications for valve intervention (transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR)) in patients with haemodynamically severe AS.[1 2] Without valve replacement, patients with severe AS are at substantially high risk of cardiovascular complications and death.[1 2] In AS, LV remodelling (LV hypertrophy (LVH) or concentric remodelling) initially reflects an adaptive response to normalise wall stress and maintain LV systolic function.[3] However, during the disease progression, afterload and consequently LV wall stress will increase and the contractile function will decline. Such a maladaptive response will typically lead to systolic and diastolic LV dysfunction, subendocardial ischaemia, fibrosis, increased end-diastolic pressure, pulmonary hypertension, symptoms and death.[3] The reduction in LVEF in patients with AS may be either: (1) due to afterload-contractility mismatch: a condition in which LV has preserved intrinsic

contractile function, but an increase in afterload causes reduction in stroke volume (SV) and decline in LVEF[4 5] or (2) due to irreversible myocardial damage related to fibrosis or concomitant coronary artery disease.[6–8] The reduction in LVEF due to afterload mismatch may be reversible if valve stenosis is removed by TAVI or SAVR. TAVI has become an established therapeutic option for patients with symptomatic severe AS who are ineligible for SAVR. The overall expected clinical benefits following TAVI are reduction in mean pressure gradient, improvement in LV systolic function, normalisation of SV, regression of LV mass, relief of symptoms and increased survival. LV mass regression after TAVI is achievable and associated with improved outcome.[9 10] However, the level of baseline cardiovascular comorbidity may affect clinical outcome and survival. Furthermore, the evidence on LV functional recovery and LV mass regression after TAVI based on contemporary registry data is scarce. Similarly, the impact of residual risk of hypertension following TAVI on the arterial vasculature is less explored. In the present paper, we will describe the study design, major scientific objectives and echocardiography imaging protocol of the TAVI-NOR (TAVI in western NORway) registry.

Box 1 Procedure and device-related complications

Intraprocedural complications
- Coronary artery occlusion.
- Aortic dissection.
- Cardiac tamponade.
- Annular rupture.
- Device migration (embolisation).
- Valve thrombosis.
- Re-intervention.
- Need for acute open heart surgery.
- Conversion to alternative access.
- Access site/vascular complications.

In-hospital complications.
- Significant paravalvular leak.
- Implantation of permanent pacemaker.
- Stroke/transient ischaemic attack.
- Major vascular complications.
- Acute renal failure and need for dialysis.
- Major bleeding and need for transfusion.
- Cardiac arrest.

Late complications
- Prosthetic valve endocarditis.
- Subclinical leaflet thrombosis.
- Structural valve deterioration.
- Patient–prosthesis mismatch.

METHODS

Study design

Between January 2012 and July 2019, a total of 600 patients with AS were treated with TAVI at the Department of Heart Disease, Haukeland University Hospital, Bergen in Western Norway. All patients were symptomatic and had clinically significant AS. The indication for TAVI was based on a joint decision taken by the heart valve team according to guidelines and technical suitability for the procedure. During the initial phase of the study, each patient was assessed by an experienced cardiologist within the TAVI-team for informal frailty testing. During the late phase of study, particularly following the 2017 European Society of Cardiology guidelines,[2] we included formal frailty testing (Short Physical Performance Battery, the Mini-Mental State Examination, nutrition status) in cooperation with a geriatrician in our team. Patients with substantial comorbidities, high grade of frailty, life expectancy <1–2 years, severely reduced cognitive function or technically not suited for TAVI were not treated and thereby excluded from this registry (table 1).

Demographic, clinical and echocardiographic data at baseline were prospectively collected (box 1), and entered into the Norwegian Registry of Invasive Cardiology (NORIC), a national mandatory healthcare and quality improvement registry established in 2012. NORIC includes data on virtually all invasive cardiology procedures (coronary angiography, percutaneous coronary interventions and TAVI). In the present dataset, all patients had at least three transthoracic echocardiograms: Baseline echocardiography immediate before TAVI, first follow-up within approximately 1-month and second follow-up at 6–12 months clinical visit following TAVI.

Table 1 Eligibility criteria for TAVI-NOR (TAVI in western NORway) registry

Inclusion criteria	Patients with symptoms and clinically significant aortic stenosis.
	Anticipated life expectancy >1–2 years.
	Patients undergoing TAVI according to guidelines.
Exclusion criteria	Patients with substantial comorbidities.
	High grade of frailty.
	Severely reduced cognitive function.
	Technically not suited for TAVI.

