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# ECG, clinical and novel CT-imaging predictors of necessary pacemaker implantation after transfemoral aortic valve replacement

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ABSTRACT

*Purpose:* Newly onset conduction disturbances with the need for permanent pacemaker (PPM) implantation remain the most common complication of transcatheter aortic valve replacement (TAVR). The objective was to evaluate the predictive value of clinical, ECG and new pre-procedural CT-imaging parameters for the requirement of PPM-implantation after TAVR.
*Methods:* 2105 consecutive patients receiving TAVR using a balloon expandable prosthesis (Sapien 3, Edwards Lifesciences, Irving, CA, USA) at our institution were enrolled. Patients receiving a valve-in-valve prosthesis, TAVR after surgical repair, with missing or non-diagnostic CT-scans, with pre-implanted PPM and after TAVR in mitral position were excluded. The most suitable classification model for the given dataset was first identified through benchmark testing and later applied for prediction analysis.
*Results:* 312 eligible patients requiring PPM implantation were compared to an age- matched control group of 305 patients not requiring PPM implantation. A scaled LASSO model allowed for most accurate prediction with an AUC of 0.70. Right bundle branch block was the strongest predictor (OR 2.739), followed by atrioventricular block 1° (OR 2.091), prosthesis diameter (OR 1.351), atrial fibrillation (OR 1.255), arterial hypertension (OR 1.215), coronary artery disease (1.070), the angle of ventricle axis and aortic root (OR 1.030), sinotubular junction height (OR 1.014) and the calcification of the left coronary cuspid (OR 1.007).
*Conclusions:* ECG- and clinical outperform imaging parameters in predicting PPM-implantation following TAVR. Right bundle branch block emerged as the most significant predictor overall, while the angle of ventricle axis and aortic root as a novel imaging-based predictor.

## 1. Introduction

Aortic stenosis is the most common valvular heart disease in the developed world [1]. With an increase in prevalence among the aging population and considering the poor prognosis of untreated symptomatic aortic stenosis, the indication for interventional treatment is more relevant than ever [2].

In the last decade transcatheter aortic valve replacement (TAVR) has

*Abbreviation:* AF, atrial fibrillation; aHTN, arterial hypertension; AoA, aortic anulus; AVB I, atrioventricular block I; Ca, calcification; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM2, Diabetes mellitus type II; HLP, hyperlipidaemia; LAHB, left anterior hemiblock; LBBB, left bundle branch block; LCA, left coronary artery; LCC, left coronary cuspid; LVOT, left ventricular outflow tract; NCC, non coronary cuspid; PAD, peripheral artery disease; PHT, pulmonary hypertension; PPM, permanent pacemaker; PS, prosthesis; RBBB, right bundle branch block; RCA, right coronary artery; RCC, right coronary cuspid; ST, sinotubular; SV, Sinus of Valsalva.

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been shown to be a viable therapeutic option compared to surgical aortic valve replacement (SAVR) not only in patients at high risk for surgical complications, but also for intermediate –, and low-risk patients [3–6]. Furthermore, due to TAVR being especially recommended in elderly patients who cannot undergo surgery, its use has dramatically increased in recent years [7].

TAVR is generally a safe and effective procedure. However, the site of valve implantation at the aortic anulus is in close proximity to the His bundle and left bundle branch [8]. Hence newly onset conductions disturbances (CD) as in left bundle branch block (LBBB) and atrioventricular block (AVB) requiring permanent pacemaker implantation (PPM) still remain the most common complications, occurring in approximately 2–51 % of patients depending on prosthesis type used and various other factors [9]. This is known to have a substantially negative effect on prognosis [8].

Numerous studies have evaluated clinical and procedural predictors for subsequent PPM implantation after TAVR [10–12].

Pre-TAVR CT imaging provides essential information required for planning and peri- and intraprocedural risk assessment due to its high-resolution, three dimensional visualization of the aortic root and safe transcutaneous access route [13]. However, data on several CT-imaging parameters that could predict PPM implantation after TAVR is still scarce [14,15].

Hence, the objective of this study was to identify additional CT-imaging and clinical parameters associated with the need for PPM implantation after TAVR using a multivariate prediction model for peri-procedural risk assessment.

## 2. Methods

The study was conducted in accordance with the declaration of Helsinki and approved by the institution ethics committee board. The requirement for informed consent was waived.

### 2.1. Population

In this retrospective single-center study, all patients over the age of 18 years, who underwent TAVR at our hospital between May 2012 and December 2019 using a balloon-expandable prosthesis (Sapien 3, Edwards Lifesciences, Irvine, California) were enrolled [16]. Three different prosthesis diameters (*PS diameter*) were used: 23, 26 and 29 mm, selected after assessment of anatomical features on pre-TAVR imaging. Patients who received valve-in-valve prostheses, underwent TAVR after surgical repair, had missing or non-diagnostic in house CT-scans, had pre-implanted pacemakers or underwent TAVR in mitral position were excluded from the study. A maximum time period of 3 months for the post-procedure follow-up was chosen to adequately register patients with TAVR associated conduction disturbances. All patients who required PPM-implantation after TAVR (*PPM-group*) were age matched and compared to patients who did not require PPM-implantation (*NPPM-group*).

Clinical parameters including ECG-abnormalities, other pre-existing cardiopulmonary conditions and cardiac risk factors were recorded.

