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Permanent pacemaker implantation and left bundle branch block with self-expanding valves – a SCOPE 2 subanalysis

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KEYWORDS

- aortic stenosis
- atrio-ventricular block
- femoral

Abstract

Background: No detailed data on left bundle branch block (LBBB) and permanent pacemaker implantation (PPI) exist from randomised clinical trials comparing the ACURATE *neo* and CoreValve Evolut devices.

Aims: Our aim was to assess the incidence and impact of new LBBB and PPI with self-expanding prostheses from a powered randomised comparison.

Methods: From the SCOPE 2 trial, 648 patients with no previous pacemaker were analysed for PPI at 30 days, and 426 patients without previous LBBB were adopted for analysis of LBBB at 30 days.

Results: At 30 days, 16.5% of patients required PPI; rates were higher in CoreValve Evolut compared to ACURATE *neo* recipients (21.0% vs 12.3%; p=0.004). Previous right bundle branch block (odds ratio [OR] 6.11, 95% confidence interval [CI]: 3.19-11.73; p<0.001) was associated with an increased risk of PPI at 30 days, whereas the use of the ACURATE *neo* (OR 0.50, 95% CI: 0.31-0.81; p=0.005) was associated with a decreased risk. One-year mortality was similar in patients with and without new PPI. A total of 9.4% of patients developed persistent LBBB at 30 days, with higher incidences in CoreValve Evolut recipients (13.4% vs 5.5%; p=0.007). New LBBB at 30 days was associated with lower ejection fraction at 1 year (65.7%±11.0 vs 69.1%±7.6; p=0.041).

Conclusions: New LBBB and PPI rates were lower in ACURATE *neo* compared to CoreValve Evolut recipients. The ACURATE *neo* valve was associated with a lower risk of PPI at 30 days. No effect on 1-year mortality was determined for PPI at 30 days, while LBBB at 30 days was associated with reduced ejection fraction at 1 year.

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Abbreviations

LBBB	left bundle branch block
PPI	permanent pacemaker implantation
TAVR	transcatheter aortic valve replacement
THV	transcatheter heart valve

Introduction

Transcatheter aortic valve replacement (TAVR) has developed from a therapeutic option initially reserved for inoperable and high-risk patients to an accepted alternative to surgery in intermediate- and low-risk patients[1-5]. Through technological refinement and increased operator experience, complication rates have drastically reduced over the years; however, the development of post-operative conduction abnormalities, such as new left bundle branch block (LBBB) and higher degree conduction disturbances needing new permanent pacemaker implantation (PPI), have persisted as concerning complications[6]. While some studies showed no prognostic impact, recent investigations have attributed an increased risk of mortality or impaired recovery of left ventricular (LV) function[7-9] to LBBB and PPI.

Rates of new LBBB and PPI differ considerably between transcatheter heart valves (THV); yet, to date, randomised comparative evidence remains scarce. The SecOnd-generation seLf-expandable Versus Balloon-expandable Valves and gEneral Versus Local Anesthesia in TAVI (SOLVE-TAVI) randomised trial showed a trend towards higher PPI rates in recipients of the CoreValve Evolut R (Medtronic) versus the SAPIEN 3 (Edwards Lifesciences)[10], while the SCOPE I randomised trial showed similar PPI rates between the SAPIEN 3 and the ACURATE *neo* (Boston Scientific) THV[11]. The SCOPE 2 randomised trial was designed to compare the performance of the ACURATE *neo* and the CoreValve Evolut R THV and was appropriately powered to detect a difference in PPI rates among these THV at 30 days. The ACURATE *neo* THV was reported to have exhibited significantly lower PPI rates as compared to the CoreValve Evolut THV in this trial[12].

Despite the existence of registry-based attempts to identify the predictors of new PPI and conduction disturbances after TAVR with the ACURATE *neo* and the CoreValve Evolut THV[13-15], solid evidence from prospective randomised controlled data with centrally adjudicated outcomes has remained an unmet clinical need.

In this non-prespecified subanalysis of the SCOPE 2 randomised trial, we aimed to i) assess independent predictors of new PPI after TAVR, focusing on clinical baseline characteristics, computed tomography (CT)-assessed valve morphology and pre-existing electrocardiographic variables; ii) assess whether newly developed conduction abnormalities resolve or persist from discharge to follow-up at 30 days and 1 year; iii) establish whether new LBBB or PPI after TAVR have an impact on mortality at 1 year between 2 contemporary self-expanding THV prostheses.

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Methods

STUDY DESIGN AND DEFINITION OF ENDPOINTS

The SCOPE 2 trial was a multicentre, randomised, parallel design, non-inferiority, open-label trial conducted at 23 high-volume heart valve centres in Europe. Details of the trial design and study population have been previously described[12]. In short, eligible patients were randomly assigned in a 1:1 ratio to undergo TAVR with either the ACURATE *neo* THV or the CoreValve Evolut R THV and its later iterations. The primary endpoint was a composite of all-cause death or any stroke at 1 year powered for non-inferiority of the ACURATE *neo* THV, which was not met (absolute risk difference 1.8%, upper 1-sided 95% confidence limit: 6.1%; p=0.0549 for non-inferiority). The prespecified and powered key secondary endpoint was new PPI at 30 days. Additional secondary endpoints included the components of the primary endpoint at 30 days and 1 year, as well as, among others, the incidence of new LBBB. Endpoints were defined according to the Valve Academic Research Consortium 2[16] and an independent clinical events committee (Cardiovascular European Research Center [CERC], Massy, France) adjudicated all endpoint-related adverse events. All follow-up echocardiograms were assessed by an independent core laboratory (CERC).