TAVI, transcatheter aortic valve implantation.

Objectives

The main objectives of the TAVI-NOR registry are:

1. To explore the impact of TAVI on cardiac structure and function in patients with AS.
2. To identify the echocardiographic predictors of reverse LV remodelling.
3. To assess survival benefits according to baseline risk profile.
4. To evaluate long-term therapeutic success as reflected by reduction in valvular-arterial impedance.
5. To assess the impact of various types of blood pressure (BP) response immediately after TAVI on cardiac structure, function and clinical outcome.

End-points

The primary outcome is all-cause mortality. Date and cause of death will be verified by the linkage between NORIC and The Norwegian Cardiovascular Disease Registry. The secondary end-points of interest are LV mass regression and functional recovery at 6–12 months follow-up and clinical events such as cardiac-related hospitalisations during follow-up. Follow-up time will be calculated from the baseline echo immediately before TAVI until censoring or death.

Measurement and data collection

Cardiovascular risk factors and BP measurements

At study entry, anthropometric measures (height, weight, body mass index, body surface area), severity of symptoms by New York Heart Association classification and/or Canadian Cardiovascular Society angina score, cardiovascular risk factors and comorbidities (smoking, hypertension, diabetes, hypercholesterolaemia, previous stroke/transient ischaemic attack, coronary artery disease, chronic kidney disease, atrial fibrillation, pacemaker or implantable cardioverter defibrillator, type and frequencies of previous valve interventions, chronic obstructive pulmonary disease), type of antihypertensive treatment, use of statin, antiplatelets and direct oral anticoagulants were collected. The procedure and device-related complications according to the Valve Academic Research Consortium were entered into NORIC registry (box 1).[11]

Brachial BP was measured prior to each echocardiogram according to the standard methodology after an initial 5 min rest in the sitting position. An average of all BP measurements obtained during hospitalisation after TAVI (measured at least 3–4 times a day) will be carefully calculated and used as post-TAVI BP to assess the types BP response after TAVI.

Hypertension was defined as a history of hypertension, use of antihypertensive medications or elevated brachial BP (≥140/90 mm Hg) at study entry. Hypercholesterolaemia was defined as use of statin. Coronary artery disease was defined as previous myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention or angiographic evidence of significant stenosis in the epicardial coronary arteries defined by diameter stenosis ≥50%, or by invasive pressure measurements.

Electrocardiogram

Standard ECGs were recorded prior to each echocardiogram to assess rhythm, LVH, QRS duration and LV strain (≥0.1 mV (≥1 mm) convex downsloping ST segment depression with asymmetrical T-wave inversion in leads V5–V6).

Echocardiography

All echocardiograms were performed using commercially available ultrasound machines (Acuson Sequoia C512, Siemens, Mountain View, California, USA; Philips iE33; Philips Medical Systems, Eindhoven, The Netherlands; Philips 'Epiq 7'; Philips Medical Systems, Bothell, Washington, USA; and Vivid E9 GE Vingmed Ultrasound, Horten, Norway). Studies were acquired and stored digitally, and transferred to a secure server. Studies performed by certified echotechnicians were reviewed and quality assured by imaging cardiologists.

Image acquisition

ECG leads were placed on the patient before imaging. A particular emphasis was put on adequate ECG signal. For patients in atrial fibrillation or atrial flutter, the sonographer was instructed to obtain 3–5 cardiac cycle acquisitions per view. Colour Doppler imaging was optimised with appropriate Nyquist limit. Special attention was directed to obtain optimal spectral Doppler signals through the aortic valve with best alignment between ultrasound beams and direction of the blood flow. Sector depth, sample volume size and spatial and temporal resolution were optimised.