### 2.2. Preprocedural imaging

All patients received in-house preprocedural CT imaging planning. All scans were performed using one of three different dual-source CT scanners with a total of 256 slices and a temporal resolution of 75 ms (Siemens SOMATOM Flash and SOMATOM Drive, Siemens, Forchheim, Germany) or 384 slices and a temporal resolution of 66 ms (Siemens SOMATOM Force, Siemens, Forchheim, Germany). Tube voltage and current were selected based on patient characteristics (CARE Dose 4D and CARE kV, Siemens, Forchheim, Germany). Collimation was set at 2 x 128 x 0.6 mm (Flash and Drive) or 2 × 192 × 0.6 mm (Force). The imaging protocol consisted of a non-contrast scan of the heart for quantification of calcifications. A high-pitch contrast enhanced scan (Flash, Siemens, Forchheim, Germany) in end-systolic phase (30–40 % RR-interval) ranging from the skull base to the femoral arteries was subsequently conducted. The aortic valve plane was then reconstructed from the contrast enhanced scan. Patients were administered 70–140 cc of iomeprol-400 (Iomeron, Bracco Imaging SpA, Milan, Italy) at a rate of 3–7 cc/s followed by a 30 cc saline chaser.

### 2.3. Imaging measurements

All imaging measurements were carried out using dedicated software (CVI 42 5.12, Circle Cardiovascular Imaging Inc. Calgary, Canada) according to established guidelines by two experienced readers in consensus agreement [17].

Measurements of the aortic left ventricular outflow tract and aortic root were taken in multiplanar reformatted images and recorded in the transverse double oblique view (Fig. 1a). Following possible imaging predictors were selected:

- area (*valve*), perimeter (*AoA perimeter*) as well as minimum (*AoA diameter* min) and maximum diameter (*AoA diameter* max) of the anulus (*AoA*). The anulus was defined as the lowest insertion point of all three cusps (Fig. 1b).
- perpendicular distance of the anulus to the lowest point of left (*distance AoA LCA*) and right coronary ostium (*distance AoA RCA*) (Fig. 1c, right).
- sinotubular junction height (*st-junction ht.*) defined by the perpendicular distance between the anulus and the lowest point of sinotubular junction (Fig. 1c, left).
- diameter of the sinus of Valsalva (*sv diameter*) defined by the widest point in the annular plane visualizing the commissures (Fig. 1d).
- angle of left ventricle to aortic root (*angle ventricle axis, aortic root*) defined by the angle between the long axis of the left ventricle and a line drawn through the center of the aorta (Fig. 1e).
- length of LVOT (*LVOT length*) defined by the perpendicular distance between the anulus and the basal insertion point of the anterior cusp of the mitral valve (Fig. 1e).

Calcium scoring was performed in the approximate device landing zone, consisting of the left ventricular outflow tract and aortic cusps. The calcifications of the right, left and non-coronary cusps were measured below (*LCC Ca LVOT, RCC Ca LVOT, NCC Ca LVOT*) and above (*LCC Ca, NCC Ca, RCC Ca*) the anulus plane. The total calcification of the aortic valve (*upper LVOT Ca)* was calculated. The presence of severe calcification ranging from the mitral valve to the anulus plane without interruption *(Ca LVOT mitral hinge*) was noted (Fig. 1f).

### 2.4. Statistical analysis

All analyses were performed with R software (version 4.1.2) [18]. Categorical variables are presented as count (percentages). Ordinal and continuous variables are presented as median (interquartile range) and mean (standard deviation).

### 2.5. Univariate analysis

Univariate analyses were performed to compare the PPM group to the matched NPPM group using the $\chi^2$-test for categorical variables and the Mann-Whitney U/ Wilcoxon rank test for numeric variables. The confidence interval was set at 95 % with a p-value $< 0.05$ considered statistically significant. To compensate for multiple testing we used the Benjamin-Hochberg-procedure with a q-value representing corrected p-values.