For the purpose of this subanalysis from the SCOPE 2 trial, which was designed to specifically identify the predictors of new conduction abnormalities and PPI, an as-treated population from the SCOPE 2 database was adopted, considering the treatment actually received by the participants, regardless of their adherence to the randomisation assignment. Unlike the original analyses, which applied intention-to-treat (ITT) and per-protocol populations, the as-treated population was adopted to specifically evaluate THV-dependent endpoints. Furthermore, only patients who survived at 30 days or with known pacemaker status at 30 days were included and 2 study populations were defined: (i) to analyse the incidence and impact of new PPI at 30 days, patients with prior pacemakers were excluded, resulting in the designated PPI 30 cohort; and (ii) to analyse the incidence and impact of novel LBBB after TAVR, patients with missing or uninterpretable electrocardiogram (ECG) at baseline, discharge or 30 days, as well as patients with prior LBBB, were excluded. The remaining patients became the designated LBBB 30 cohort. A detailed study flow chart is depicted in **Figure 1**. New persistent LBBB at 30 days was defined as new-onset LBBB after TAVR, which persisted up to 30 days, while LBBB resolution on ECG at 30 days was considered transient LBBB. Annular eccentricity was assumed for an eccentricity index (EI) >0.25, calculated as: 1 − minimum diameter/maximum diameter[17,18].

Follow-up was conducted up to 1 year after TAVR and included the assessment of all-cause mortality, development of New York Heart Association (NYHA) Functional Class and left ventricular (LV) function on echocardiography. Approval from an appropriately constituted competent ethics committee was sought at each site, and the study conduct complied with the Declaration of Helsinki.

STATISTICAL ANALYSIS

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR), and were compared using the Student's t-test or the Mann-Whitney U test,

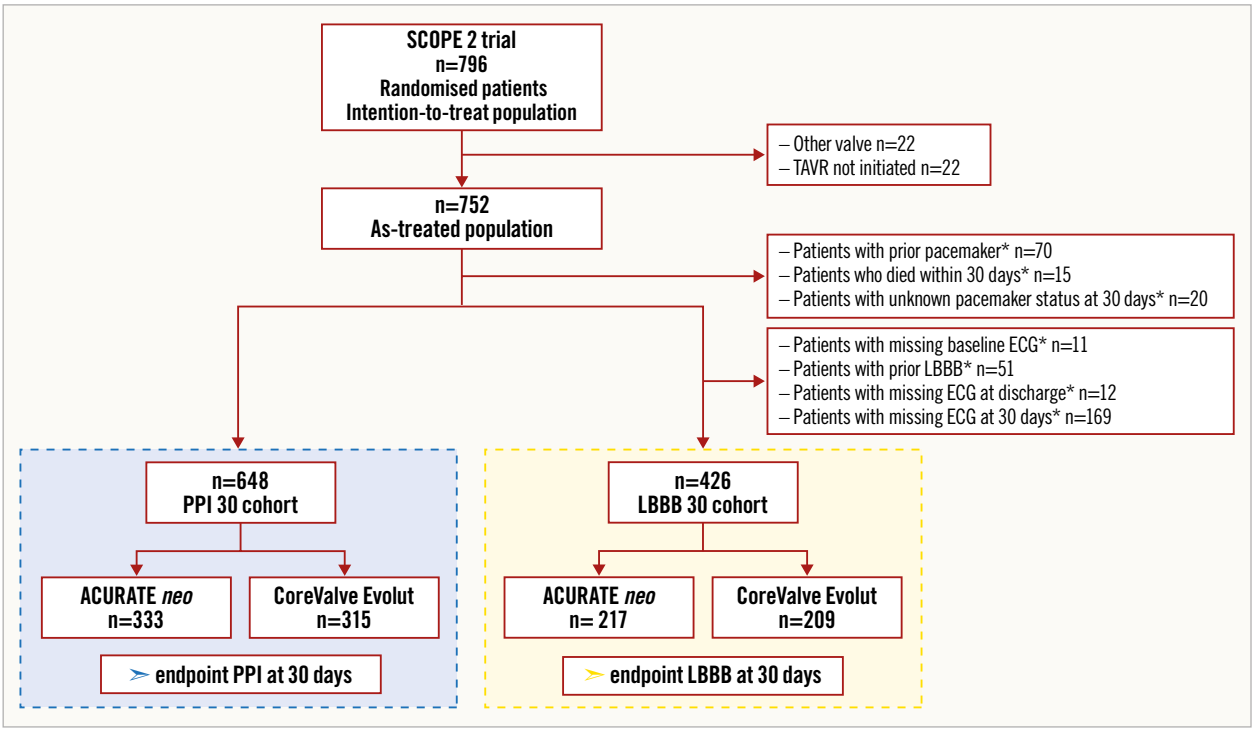

Figure 1. *Study flow chart. Study flow chart showing exclusion criteria and the two adopted patient cohorts. *multiple events possible. ECG: electrocardiogram; LBBB: left bundle branch block; PPI: permanent pacemaker implantation; TAVR: transcatheter aortic valve replacement*

respectively. Categorical and ordinal variables are expressed as frequencies and proportions and were compared using the chi-square or Fisher's exact tests. Nominal logistic regression with the computation of odds ratios (OR) and 95% confidence intervals (CI) was used to assess the association between the type of THV and need for PPI at 30 days. To avoid overfitting, the selection of covariates in the multivariable regression model was performed using the least absolute shrinkage and selection operator regression method after entering baseline and procedural characteristics with a potential effect on outcome as candidates. These included the use of the ACURATE *neo* THV, the logistic EuroSCORE, history of atrial fibrillation, complete right bundle branch block (RBBB) and LBBB at baseline, moderate-to-severe aortic valve and left ventricular outflow tract (LVOT) calcification, as well as pre- and post-dilatation. Observations with missing data were excluded. As an additional sensitivity analysis, the association between the type of THV and need for PPI at 30 days was analysed in the ITT population, as well as in a "modified PPI 30 cohort". The latter included patients who died within 30 days (n=662). To explore the effect of THV on PPI at 30 days in subsets of patients, subgroup analyses were performed for patients with pre-existing RBBB, history of atrial fibrillation, small aortic annuli (defined as annulus perimeter ≤72 mm), eccentric annuli (defined as EI >0.25) and based on aortic valve and LVOT calcification (none/mild vs ≥moderate). For patients with known clinical status at 30 days, Kaplan-Meier survival curves, according to LBBB and PPI at 30 days, were computed for all-cause mortality during 1-year follow-up. A comparison of cumulative event rates between these groups was performed by the log-rank test. For the comparison of LV function during follow-up the Wilcoxon matched-pairs signed-rank test was applied.