Measurement protocol

Echocardiographic parameters will be measured offline in an Echopac work station for research purpose according to international guidelines (box 2).[1 2 12–14]

Aortic dimensions were measured at the levels of aortic root, sinotubular junction and ascending aorta from a dedicated parasternal long-axis view. Right ventricular free wall thickness, LV wall thicknesses and cavity dimensions, left atrial anterior–posterior diameter were measured from a parasternal long axis view.[13] Right ventricular basal diameter was measured from an apical four-chamber view.[14] LV volumes and LVEF were derived from the biplane Simpson method. LV mass in grams was calculated according to the Devereux formula,[15] and indexed for body surface area:

$$\text{LVMi} = 0.8\{1.04[([\text{LVEDd} + \text{IVSd} + \text{PWd}]^3 - \text{LVEDd}^3)]\} + 0.6\ \text{g/m}^2\ \text{body surface area}$$

LVEDd is the end-diastolic dimension and LVEDs the end-systolic dimension of LV, IVSd interventricular septum thickness in diastole and PWd is posterior wall thickness in diastole. Normal LV mass index was defined as ≤95 g/m^2 in women and ≤115 g/m^2 in men.[13] Relative wall thickness was calculated as: 2x LV posterior wall thickness/LV internal diameter at end-diastole and considered normal if ≤0.42. Transmitral flow (E and A wave velocities, and E

Box 2 Echocardiographic data and arterial haemodynamics

- Heart rate (beat per minute).
- Aortic annulus diameter (cm).
- Aortic root diameter (cm).
- Ascending aorta diameter (cm).
- Left atrial anterior–posterior diameter at end-systole (cm).
- Right ventricular free wall thickness in end-diastole (cm).
- Right ventricular basal diameter (cm).
- LV end-diastolic and end-systolic diameter (cm).
- Septum and posterior wall thickness at end-diastole and end-systole (cm).
- LV mass (g).
- Peak aortic jet velocity (m/s).
- Peak and mean aortic pressure gradients (mm Hg).
- Aortic valve area (cm^2).
- Doppler stroke volume index (mL/m^2).
- Trans-aortic flow rate (mL/s).
- Peak LVOT velocity (cm/s).
- Mitral flow (E and A wave velocities, E/A ratio, E-deceleration time).
- Isovolumic relaxation time (ms).
- E/e' ratio.
- Septal and lateral mitral annulus S' (cm/s).
- LV ejection fraction (%).
- Mid-wall fractional shortening (%).
- Circumferential end-systolic stress ($kdynes/cm^2$).
- The severity grade of tricuspid, mitral and aortic regurgitation.
- The severity grade of mitral stenosis.
- Systemic vascular resistance ($dynes \times s/cm^5$).
- Systemic arterial compliance (stroke volume was indexed/pulse pressure) ($mL/m^2/mm$ Hg).
- Valvular-arterial impedance (Zva) (mm Hg/mL/m^2).

LV, left ventricular; LVOT, LV outflow tract.

deceleration time) was measured by pulsed-wave Doppler from the apical 4-chamber view with the sample volume positioned between the tips of mitral leaflets. Peak tissue Doppler velocities (S' and e') were measured at lateral and septal levels. LV filling pressure was assessed by E/e' ratio. The severity of AS was defined according to the joint European Association of Cardiovascular Imaging and American Society of Cardiology guidelines[1 2 12] using a standard three-step approach: (1) measurement of LV outflow tract (LVOT) diameter in mid-systole at the aortic annulus level; (2) Pulsed-waved Doppler in the LVOT to derive velocity time integral (VTI), peak LVOT velocity and SV (LVOT VTI x LVOT area); (3) Transaortic VTI by continuous-waved Doppler from different windows by imaging and non-imaging transducers to measure peak aortic jet velocity (Vmax), peak and mean pressure gradients and aortic valve area (AVA) (figure 1). Moderate AS was defined as AVA 1.0–1.5 cm^2 and severe as AVA <1.0 cm^2.[1 2] SV was indexed to body surface area (SVi). Systolic ejection time and time to peak (acceleration time) will be measured retrospectively from transaortic continuous wave Doppler signal through the aortic valve to derive flow rate (SV divided by systolic ejection time) (figure 1).[16] Patient–prosthesis mismatch was defined on the basis of the prosthetic valve effective orifice area (EOA) indexed to the patient's BSA: absent or not clinically significant if indexed EOA was >0.85 cm^2/m^2, moderate when it was between 0.65 and 0.85 cm^2/m^2, and severe when<0.65 cm^2/m^2.[17] The preprocedural haemodynamic classification of AS severity grade was assessed according to flow-gradient subtypes (figure 2). Subendocardial and mid-wall fractional shortening (MWFS) were calculated according to the standard methodology,[18 19] and contractility-afterload mismatch by MWFS in relation to end-systolic stress.