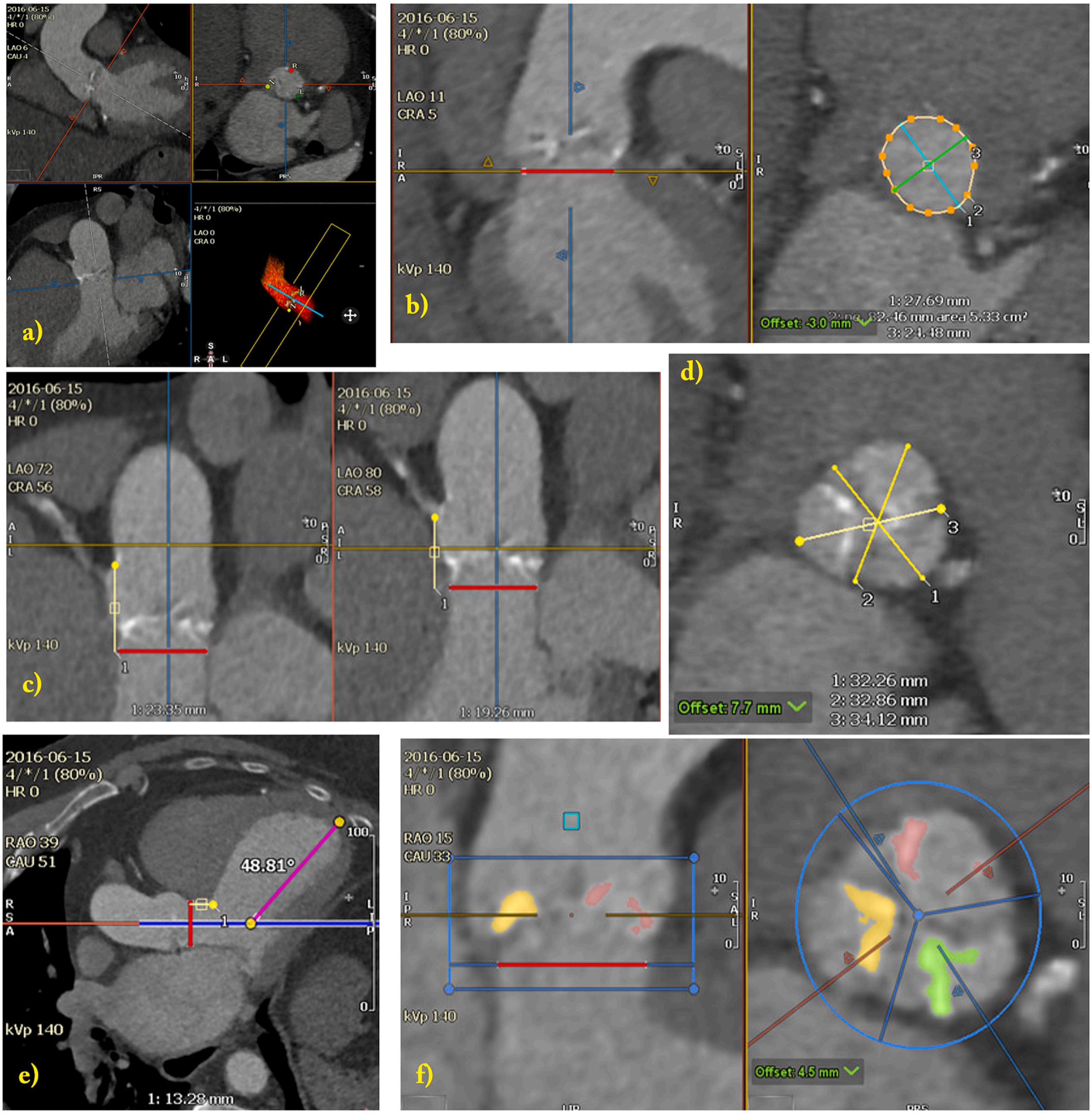



**Fig. 1.** Measurement of imaging parameters; *a) standard measurement setting in transverse double oblique view; b) aortic anulus plane and hinge points (left) with aortic diameter, area and perimeter (right); c) distance between anulus and coronary artery (right) and sinotubular junction height (left); d) diameter of sinus of Valsalva; e) length of left ventricular outflow tract (yellow line) and angle between ventricle axis and aortic root; f) calcification of mitral valve to anulus plane (right) and of the coronary cuspids (left)*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### *2.6. Feature selection and model benchmarking for multivariate analyses*

In the multivariate analysis of predictors for post-procedural PPM-implantation, all available features for model building were employed. Additionally, interactions between specific pairs of variables, such as prosthesis diameter, AoA perimeter, LVOT length, and distances of AoA LCA and AoA RCA, and between AoA diameter min and AoA diameter max were explored. The consideration of these interactions in subsequent analyses hinged on their significance in predicting PPM-implantation after TAVR, particularly within the minimal model (feature 1 + feature 2 + interaction) where the interaction term's significance was a determining factor.

To determine a suitable model for the classification task, a benchmark analysis with 10-fold cross-validation (CV) was conducted. Four distinct model setups evaluated based on the area under the receiver operating characteristic curve (AUC) were compared. These setups included a full model with all features, a regularized model using LASSO, and variations with and without feature scaling (normalization). The goal of the model building process was to discern the most effective approach for predicting post-procedural PPM-implantation after TAVR. The model building process is visualized in Fig. 2.

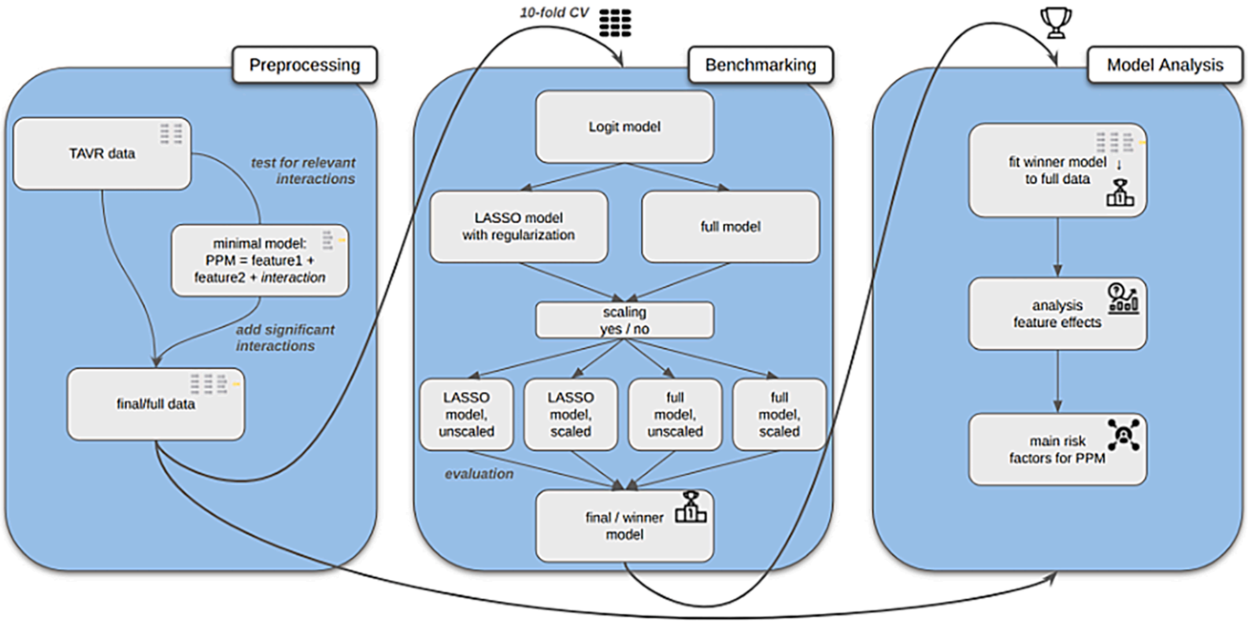



**Fig. 2.** comprehensive overview of the model building process: preprocessing steps with interaction considerations, benchmark analysis, and winner model evaluation for post-TAVR PPM necessity; *PPM: patients requiring permanent pacemaker implantation post TAVR.*