A 2-sided p-value of <0.05 was considered statistically significant for all analyses. IBM SPSS Statistics (Version 27.0.1.0; IBM), JMP Version 13.0 software (SAS) and R (Version 4.0.3; The R Foundation) were used for statistical analyses.

Results

PATIENT POPULATION

A total of 796 patients were enrolled in the SCOPE 2 trial, 398 of which were allocated to the ACURATE *neo* and 398 to the CoreValve Evolut THV. Applying the above-mentioned exclusion criteria (detailed in **Figure 1**), 648 patients formed the PPI 30 cohort, 333 of which were treated with the ACURATE *neo* and 315 with the CoreValve Evolut THV. Furthermore, 426 patients formed the LBBB 30 cohort, 217 and 209 of which were treated with the ACURATE *neo* and the CoreValve Evolut THV, respectively.

PERMANENT PACEMAKER IMPLANTATION - PREDICTORS AND IMPACT ON OUTCOME

Overall, 16.5% (107/648) of patients required a PPI at 30 days, 72.9% of which were implanted within 3 days from the TAVR procedure, while only 3 patients required PPI between 30 days and 1 year. A total of 79.4% of patients who required PPI at 30 days had a dual chamber device implanted, 17.8% had a single chamber

device and 1.9% had a biventricular device (0.9% unknown). The indication for PPI at 30 days was a Mobitz type II atrioventricular (AV) block or a Mobitz type III AV block in the vast majority of patients, showing no significant difference between the ACURATE *neo* and CoreValve Evolut recipients (78.0% vs 75.8%; p=0.785). Infrequent indications, comprising LBBB, first degree atrioventricular block (AV block I) etc., are reported in **Supplementary Table 1**. Baseline characteristics of the PPI 30 cohort according to the implanted THV are depicted in **Supplementary Table 2** and showed no significant differences, except for a higher rate of AV block I and larger aortic annulus perimeter for patients receiving the ACURATE *neo* compared to the CoreValve Evolut THV. Baseline characteristics according to need for PPI at 30 days are shown in **Table 1**: the only differences were higher rates of RBBB and moderate to severe aortic valve calcification, as well as lower rates of LBBB in patients who required PPI at 30 days. Pre- and post-dilatation strategy did not differ between patients with or without PPI at 30 days **(Table 1)**.

The crude rate of new PPI at 30 days was 12.3% (41/333) with the ACURATE *neo* THV, which was significantly lower than with the CoreValve Evolut THV (21.0% [66/315]; p=0.004) **(Central illustration)**. In a multivariable model, RBBB was associated with an increased risk (OR 6.11, 95% CI: 3.19-11.73; p<0.001) and use of the ACURATE *neo* with a decreased risk of PPI at 30 days (OR 0.50, 95% CI: 0.31-0.81; p=0.005) **(Supplementary Table 3, Figure 2)**. A sensitivity analysis of the multivariable model in the ITT population confirmed RBBB to be associated with an increased risk (OR 4.63, 95% CI: 2.62-8.20; p<0.001) and use of the ACURATE *neo* with a decreased risk of PPI at 30 days (OR 0.56, 95% CI: 0.37-0.85; p=0.006) **(Supplementary Table 4, Figure 2)**. Similar findings were obtained in the multivariable model of the "modified PPI 30 cohort", where RBBB was associated with increased risk (OR 4.75, 95% CI: 2.59–8.72; p<0.001) and use of the ACURATE *neo* was associated with decreased risk of PPI at 30 days (OR 0.63, 95% CI: 0.41-0.96; p=0.002) **(Supplementary Table 5, Figure 2)**.There was no significant interaction of the effect of THV on PPI at 30 days across subgroups of pre-existing RBBB ($p_{interaction}$=0.447), history of atrial fibrillation ($p_{interaction}$=0.310), small aortic annuli ($p_{interaction}$=0.105), eccentric annuli ($p_{interaction}$=0.439) and aortic valve ($p_{interaction}$=0.145) and LVOT calcification ($p_{interaction}$=0.702) **(Supplementary Figure 1)**.

There was no significant association between new PPI at 30 days and the clinical outcome at 1 year: neither for all-cause mortality (7 [7.2%] vs 42 [8.1%]; log-rank=0.775) **(Figure 3A)**, nor symptomatic benefit in terms of NYHA Functional Class **(Supplementary Figure 2A)**. While LV function significantly improved after TAVR, there was no difference at 30 days and 1 year between patients with or without PPI at 30 days **(Supplementary Figure 3A)**.

NEW LEFT BUNDLE BRANCH BLOCK – DEVELOPMENT AND IMPACT ON OUTCOME

Overall, 16.9% (72/426) of patients developed post-operative LBBB, which persisted in only 9.4% (40/426) at 30 days **(Figure 4)**.

Table 1. Baseline characteristics of the PPI 30 cohort according to the need for PPI at 30 days.