Low-dose dobutamine stress echocardiography

Low-dose dobutamine stress echocardiography was performed in selective patients with classical low flow (SVi <35 mL/m^2), low gradient (mean pressure gradient

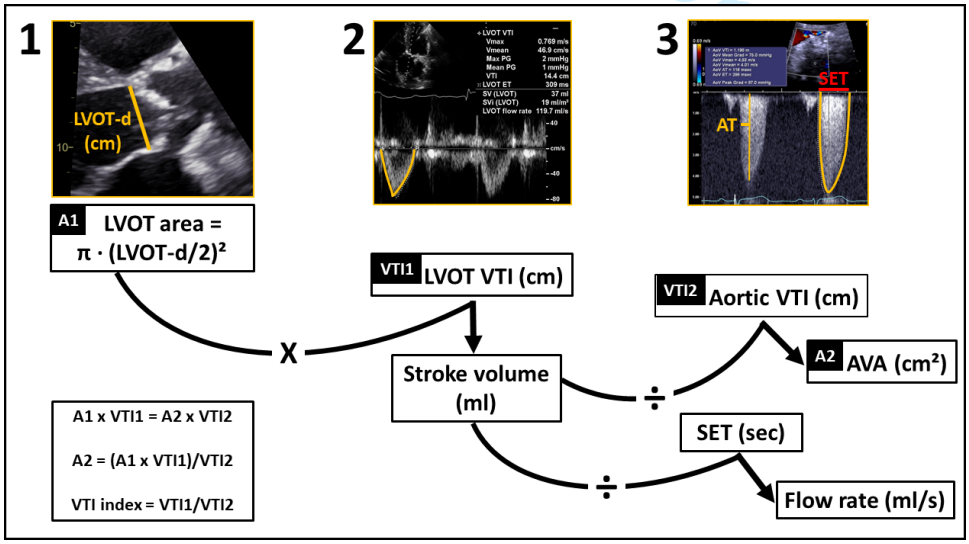
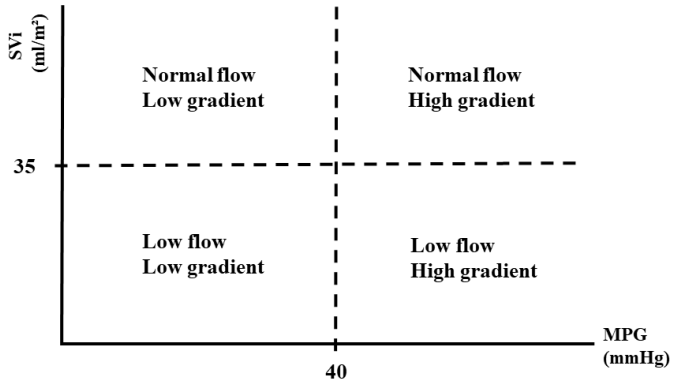


Figure 1 Measurement of LVOT diameter,[1] VTI and stroke volume[2] and peak aortic jet velocity, VTI, pressure gradients and AVA.[3] AT, acceleration time; AVA, aortic valve area; LVOT, left ventricular outflow tract; SET, systolic ejection time; VTI, velocity time integral.



	Normal flow High gradient	Normal flow Low gradient	Low flow High gradient	Low flow Low gradient	
				EF <50%	EF ≥50%
SVi	≥35	≥35	<35	<35	<35
MPG	≥40	<40	≥40	<40	<40
AVA	<1.0	<1.0	<1.0	<1.0	<1.0

Figure 2 The subtypes of severe aortic stenosis by flow gradient. AVA, aortic valve area; EF, ejection fraction; MPG, mean pressure gradient; SVi, stroke volume index.

<40 mmHg) severe AS and LV dysfunction (LVEF <50%) to assess: (1) myocardial contractile reserve; (2) to differentiate true severe AS from pseudosevere (moderate) AS.[20] A standard protocol of low dose dobutamine stress echocardiography was used, starting with 5 µg/kg/min, increasing the infusion to 10, 15 and 20 µg/kg/min in 3 min stages).[20] ECG was continuously monitored and BP and heart rate were measured in each stage. In case of symptoms, BP fall or development of any arrhythmias, the infusion was terminated. Low flow low gradient AS was considered true severe if mean pressure gradient exceeded ≥40 mm Hg and AVA remained <1.0 cm^2. Contractile reserve was defined as an increase in SV >20%. Symptomatic coronary artery disease (unstable angina), recent myocardial infarction, previous ventricular tachycardia, significant LVOT obstruction at rest and severely uncontrolled hypertension were considered contraindications for dobutamine stress echocardiography.