## 3. Results

### 3.1. Population

In the selected time period, 2105 patients underwent TAVR at our institution. 350 patients (16.6 %) required PPM implantation within 3 months post-procedure. To improve the workflow for this large patient population PPM- and NPPM-patients were matched before analyzing exclusion criteria in detail. Every PPM-patient was age-matched to a subject without the need for PPM after TAVR. After applying the aforementioned exclusion factors, in total 617 patients remained, 305 patients for the PPM-group, and 312 patients for the NPPM group (Fig. 3). The median time to PPM-implantation post-TAVR was 6 days (IQR: 3;8).

### 3.2. Univariate analysis of clinical parameters

Univariate comparison of the PPM and NPPM groups regarding clinical parameters are given in Table 1 with corresponding p- or q-values. Due to age-matching of the PPM and NPPM group, no difference in age was reported ($80.21 \pm 6.69$ vs. $79.97 \pm 6.82$ years, $q = 0.8$). Less women were noted in the NPPM group (31.8 % vs. 50.0 %, $q < 0.001$). Clinical parameters that were more frequently observed in the NPPM group was the presence of RBBB (27.5 % vs. 9.0 %, $q < 0.001$) as well as AVB I (29.5 % vs. 13.8 %, $q < 0.001$). In summary, smaller prosthesis diameters were utilized in the NPPM group ($q < 0.001$).

### 3.3. Univariate analysis of imaging parameters

Univariate comparison of the PPM and NPPM groups regarding

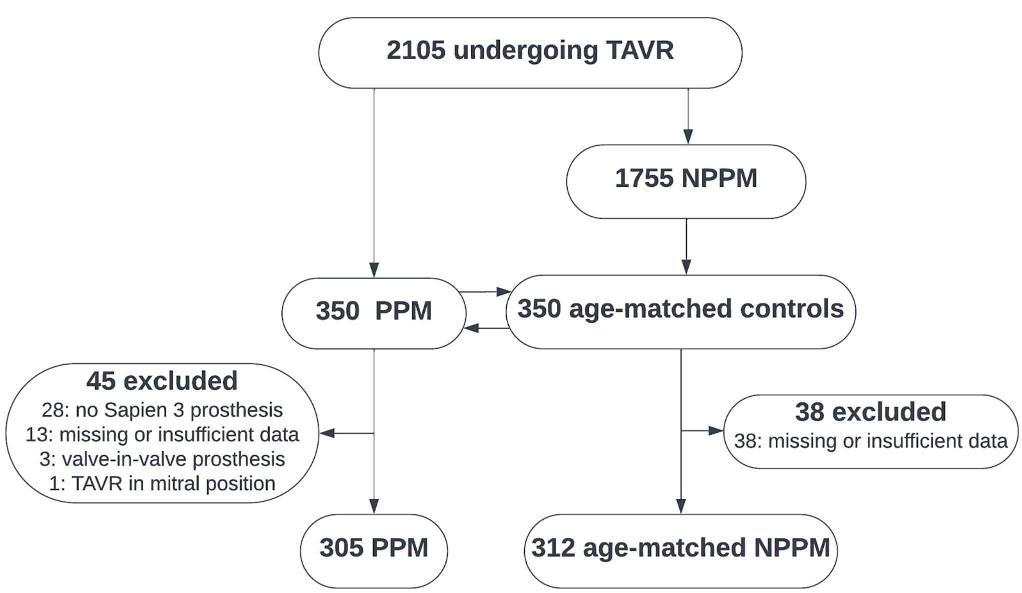



**Fig. 3.** Flow chart of study population with exclusion factors; *PPM: patients requiring permanent pacemaker implantation post TAVR; NPPM: patients not requiring permanent pacemaker implantation post TAVR.*

**Table 1**
Acquired clinical parameters for nppm and ppm groups;[1]*n (%) or mean and standard deviation;* [2]*χ2-test, Wilcoxon rank test;* [3]*Benjamini-Hochberg-correction for multiple testing.*