	PPI 30 – n=541	PPI 30 + n=107	*p*-value
Baseline characteristics			
Age, years	83.2±4.3	82.7±3.8	0.258
Female gender	381 (70.4)	76 (71.0)	0.901
Body mass index, kg/m^2	27.1±5.0	27.6±5.2	0.297
NYHA Class III or IV	345 (63.8)	62 (57.9)	0.255
EuroSCORE I, %	11 [8-15] (n=512)	11 [8-15] (n=101)	0.369
STS score, %	4 [3-5] (n=531)	4 [3-6] (n=105)	0.139
Diabetes mellitus	144 (26.6)	28 (16.3)	0.923
Hypercholesterolaemia	270 (49.9)	59 (55.1)	0.323
Arterial hypertension	462 (85.4)	89 (83.2)	0.556
Coronary artery disease	207 (38.3)	43 (40.2)	0.709
Previous myocardial infarction	35 (6.5)	11 (10.3)	0.161
Peripheral artery disease	47 (8.7)	11 (10.3)	0.598
COPD	62 (11.5)	10 (9.3)	0.525
ECG			
History of atrial fibrillation	167 (30.9)	39 (36.4)	0.257
Bradycardia, beats/min	97/529 (18.3)	21/105 (20.0)	0.689
First degree atrioventricular block	69/535 (12.9)	15/107 (14.0)	0.753
Left bundle branch block	48/530 (9.1)	3/107 (2.8)	0.030
Right bundle branch block	27/530 (5.1)	25/107 (23.4)	<0.001
QRS duration, ms	100.02±23.19 (n=518)	107.53±27.27 (n=103)	0.004
MSCT			
Aortic annulus area, mm^2	426.69±162.00 (n=521)	422.70±54.00 (n=99)	0.809
Aortic annulus perimeter, mm	73.7±4.8 (n=506)	73.8±4.8 (n=99)	0.801
Moderate and severe aortic calcification	375/533 (70.4)	84/105 (80.0)	0.044
Moderate and severe LVOT calcification	77/533 (14.4)	22/104 (21.2)	0.084
Procedural characteristics			
Conscious sedation	469 (86.7)	93 (86.9)	0.950
Predilatation	326 (60.3)	63 (58.9)	0.790
Post-dilatation	222 (41.0)	42 (39.3)	0.732

All data are mean±standard deviation, median [interquartile range] or absolute number (percentage). P-values are derived from chi-square or Fisher's exact tests for categorical variables and Student's t-tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given. COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; LVOT: left ventricular outflow tract; MSCT: multislice computed tomography; NYHA: New York Heart Association; PPI: permanent pacemaker implantation; STS: Society of Thoracic Surgeons

The baseline characteristics of the LBBB 30 cohort according to the implanted THV are outlined in **Supplementary Table 6** and showed no significant difference, except for AV block I, larger aortic annulus anatomies and higher rates of pre-and post-dilatation for the ACURATE *neo* compared to the CoreValve Evolut THV.

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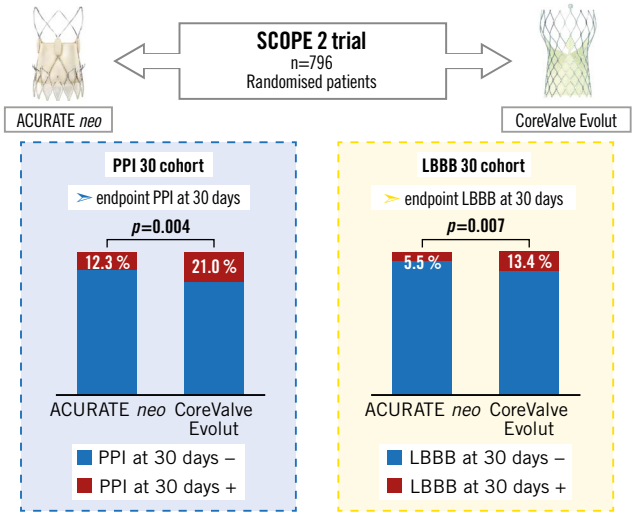
CENTRAL ILLUSTRATION A SCOPE 2 subanalysis – randomised comparison of pacemaker and LBBB in the ACURATE *neo* and CoreValve Evolut.



Comparison of the ACURATE neo and the CoreValve Evolut THV from the randomised SCOPE 2 trial, showing significantly lower rates of permanent pacemaker implantation and new-onset left bundle branch block at 30 days in ACURATE neo recipients. LBBB: left bundle branch block; PPI: permanent pacemaker implantation

Baseline and procedural characteristics according to new LBBB at 30 days are shown in **Table 2**: no significant differences were observed. In the univariable analysis, patients treated with the ACURATE *neo* showed significantly lower rates of new LBBB at 30 days compared to patients treated with the CoreValve Evolut THV (12 [5.5%] vs 28 [13.4%]; p=0.007) **(Central illustration)**.

Patients who developed new LBBB at 30 days showed similar all-cause mortality **(Figure 3B)** and symptomatic benefit in terms of NYHA Functional Class at 1 year **(Supplementary Figure 2B)**. LV function significantly improved after TAVR; however, LV function at 1 year was significantly lower in patients with new LBBB at 30 days compared to those without (65.7%±11.0 vs 69.1%±7.6; p=0.041) **(Supplementary Figure 3B)**.

Discussion

The results of this study can be summarised as follows: i) in an in-depth analysis of a randomised clinical trial, rates of new LBBB and new PPI at 30 days were significantly lower

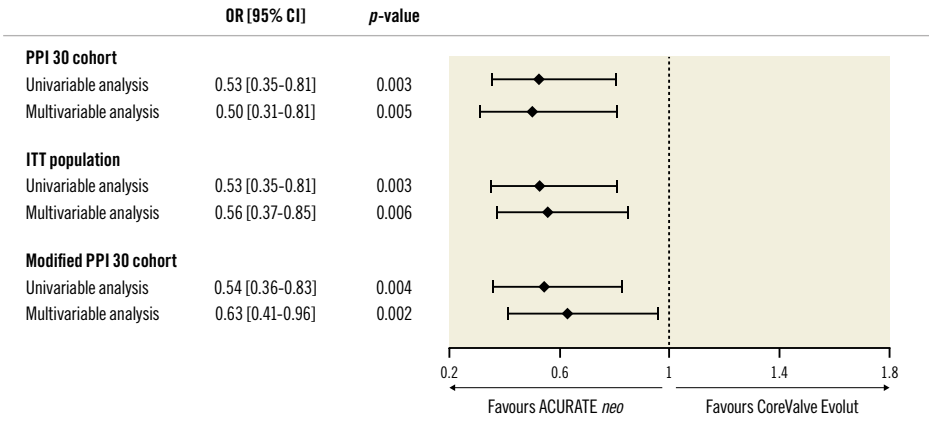


Figure 2. *Risk of PPI at 30 days according to THV in the designated PPI 30 cohort, in the ITT population and in the modified PPI 30 cohort. Risk of PPI at 30 days according to THV. CI: confidence interval; ITT: intention-to-treat population; OR: odds ratio; PPI: permanent pacemaker implantation*