Afterload assessment

Valvular-arterial impedance (Z_{va}), a measure of global LV afterload, will be retrospectively calculated as: (systolic BP+mean aortic pressure gradient)/SVi.[21] Systemic arterial distensibility, a measure of pulsatile arterial load, will be calculated from the ratio of SVi divided by central pulse pressure (PP) (SVi/PP) (mL/m^2/mm Hg),[22] where central PP is calculated as: brachial PP x 0.49+ age x 0.30+7.11. Systemic vascular resistance, a measure of non-pulsatile vascular load, will be calculated as: 80×mean BP÷cardiac output (dyne×s×cm−5).

Statistical analysis

The latest version of SPSS (IBM) and R (The R Foundation for Statistical Computing, Vienna, Austria) will be used for data management and statistical analyses. All variable distribution will be inspected visually including Q-Q plots and presented as mean (±SD) for normally distributed data and median (IQR) for skewed distributions. Comparison between two groups will be performed using the two-sided Student's t-test and χ^2 test or Fisher's exact test, as appropriate. When sex and age adjustment is warranted, logistical or median quantile regression will be applied. Subgroup analyses will be performed in an exploratory fashion. Analysis of variance and generalised linear or additive models will be used as appropriate. If substantially different patient characteristics are associated with specific subgroups implying selection bias, propensity score adjustment or matching will be applied. The predictors of functional recovery, LV mass regression and afterload mismatch will be identified in univariable and multivariable regression analyses. Survival will be evaluated by using the Kaplan-Meier method and Cox proportional hazard modelling to adjust for confounders and produce estimates. A two-sided p<0.05 will be considered statistical significant.

Patient and public involvement

Patients were not invited to comment on the conception of study or research questions, outcome measures, study design, recruitment or conduct, or dissemination plans of our research. Patients were not asked to contribute to the writing or editing of this protocol paper.

Ethics and dissemination

All patients were treated with TAVI as clinically indicated and followed according to hospital routines. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK vest, ref. number 33814) and the Institutional Data Protection Services. Patients' consent was waived. The study findings will be disseminated via peer-reviewed publications and presentation in national and international scientific meetings and conferences.

DISCUSSION

The prevalence of AS is expected to increase due to increasing life expectancy and changing demographic of our Western populations. Aortic valve calcification and systemic atherosclerosis share the same cardiovascular risk factors. Although systemic atherosclerosis can be modified by statin and antiplatelet treatment, no medical treatment has so far been proven to stop or delay the progression of aortic valve calcification.[23–25] The development of symptoms in patients with severe AS is associated with a poor prognosis. Thus, TAVI or SAVR are the only proven treatment options to reduce morbidity and mortality. TAVI has emerged as a relatively safe and effective treatment, initially for elderly frail patients with severe AS at high risk for conventional surgery,[26] but later also for intermediate[27] and low-risk patients.[28 29] However, it is crucial to undertake a careful selection of patients who will benefit from TAVI as it may also carry a high risk of periprocedural complications as well as being a huge economic burden for the society. The present TAVI-NOR

study is a prospective cohort study of 600 patients with predominantly severe AS which aims to explore the impact of TAVI on LV function and structure, and prognosis. A comprehensive echocardiographic assessment was performed at baseline, 1 month and 6–12 months after TAVI. The main echocardiographic characteristics of interest are aortic flow, LV and right ventricular dimensions, and systolic and diastolic function (box 2). Vascular haemodynamics in terms of brachial BP, systemic arterial compliance, and valvular-arterial impedance (Zva) are other outcome measures.