| Parameter | NPPM, N = 312[1] | PPM, N = 305[1] | p-value[2] | q-value[3] |
|---|---|---|---|---|
| age (years) | 79.97 ± 6.82 | 80.21 ± 6.69 | 0.7 | 0.8 |
| women | 156 (50.0 %) | 97 (31.8 %) | **< 0.001** | **< 0.001** |
| CRF | 92 (29.5 %) | 101 (33.1 %) | 0.4 | 0.5 |
| COPD | 47 (15.1 %) | 43 (14.1 %) | 0.8 | 0.8 |
| DM | 89 (28.5 %) | 100 (32.8 %) | 0.3 | 0.4 |
| smoker | 51 (16.3 %) | 61 (20.0 %) | 0.3 | 0.4 |
| PAD | 41 (13.1 %) | 37 (12.1 %) | 0.8 | 0.8 |
| PHT | 20 (6,4 %) | 19 (6,2 %) | > 0.9 | > 0.9 |
| aHTN | 277 (88.8 %) | 284 (93.1 %) | 0.083 | 0.2 |
| CAD | 191 (61.2 %) | 212 (69.5 %) | 0.038 | 0.090 |
| HLP | 170 (54.5 %) | 157 (51.5 %) | 0.5 | 0.6 |
| AF | 101 (32.4 %) | 126 (41.3 %) | 0.027 | 0.079 |
| LBBB | 26 (8.3 %) | 31 (10.2 %) | 0.5 | 0.6 |
| RBBB | 28 (9.0 %) | 84 (27.5 %) | **<0.001** | **<0.001** |
| LAHB | 24 (7.7 %) | 35 (11.5 %) | 0.14 | 0.2 |
| BB | 8 (2.6 %) | 20 (6.6 %) | 0.029 | 0.079 |
| AVB I | 43 (13.8 %) | 90 (29.5 %) | **<0.001** | **<0.001** |
| PS diameter (23 mm) | 118 (37.8 %) | 61 (20.0 %) | **<0.001** | **< 0.001** |
| PS diameter (26 mm) | 130 (41.7 %) | 124 (40.7 %) | | |
| PS diameter (29 mm) | 64 (20.5 %) | 120 (39.3 %) | | |

PPM-group: patients requiring permanent pacemaker implantation; NPPM-group: patients not requiring permanent pacemaker implantation; AF: atrial fibrillation; LBBB: left bundle branch block; RBBB: right bundle branch block; LAHB: left anterior hemi block; BB: bifascicular block; AVB I: atrioventricular block I; CAD: coronary artery disease; CRF: chronic renal dysfunction; aHTN: arterial hypertension; PHT: pulmonary hypertension; DM: diabetes mellitus; HLP: hyperlipidemia; PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; PS diameter: prosthesis diameter.

**Table 2**
Acquired imaging parameters for nppm and ppm groups;[1]*n (%) or median and interquartile range;* [2]*χ2-test, Wilcoxon rank test;* [3]*Benjamini-Hochberg-correction for multiple testing.*

| Parameter | NPPM, N = 312[1] | PPM, N = 305[1] | p-value[2] | q-value[3] |
|---|---|---|---|---|
| Ca LVOT mitral hinge | 85 (27.2 %) | 93 (30.5 %) | 0.4 | 0.5 |
| AoA diameter max (mm) | 28 (26, 30) | 29 (27, 31) | **< 0.001** | **< 0.001** |
| AoA diameter min (mm) | 22 (20, 23) | 22 (21, 24) | 0.004 | 0.012 |
| AoA perimeter (mm) | 79 (74, 84) | 82 (77, 87) | **<0.001** | **<0.001** |
| valve ($cm^2$) | 0.76 (0.61, 0.90) | 0.80 (0.60, 0.90) | 0.7 | 0.7 |
| st-junction ht. (mm) | 22 (20, 24) | 23 (21, 25) | **<0.001** | **0.004** |
| sv diameter (mm) | 33 (31, 36) | 35 (32, 37) | **<0.001** | **<0.001** |
| distance AoA LCA (mm) | 15 (13, 17) | 15 (13, 18) | 0.046 | 0.10 |
| distance AoA RCA (mm) | 17 (15, 20) | 18 (15, 21) | 0.086 | 0.2 |
| angle ventricle axis, aortic root (°) | 51 (45, 57) | 52 (47, 58) | 0.035 | 0.090 |
| LVOT length (mm) | 15 (12, 18) | 15 (13, 18) | 0.13 | 0.2 |
| LCC Ca ($mm^3$) | 192 (92, 335) | 243 (117, 435) | **0.003** | **0.009** |
| RCC Ca ($mm^3$) | 170 (85, 308) | 204 (116, 377) | **0.002** | **0.008** |
| NCC Ca ($mm^3$) | 263 (145, 454) | 304 (175, 442) | 0.11 | 0.2 |
| upper LVOT Ca ($mm^3$) | 6 (0, 57) | 10 (0, 75) | 0.2 | 0.3 |
| LCC Ca LVOT ($mm^3$) | 1 (0, 22) | 1 (0, 37) | 0.3 | 0.4 |
| RCC Ca LVOT ($mm^3$) | 0 (0, 1) | 0 (0, 1) | 0.5 | 0.6 |
| NCC Ca LVOT ($mm^3$) | 0 (0, 3) | 0 (0, 11) | 0.2 | 0.3 |

PPM-group: patients requiring permanent pacemaker implantation; NPPM-group: patients not requiring permanent pacemaker implantation; AoA: aortic annulus; LCA: left coronary ostium; RCA: right coronary ostium; st-junction ht.: sinutubular junction height; sv: sinus of Valsalva; LVOT: left ventricular outflow tract; Ca: calcification; L/R/NCC: left/right/non-coronary cuspid.

imaging parameters are given in Table 2 with corresponding p- or q-values. The PPM-group presented with a larger minimum diameter (22 [21,24] vs. 22 [20,23] mm, q = 0.012), a larger maximum diameter (29 [27,31] vs. 28 [26,30] mm, q < 0.001) and a larger perimeter (82 [77,87] vs. 79 [74,84] mm, q < 0.001) of the aortic anulus. Furthermore, the PPM-group showed a larger sinotubular junction height (23 [21,25] vs. 22 [20,24] mm, q = 0.004) and diameter of the sinus of Valsalva (35 [32,37] vs. 33 [31,36] mm, q < 0.001). Concerning calcification measurements, only the calcification of the LCC (243 [117,435] vs. 192 [92,335], p = 0.009) and of the RCC (204 [116,377] vs. 170 [85,308], p = 0.008) was higher in the PPM-group.