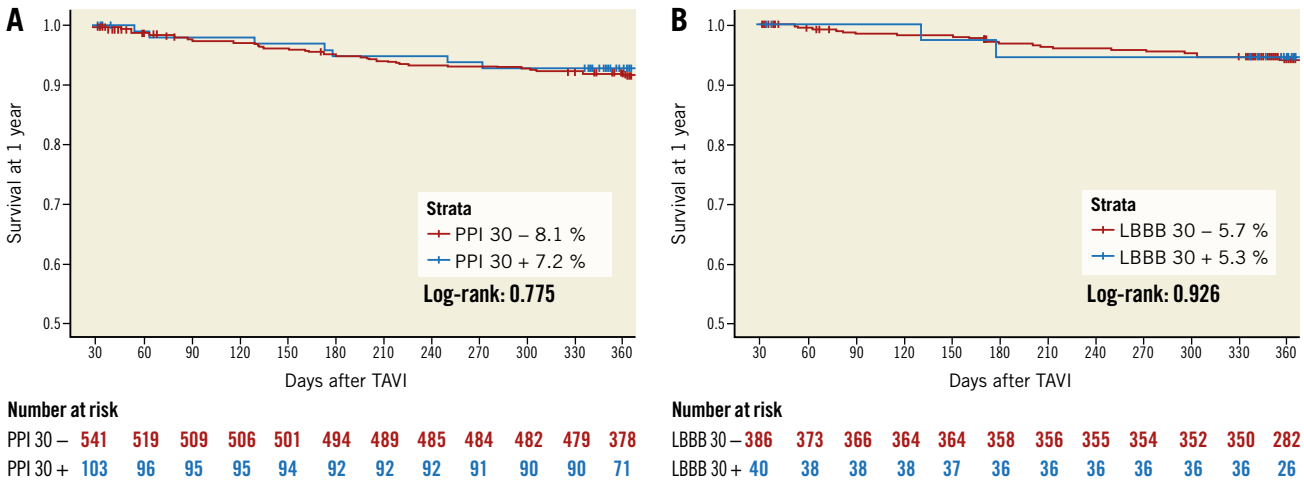


Figure 3. *Survival according to new PPI at 30 days and new LBBB at 30 days. Kaplan-Meier survival curves for all-cause mortality stratified for new PPI at 30 days (A) and new LBBB at 30 days (B). LBBB: left bundle branch block; PPI: permanent pacemaker implantation; TAVR: transcatheter aortic valve replacement*

in patients treated with the ACURATE *neo* compared to the CoreValve Evolut THV; ii) pre-existing RBBB was associated with an increased, and the use of the ACURATE *neo* THV with a decreased, risk of PPI at 30 days; iii) at 1-year follow-up, there was no difference in clinical outcome regarding all-cause mortality in patients with or without new LBBB and new PPI at 30 days, respectively; iv) new LBBB at 30 days was associated with reduced LV function at 1 year.

New conduction abnormalities and the need for PPI remain the most frequent complications after TAVR, despite improvements in THV technology and adapted implantation strategies[6]. While early randomised comparisons between THV showed higher rates of conduction abnormalities and pacemaker rates with self-expanding THV compared to balloon-expandable THV[18], more recent investigations showed favourable comparative results: use of the ACURATE *neo* THV led to comparable or even lower rates of PPI compared with balloon-expandable platforms, ranging from 2% to 10%[11,17,19]. In contrast, conduction disturbances leading to pacemaker implantation remained high with early-generation CoreValve and Evolut R devices, ranging from 17.4% to 25.9%[10,20,21]. However,