The impact of TAVI on functional recovery and LV mass regression

Patients treated with TAVI show improvement in symptoms, quality of life and systolic LV function, and regression of LV mass. A subset of patients with severe AS (AVA <1.0 cm^2) and EF <50% may not have impaired LV systolic function and the ventricle is demonstrating a normal response to high afterload (AS and increased arterial load). In afterload mismatch even if LVEF is severely reduced, LV may recover and return to normal after valve intervention. By contrast, in the presence of irreversible myocardial damage due to infarct/scar tissue or fibrosis, functional recovery of the LV and regression of LVH may not be feasible. These patients often carry a markedly increased procedural risk.[30] In a study by Kamperidis *et al*[31] functional recovery of the LV as reflected by improvement in global longitudinal strain occurred during the first 6 months after TAVI and remained stable for the next 6 months. In other studies, improvement in LVEF was more likely in women,[32 33] which may partly be explained by the lower burden of myocardial fibrosis in women.[34] In our study, in addition to LVEF and systolic tissue Doppler velocities (S'), the measurements of LV wall thicknesses and dimensions enable us to examine MWFS, a robust marker of systolic LV function, as well as examine afterload/wall stress. In early TAVI studies, patients were typically elderly with prohibitively high surgical risk.[3] In recent TAVI studies, however, patients are younger and have lower-risk profile.[3] Hence, the rate and extent of reverse LV remodelling may differ according to the baseline cardiovascular risk profile.

Furthermore, assessment of right ventricle in AS is somehow neglected. In our study, right ventricular free wall thickness and basal diameter may provide useful insights on the impact of TAVI on RV structure. Finally, it is important to compare the echocardiographic features of the various biological TAVI prosthesis (eg, the CoreValve prosthesis compared with the Edwards Sapien) which may affect the rate and severity of residual paravalvular leak and its relation with functional recovery and prognosis.

Arterial haemodynamics and bp response to TAVI

Valvular-arterial impedance

In AS, LV is exposed to increased afterload due to valvular stenosis, systemic hypertension and increased aortic stiffness.[3] After TAVI, LV is partially unloaded and the normalisation of mean pressure gradient and flow (SVi) is normally used to evaluate short-term therapeutic success. However, reduction in ZVa which incorporates the markers of valvular and arterial load (global LV load), and is associated with adverse LV remodelling and impaired outcome in AS,[3] may be a better marker of long-term therapeutic success. Reduction in Zva is only possible if hypertension is optimally treated.

Excessive bp rise immediate after TAVI

Some patients may exhibit an excessive BP rise immediately after TAVI, which is believed to be caused by a sudden rise in SV and increase in LVEF, particularly in patients with afterload mismatch. These patients often require intravenous infusion of alpha- and beta-blocker drugs such as Labetalol with careful BP monitoring. However, the optimal BP target in acute setting is not clear. Furthermore, the clinical significance and prognostic value of excessive BP rise immediately after TAVI is not fully explored, and the results are conflicting.[35 36] In our study, BP was carefully measured during hospitalisation for TAVI, and an average BP (post-TAVI BP) will be calculated from all valid measurements. Hence, TAVI-NOR has the potential to examine the clinical significance and prognostic value of an exaggerated BP rise, as well as other patterns of BP response immediately after TAVI.

Limitations

First, global longitudinal strain measured by speckle tracking echocardiography has been shown to predict survival in patients with AS. Strain imaging was not a part of the study protocol. Second, in the earlier period of the study the patient selection criteria were somehow strict and mainly restricted to elderly patients with severe AS who had prohibitively high risk for conventional surgery. These patients had often degenerative stenosis of a tricuspid aortic valve. By contrast, patients with a bicuspid aortic valve are often <65 years and normally assigned for a conventional AVR in combination with coronary bypass grafting. Therefore, in the present study we may to some extent have underestimated the true prevalence of bicuspid aortic valve. Furthermore, we do not have any registration or follow-up data on patients rejected for TAVI. The information on the change in antihypertensive treatment during follow-up (posthospitalisation) was not a part of the study protocol and may affect study outcome. Finally, there is some uncertainty on the proportion of patients who completed 6–12 months echocardiographic follow-up.

In conclusion, TAVI-NOR study is a large prospective cohort study of patients with severe AS that will provide important clinical insights on the effect of TAVI on cardiac structure and function. It will help to determine the echocardiographic predictors of reverse LV remodelling as well as identify patients who are at high risk of procedure-related complications. TAVI-NOR will also assess the association of various types of abnormal BP response immediately after TAVI with cardiac structure and function, vascular haemodynamics and prognosis.

Collaborators John B. Chambers.

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