### 3.4. Feature selection and model benchmarking for multivariate analyses

At first possible interaction terms were selected and tested to be incorporated in the final model. With respect to the p-values only the interaction of PS diameter [mm] with LVOT length [mm] had a significant effect (p = 0.015). Therefore, only this interaction was incorporated in the full LASSO model.

With presented settings, the benchmark comparison for the different logistical models was performed with results averaged over 10 CV iterations. According performance values and their ROC curves are presented in Fig. 4. Especially the AUC values of the four models were nearly equal. In summary, the scaled LASSO model slightly outperformed the others with respect to most of the performance metrics (except specificity), although not significantly. However, it is especially useful for interpretation as it incorporates regularization and scaling which enhances interpretability and therefore was used as the final prediction model.

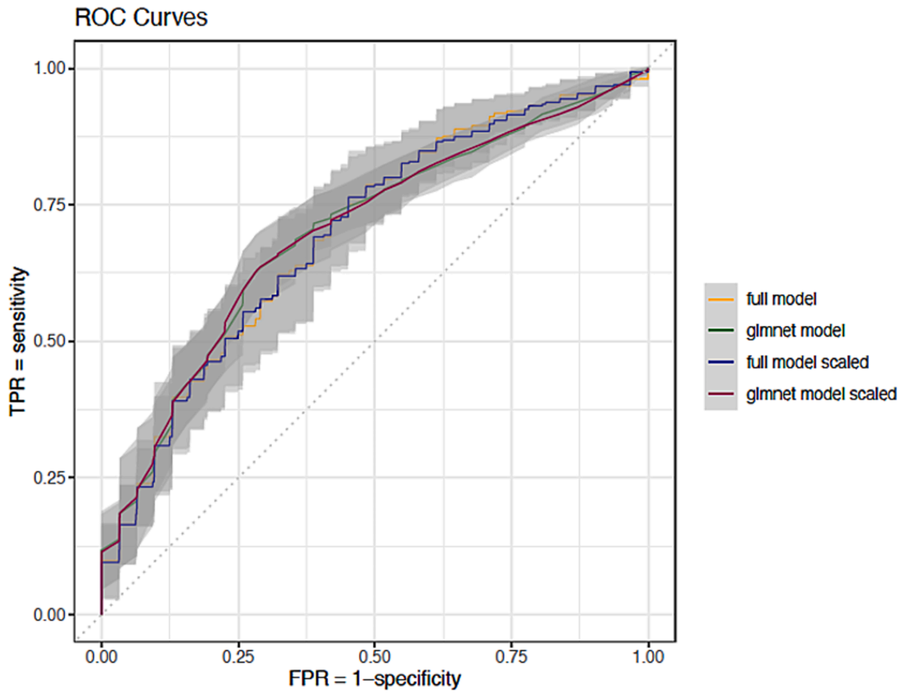
### 3.5. Multivariate analyses of clinical and imaging parameters

Ultimately, fitting the scaled LASSO model to all available observations identified the following terms as relevant predictors for PPM-implantation after TAVR: LCC Ca [$mm^3$], angle ventricle axis, aortic root [°], PS diameter [mm], st-junction ht. [mm], aHTN, AVB I, CAD, RBBB, AF. However, no interaction terms were deemed relevant.

RBBB demonstrated the most pronounced impact, with an odds ratio (OR) suggesting that the risk of PPM-implantation after TAVR increases by a factor of 2.739 when RBBB is present. This was followed by AVB I (OR 2.091) and prosthesis diameter (OR 1.351). Regarding imaging predictors, angle ventricle axis, aortic root [°] was the strongest predictor (OR 1.03), followed by st-junction ht. [mm] (OR 1.014) and LCC Ca [$mm^3$] (OR 1.007) (Fig. 5). In summary, clinicals predictors were stronger than imaging predictors for PPM-implantation after TAVR. Due to the regularization process no confidence intervals can be provided.

## 4. Discussion

The purpose of this study was to evaluate clinical and CT-imaging predictors for necessary post procedural PPM implantation after TAVR. Numerous studies have evaluated various clinical and imaging factors contributing to newly onset conduction disturbances after TAVR [14,19]. However, data on imaging predictors are far less established and limited to only a few imaging measurements (calcification of the cusps, length of the membranous septum etc.) and often tested in smaller patient cohorts [20,21]. Consequently, this study aimed to find further relevant predictors gathered from a reasonably large study population undergoing TAVR with one specific prosthesis. Furthermore, an important objective was to set up a comprehensive multivariate prediction model for periprocedural risk assessment. In this context this study found that a scaled prediction model was non inferior to full models. In concordance with previous studies, pre-existing arrhythmias were the strongest predictor for post-procedural PPM-implantation [14,19]. Clinical and imaging predictors showed weaker predictive value, with the angle of the ventricle axis and aortic root emerging as a




| Model | AUC | Sens. | Spec. | PPV | NPV | ACC | BACC | F1 Score |
|---|---|---|---|---|---|---|---|---|
| full model | 0.6972 | 0.6160 | 0.6534 | 0.6363 | 0.6371 | 0.6352 | 0.6347 | 0.6240 |
| LASSO model | 0.6995 | 0.6257 | 0.7015 | 0.6798 | 0.6574 | 0.6641 | 0.6636 | 0.6473 |
| full model scaled | 0.6961 | 0.6323 | 0.6629 | 0.6505 | 0.6496 | 0.6480 | 0.6476 | 0.6389 |
| LASSO model scaled | 0.6997 | 0.6451 | 0.6983 | 0.6828 | 0.6692 | 0.6722 | 0.6717 | 0.6592 |

**Fig. 4.** ROC-plot comparing performance for four different logistic models predicting PPM-implantation after TAVR; *full model: all variables; glmnet model: variable selection via LASSO.*

novel imaging factor for post-procedural PPM-implantation.