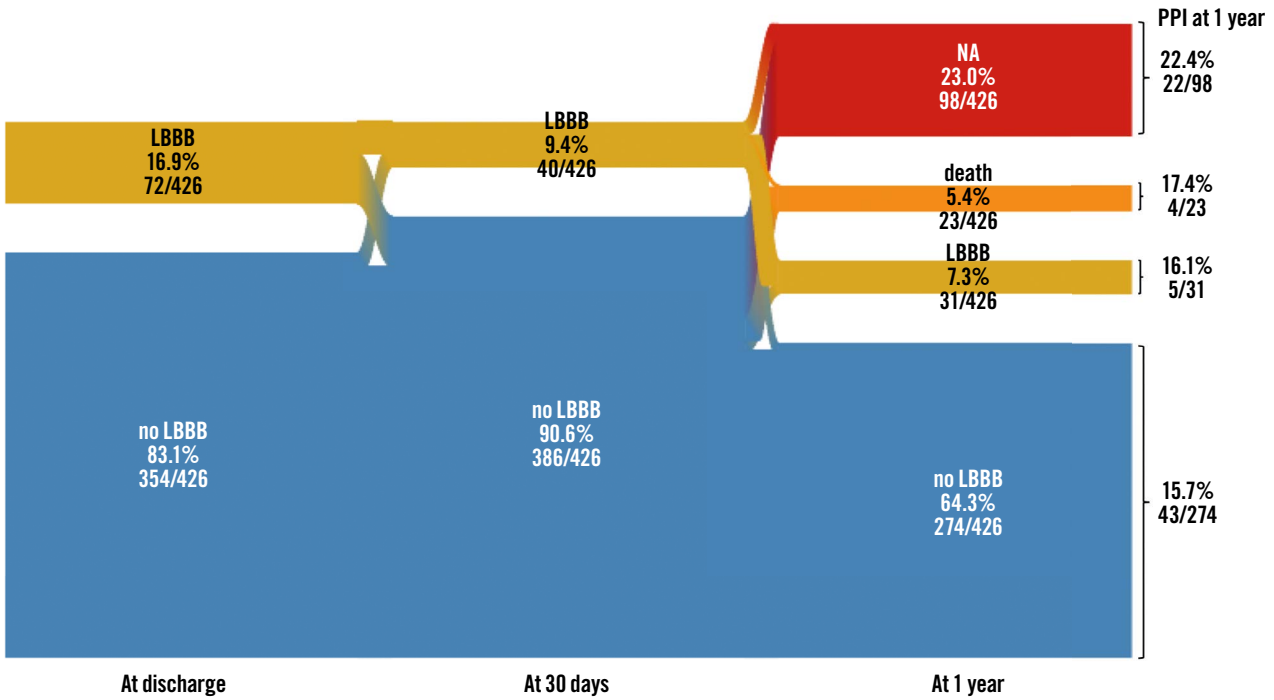


Figure 4. *Evolution of LBBB over time. River plots showing dynamic evolution of LBBB at discharge, 30 days and 1 year. LBBB: left bundle branch block; NA: not available; PPI: permanent pacemaker implantation*

Table 2. Baseline characteristics of the new LBBB 30 cohort according to the presence of new LBBB at 30 days.

	LBBB 30 – n=386	LBBB 30 + n=40	*p*-value
Baseline characteristics			
Age, years	82.7±4.1	84.0±4.3	0.077
Female gender	274 (71.0)	26 (65.0)	0.430
Body mass index, kg/m^2	27.2±5.0	26.6±4.7	0.471
NYHA Class III or IV	245 (63.5)	25 (62.5)	0.903
EuroSCORE I, %	11 [8-14] (n=360)	10 [8-15] (n=37)	0.500
STS score, %	3 [2-5] (n=376)	4 [3-6] (n=40)	0.067
Diabetes mellitus	98 (25.4)	9 (22.5)	0.688
Hypercholesterolaemia	186 (48.2)	14 (35.0)	0.112
Arterial hypertension	322 (83.4)	30 (75.0)	0.181
Coronary artery disease	152 (39.4)	14 (35.0)	0.589
Previous myocardial infarction	24 (6.2)	2 (5.0)	0.999
Peripheral artery disease	28 (7.9)	3 (7.5)	0.999
COPD	44 (11.4)	5 (12.5)	0.796
ECG			
History of atrial fibrillation	116 (30.1)	11 (27.5)	0.737
Bradycardia, beats/min	70/383 (18.3)	7/39 (17.9)	0.960
First degree atrioventricular block	54 (14.0)	8 (20.0)	0.305
QRS duration, ms	97.04±21.01 (n=376)	99.62±17.83 (n=39)	0.460
MSCT			
Aortic annulus area, mm^2	420.72±54.12 (n=372)	411.86±56.44 (n=38)	0.339
Aortic annulus perimeter, mm	73.7±4.8 (n=362)	73.0±5.1 (n=37)	0.370
Moderate and severe aortic calcification	286/384 (74.5)	29/39 (74.4)	0.987
Moderate and severe LVOT calcification	51/383 (13.3)	3/39 (7.7)	0.317
Procedural characteristics			
Conscious sedation	330 (85.5)	34 (85.0)	0.933
Predilatation	246 (63.7)	26 (65.0)	0.874
Post-dilatation	160 (41.5)	12 (30.0)	0.160

All data are mean±standard deviation, median [interquartile range] or absolute number (percentage). P-values are derived from chi-square or Fisher's exact tests for categorical variables and Student's t-tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given. COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; LBBB: left bundle branch block; LVOT: left ventricular outflow tract; MSCT: multislice computed tomography; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons

subsequent CoreValve Evolut THV iterations showed improved outcome following technological adjustment and adoption of a refined implantation strategy: indeed, early results from an interim analysis of the Optimize PRO Study (ClinicalTrials.gov: NCT04091048) showed lower pacemaker rates of 8.8% at 30 days with the newest CoreValve Evolut PRO and PRO+ THV (Grubb K. An Optimized TAVR Care Pathway Using Evolut PRO and PRO+ Early Results from the Optimize PRO Study, SCAI 2021).

The SCOPE 2 trial, the only contemporary randomised clinical trial comparing the ACURATE *neo* and the CoreValve Evolut THV, was powered to detect a difference in the key secondary endpoint of new PPI at 30 days, and the ACURATE *neo* THV was found to be superior, with an absolute reduction of 7.5% in the intention-to-treat population compared to the CoreValve Evolut THV[12]. In the current substudy, designed to specifically analyse conduction abnormalities with these platforms, we confirmed original findings regarding PPI at 30 days, with lower rates for the ACURATE *neo* THV, as well as finding significantly lower rates of new LBBB at 30 days with the ACURATE *neo* THV.

PERMANENT PACEMAKER IMPLANTATION – IMPACT ON OUTCOME

Controversial data exist on the consequence of new PPI after TAVR: while some studies failed to show an adverse impact on mortality[8,22], more recent analyses have consistently suggested impaired outcome with higher mortality and LV dysfunction[9,23]. In the current analysis we could not identify an association of new PPI with impaired outcome at 1 year. Possible explanations are an inadequately powered study population as well as insufficient follow-up. PPI induces ventricular dysfunction by right ventricular stimulation, which may occur after some time delay. Furthermore, no data were available on the stimulation rates in patients requiring new PPI, as right ventricular pacing >40% has been associated with a poor outcome[24]. Future analyses, set out to determine the need for initial PPI but also pacemaker dependency over time, are warranted to identify patients in which sustained right ventricular stimulation may lead to a worse outcome. Furthermore, the impact of the indication leading to PPI must be considered: while in the early TAVR experience, indication for PPI was liberal and generous, current practice has changed over the years and resulted in more restrictive indications for PPI after TAVR. The detrimental effects of PPI are related to foreign body-associated complications (i.e., infections) and long-term right ventricular pacing. A recent analysis comparing a liberal versus restrictive indication regimen for PPI showed that the restrictive cluster significantly reduced PPI rates after TAVR and led to a numerically, although not statistically, significant reduction in the composite of mortality and hospitalisation for heart failure at 3 years[25].

With the perspective of extending TAVR to lower risk and younger patients, it is paramount to reduce post-procedural PPI rates, especially in light of the expected longer survival. Against this background, THV selection should aim for the lowest possible complication rates and a THV choice tailored to patients' characteristics. In this analysis we found that the use of the ACURATE *neo* THV reduced the risk of new PPI at 30 days, promoting its use in patients at high risk for conduction abnormalities, such as those with pre-existing RBBB, one of the strongest PPI predictors in general[26,27]. However, potential benefits should always be weighed against possible downsides. Compared to the CoreValve Evolut, the ACURATE *neo* THV showed higher rates of moderate-to-severe paravalvular regurgitation, which should be taken into consideration. As new

iterations for both platforms, the ACURATE *neo*2 and the Evolut R PRO and PRO+, have recently become available, with refinements addressing previous shortcomings and adapted implantation techniques, new randomised clinical trials are warranted to corroborate the current findings. The DOUBLE-CHOICE randomised clinical trial (ClinicalTrials.gov: NCT05036018) is setting out to demonstrate non-inferiority of the ACURATE *neo*2 in comparison to the CoreValve Evolut PRO/PRO+ THV, and isolated local anaesthesia in comparison with local anaesthesia and conscious sedation, with respect to safety and efficacy in patients with severe symptomatic aortic stenosis undergoing TAVR.

NEW LEFT BUNDLE BRANCH BLOCK – DEVELOPMENT AND IMPACT ON OUTCOME

Development of new LBBB is the most common conduction abnormality after TAVR with incidences ranging from 6% to 77%[9,28]. Multiple factors may influence these varying rates; first and foremost, the choice of THV: rates around 10-13% were described with the ACURATE *neo* THV, 12%-22% for the SAPIEN 3 THV and 19%-34% for the CoreValve Evolut THV, while the highest rates up to 77% were described with the mechanically expanding Lotus (Boston Scientific) THV[15,28-30]. However, another critical aspect to consider is the dynamic development of new LBBB over time: in the immediate post-procedural phase, new LBBB rates of 85% to 94% were described, with almost half of them regressing at discharge or at 30 days (range 44% to 65%). In line with these findings, in the current analysis we found that 55% of new LBBB at discharge resolved at 30 days. It remains paramount to identify patients with persistent LBBB, to better characterise the underlying conduction disturbances, and to identify which of these patients are at risk of developing secondary complications. Indeed, a recent study from the PARTNER II trial showed that new LBBB was associated with increased all-cause and cardiovascular mortality, rehospitalisation, new pacemaker implantation and worsened LV function at 2 years following the TAVR procedure[7]. Similarly, a meta-analysis, which included >42,000 patients, confirmed an increased risk of all-cause death and rehospitalisation for heart failure at 1 year in patients with new LBBB[9]. The pathophysiological mechanism underlying this association is multifactorial: mechanical dyssynchrony caused by LBBB may lead to LV dysfunction and subsequent heart failure. Furthermore, the risk of LBBB degenerating into complete AV block and resulting in sudden cardiac death should be considered[9]. Lastly, electrical dyssynchrony caused by LBBB may promote fatal ventricular arrhythmias[7]. In our study, we found no association between new persistent LBBB and mortality or rehospitalisation; however, we detected reduced LV function compared to patients without LBBB. Possibly, LBBB-induced dyssynchrony and subsequently reduced ejection fraction demonstrate a cause-and-effect relationship, where longer follow-up is warranted to detect the impact on mortality.

Limitations

The findings of this study need to be interpreted in light of several limitations. Firstly, while the SCOPE 2 trial was powered to detect differences in pacemaker implantations, it was not powered to show differences with regard to individual clinical endpoints, such as new LBBB. Secondly, the participating centres had different levels of experience in the implantation of the ACURATE *neo* THV. In some countries the THV only became available with the participation in this study, possibly influencing the results. Furthermore, a limited clinical follow-up of 1 year and incomplete electrocardiographic and echocardiographic data during follow-up may preclude the identification of significant long-term outcomes, especially in light of the current analysis regarding the impact of new LBBB and PPI on mortality and LV function. Detailed information on THV delivery and implantation, in terms of implantation depth, recapturing and repositioning, which may have influenced the occurrence of LBBB and PPI, were not systematically collected. Information on ventricular pacing during follow-up was not available, thus precluding further analyses in this regard. The SCOPE 2 trial was not powered for the performed subgroup analyses; therefore, the results have to be considered carefully as hypothesis-generating statements.

Conclusions

In conclusion, in this in-depth analysis of the randomised SCOPE 2 clinical trial, we found that new conduction abnormalities and new PPI are significantly lower when using the ACURATE *neo* compared to the CoreValve Evolut THV. Right bundle branch block (increased risk) and use of the ACURATE *neo* (reduced risk) were the only independent predictors of PPI. Although no effect on mortality was determined for new PPI at 30 days, the development of new LBBB at 30 days was associated with reduced ejection fraction at 1 year.

Impact on daily practice

The development of post-operative new left bundle branch block (LBBB) and need for new permanent pacemaker implantations (PPI) persist as concerning complications after transcatheter aortic valve replacement with a possible adverse prognostic impact. In this comparison from a randomised clinical trial, we performed a dedicated analysis of the incidence and impact of new LBBB and PPI using 2 new-generation self-expanding devices, the ACURATE *neo* and the CoreValve Evolut. Both, LBBB and PPI rates were significantly lower in ACURATE *neo* compared to CoreValve Evolut recipients. Furthermore, use of the ACURATE *neo* was associated with a decreased risk of PPI. Besides reduced left ventricular function at 1 year in patients with new LBBB, no impact on mortality was found for patients with LBBB or PPI at 1 year.

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Guest editor

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Supplementary data

Supplementary Table 1. Indication for permanent pacemaker implantation at 30 days in the PPI 30 cohort according to implanted THV.

Supplementary Table 2. Baseline characteristics of the PPI 30 cohort according to implanted THV.