PPM still remains one of the most common complications of TAVR due to the close proximity of the site of prosthesis implantation to the AV-node and His-bundle [22]. A *meta*-analysis by Bruno et al. of 43 studies with 29113 patients in total reported a lower pooled incidence rate of PPM of 12 % in balloon-expandable valves compared to 25 % in self-expandable valves. The incidence of PPM was 31 % for Corevalve Medtronic, 31 % for Boston Lotus and 13 % for Edwards Sapien 3 [19]. This figure is comparable to our results, where 15.3 % (322) of 2105 patients in the total study population received a pacemaker within 3 months after TAVR with the Edwards Sapien 3 valve.

Higher age is a risk factor for PPM after TAVR [23]. Hence, we proceeded to age-match the control group to reduce confounding. By disregarding other clinical factors, reasonably large sample sizes could be formed. The study population's median age of 80 is in line to that of a *meta*-analysis conducted by Ulla et al. where 78 studies with 31,261 patients showed a mean age of 81 [24]. This again shows that TAVR already is an established therapy regimen for aortic stenosis in older patients [25]. According to the *meta*-analysis by Ulla et al., larger prosthesis diameter correlated with higher PPM-rates after TAVR (OR 1.49; 95 % CI, 1.06–2.08) [24].This was also noted in our study, where increasing the prosthesis diameter by one standardized unit (1.7 mm) the risk for PPM implantation after TAVR increased by 1.351. This is explained by larger prostheses putting higher tensile stress on the cardiac structure and conduction system, with the benefit of lower paravalvular leakage rates [14].

After multivariate analysis, sex was not deemed a positive predictor. This result was in line with the *meta*-analysis by Bruno et al. in patients receiving the Sapien 3 prosthesis [19].

CAD was a positive predictor of post-procedural PPM implantation (OR 1.07). This may be explained by CAD promoting ischemia of the cardiac conduction system with a subsequent higher rate of conduction disturbances [26].

Arterial hypertension also proved to be a relevant risk factor (OR 1.215). Interestingly, this result contradicts large *meta*-analyses by Sammour and Mahajan et al., who have not found a correlation between hypertension and the requirement for PPM after TAVR [8,14]. This might be explained by arterial hypertension leading to conduction disturbances through hypertensive cardiomyopathy. This is mainly caused by pressure induced remodeling of the myocardium in conjunction with other conditions, such as chronic kidney failure or coronary artery disease. Resulting myocardial fibrosis and hypertrophy of the left ventricle with a consecutive dilation of the left atrium may impair the conduction system. At last, antihypertensive medication can also induce arrhythmias, mainly through electrolyte disturbances [27].

In line with previous studies pre-existing ECG-abnormalities are a strong predictor for the requirement of PPM-implantation after TAVR due to the additional damage inflicted by valve implantation to an already disturbed cardiac conduction system [8,20,24]. In this study RBBB (OR 2.739) and AVB I (OR 2.091) were the strongest predictors. However, analogous to the *meta*-analysis of Bruno et al., LBBB was not a positive predictor [19]. This is probably explained by the prosthesis primarily pressuring the left bundle branch and hence not significantly altering already blocked pathways in pre-existing LBBB. Comparable to recent literature, AF was also associated with higher PPM-rates (OR 1.255) [28].

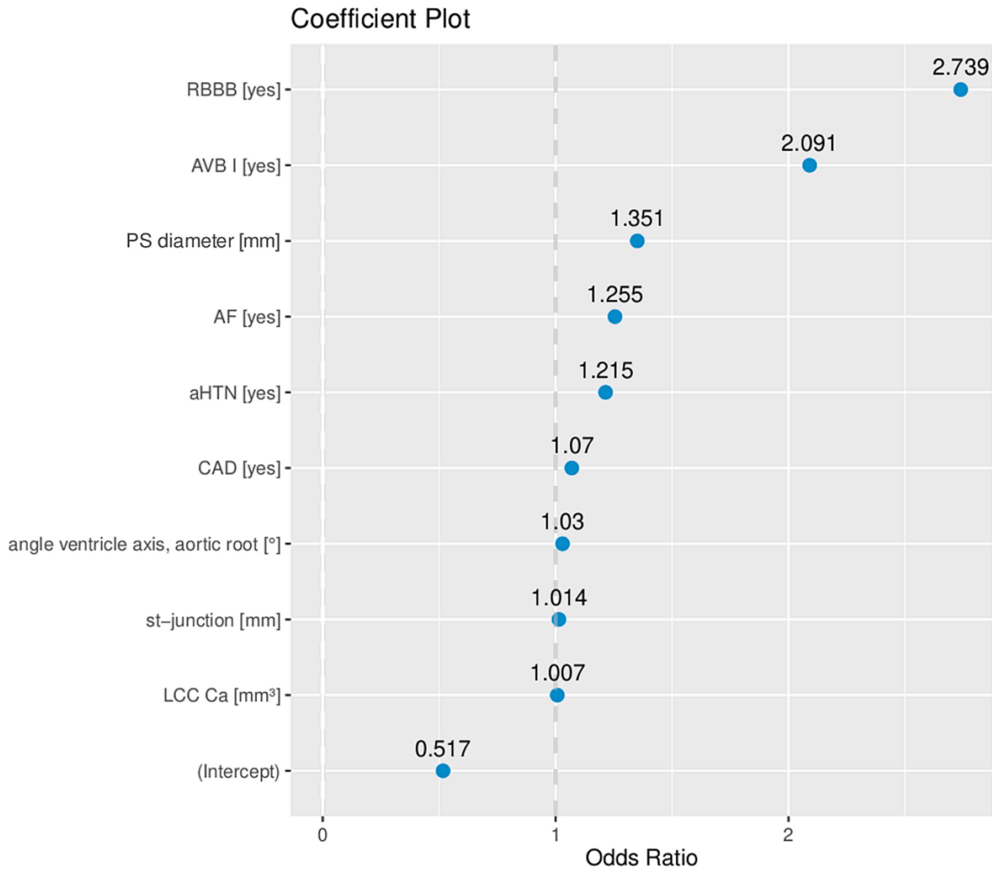



**Fig. 5.** Coefficient plot of odds ratios for significant predictors of ppm-implantation after tavr; *RBBB: right bundle branch block; AVB I: atrioventricular block °1; PS diameter: Prosthesis diameter; AF: atrial fibrillation; aHTN: arterial hypertension; CAD: coronary artery disease; st-junction: sinotubular junction height; LCC Ca: calcification of the left coronary cuspid.*

Many CT-imaging predictors for PPM-implantation after TAVR have been proposed [8,14,19]. In this univariate analysis, the PPM-group reported significantly larger aortic anulus diameters and perimeters, sinotubular junction height, sinovalvular diameter, LCC and RCC calcification. However, only the angle of ventricle axis and aortic root (OR 1.03), sinotubular junction height (1.014) and LCC calcification (1.007) remained positive predictors in the multivariate model. This notable difference to previous reviews might be explained by their pooled data of studies using different valve types compared to this population only receiving Sapien 3 prostheses. Furthermore, there is evidence in a subgroup analysis of Bruno et al. that oversizing and implantation depth in patients receiving balloon expandable prostheses only are not significant contributors to post procedural PPM implantation [19]. To our knowledge, this is the first study that directly associated a decreased angulation between the left ventricle and aortic root to PPM-requirement after TAVR. In previous studies, ventricle and root angulation also had an effect on post procedural paravalvular leakage due to the increased resistance of calcified tissue towards the prosthesis by angular stress [29]. The increased tensile force due to higher resistance might explain the increased PPM-rate in our study.

Most importantly, benchmarking multiple multivariate prediction models was crucial to ensure robustness, reliability, and transparency of this evaluation. Comparing four multivariate prediction models revealed that using a scaled LASSO model with iterative testing of only relevant variables was non-inferior to full models considering all variables. Therefore, this model was applied to assess the risk for PPM implantation after TAVR, benefiting from enhanced interpretability and clinical relevance.

Our novel combined approach to identify patients at risk for PPM could enhance predictive accuracy, allowing for closer monitoring and earlier detection of complications. This strategy may reduce the risk of malignant arrhythmias and associated mortality, while also enabling better procedural planning and resource allocation. Recent studies indicate that PPM implantation is a major cause of delayed discharge and significantly increases procedural costs [30].

### 4.1. Limitations

Being a single center retrospective study, only data from procedures specific to our institution were gathered and analyzed. This could result in limited transferability of the study results to the general population. Nonetheless, this ensured a large and homogeneous patient collective receiving high-quality in-house imaging and clinical evaluation with the opportunity of additional quality control of acquired data. These are favorable prerequisites in determining risk assessment models.

Second, only age-matching of subgroups was performed. Sex was not included in the matching process leading to fewer subjects being excluded. The groups were corrected for sex in the subsequent multivariate analysis resulting in a larger study cohort while precluding the effect of sex. Furthermore, due to the workflow of matching first and applying exclusion factors afterwards the NPPM-patient cohort yielded less patients. Nonetheless, with cohorts of 305 PPM- and 312 matched NPPM-patients statistical analysis appeared to be sufficient.

Thirdly, although standardized, imaging measurements were performed manually leaving a room for error. The problem was mitigated by performing measurements and confirming the parameters by two experienced readers.

Only patients receiving Sapien 3 prostheses via a transfemoral access route were analyzed. The results might differ for patients undergoing self-expandable valve implantation or receiving TAVR via transapical/

transaxillary access [31].

At last, the decreased rate for PPM-implantation in more recent patients may be attributed to the growing experience of the operators and improved implantation techniques over the years.

## 5. Conclusions

In this retrospective single-center analysis of 617 patients undergoing TAVR, a scaled LASSO prediction model was non-inferior to full logistical models in predicting post procedural PPM-implantation with the benefit of improved comparability due to scaling. The scaled LASSO model determined the angle of ventricle axis and aortic root as a novel imaging predictor. Imaging predictors were substantially weaker than clinical predictors, the strongest being pre-existing arrhythmia due to RBBB and AVB I.

## CRediT authorship contribution statement

**Konstantin Klambauer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Daniel Puhr-Westerheide:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Conceptualization. **Matthias P. Fabritius:** Writing – review & editing, Writing – original draft, Data curation. **Wolfgang G. Kunz:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Julien Dinkel:** Investigation, Formal analysis, Data curation. **Christine Schmid-Tannwald:** Writing – review & editing, Investigation, Conceptualization. **Christina Utz:** Validation, Investigation, Formal analysis, Data curation. **Fabian Grathwohl:** Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Nicola Fink:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Konstantinos D. Rizas:** Writing – review & editing, Resources, Project administration, Conceptualization. **Jens Ricke:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Michael Ingrisch:** Resources, Project administration, Methodology, Formal analysis, Data curation. **Anna T. Stüber:** . **Adrian Curta:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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