Supplementary Table 3. Multivariable analysis for the primary endpoint new PPI at 30 days.

Supplementary Table 4. Multivariable analysis for the primary endpoint new PPI at 30 days in the intention-to-treat population.

Supplementary Table 5. Multivariable analysis for the primary endpoint new PPI at 30 days in the "modified PPI 30 cohort"

Supplementary Table 6. Baseline and procedural characteristics of the new LBBB 30 cohort according to implanted THV.

Supplementary Figure 1. Risk of PPI at 30 days according to THV in specific subgroups.

Supplementary Figure 2. Evolution of NYHA Functional Class over time according to new PPI at 30 days and new LBBB at 30 days.

Supplementary Figure 3. Evolution of left ventricular function over time according to new PPI at 30 days and new LBBB at 30 days.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00558

Supplementary data

Supplementary Table 1. Indication for permanent pacemaker implantation at 30 days in the PPI 30 cohort according to implanted THV

	All Pacer at 30 days n=107	**ACURATE *Neo* n=41**	**CoreValve Evolut n=66**	**p-value**
AV-block II or III	82 (76.7)	32 (78.0)	50 (75.8)	0.785
AV-block I	9/107 (8.4)	3 (7.3)	6 (9.1)	0.999
Left bundle branch block	9/107 (8.4)	5 (12.2)	4 (6.1)	0.299
Other/unkonwn	7/107 (6.5)	1 (2.4)	6 (9.1)	0.247

All data are absolute numbers (percentage). P-values are derived from chi-square or Fisher's exact tests for categorical variables. AV-block: atrio-ventricular block.

Supplementary Table 2. Baseline characteristics of the PPI 30 cohort according to implanted THV

	ACURATE *neo* **n=333**	**CoreValve Evolut** **n=315**	**p-value**
Baseline characteristics			
Age, years	83.3±4.1	82.9±4.3	0.265
Female gender	229 (68.8)	228 (72.4)	0.313
Body mass index, kg/m^2	27.3±5.2	27.1±4.9	0.580
NYHA class III or IV	209 (62.8)	198 (62.9)	0.980
EuroScore I, %	11 [8-15] (n=318)	10 [8-15] (n=295)	0.886
STS Score, %	4 [3-5] (n=329)	4 [3-6] (n=307)	0.877
Diabetes mellitus	89 (26.7)	83 (26.3)	0.913
Hypercholesterolaemia	173 (52.0)	156 (49.5)	0.537
Arterial hypertension	291 (87.4)	260 (82.5)	0.084
Coronary artery disease	137 (41.1)	113 (35.9)	0.169
Previous myocardial infarction	26 (7.8)	20 (6.3)	0.470
Peripheral artery disease	26 (7.8)	32 (10.2)	0.295
COPD	33 (9.9)	39 (12.4)	0.317
ECG			
History of atrial fibrillation	104 (31.2)	102 (32.4)	0.753
Bradycardia, beats/min	61/326 (18.7)	57/308 (18.5)	0.947
First degree atrio-ventricular block	59/330 (17.9)	25/312 (8.0)	**<0.001**
Left bundle branch block	27/332 (8.2)	24/309 (7.8)	0.829
Right bundle branch block	27/328 (8.2)	25/309 (8.1)	0.948
QRS duration (ms)	101.67±24.67 (n=320)	100.84 ±23.41 (n=301)	0.670
MSCT			
Aortic annulus area, mm^2	426.41±53.56 (n=319)	425.67±208.34 (n=301)	0.951
Aortic annulus perimeter, mm	74.24±4.76 (n=315)	73.15±4.78 (n=290)	**0.005**
Moderate and severe aortic calcification	236/327 (72.2)	223/311 (35.0)	0.896
Moderate and severe LVOT calcification	50/326 (15.3)	49/311 (15.8)	0.884

Procedural characteristics

Conscious sedation	289 (86.8)	273 (86.7)	0.964
Pre-dilatation	262 (78.7)	127 (40.3)	**<0.001**
Post-dilatation	152 (45.6)	112 (35.6)	**0.009**

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P-values are derived from chi-square or Fisher's exact tests for categorical variables and Student's t-tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given. COPD: chronic obstructive pulmonary disease; LVOT: left ventricular outflow tract; MSCT: multi-slice computed tomography; NYHA: New York Heart Association Functional Class; PPI: permanent pacemaker implantation; STS score: Score of the Society of Thoracic Surgeons.

Supplementary Table 3. Multivariable analysis for the primary endpoint new PPI at 30 days in the PPI 30 cohort

	Odds ratio	**95% Confidence interval**	**p-value**
Use of ACURATE *neo*	0.50	[0.31 - 0.81]	**0.005**
Right bundle branch block	6.11	[3.19 - 11.73]	**<0.001**
Left bundle branch block	0.43	[0.91 - 1.16]	0.095
Moderate to severe aortic calcification	1.60	[0.91 - 2.80]	0.103
Moderate to severe LVOT calcification	1.30	[0.71 - 2.37]	0.397
Predilatation	1.26	[0.78 - 2.05]	0.348

Logistic regression with computation of odds ratios (OR) and 95% confidence intervals (CI) was computed. For details, refer to method section. LVOT: left ventricular outflow tract.

Supplementary Table 4. Multivariable analysis for the primary endpoint new PPI at 30 days in the intention-to-treat population

	Odds ratio	**95% Confidence interval**	**p-value**
Use of ACURATE *neo*	0.56	[0.37 - 0.85]	**0.006**
Right bundle branch block	4.63	[2.62 – 8.20]	**<0.001**
Left bundle branch block	0.58	[0.24 - 1.37]	0.214
Moderate to severe aortic calcification	1.36	[0.82 - 2.23]	0.232
Moderate to severe LVOT calcification	1.25	[0.72 - 2.17]	0.436

Logistic regression with computation of odds ratios (OR) and 95% confidence intervals (CI) was computed. For details, refer to method section. LVOT, left ventricular outflow tract.

Supplementary Table 5. Multivariable analysis for the primary endpoint new PPI at 30 days in the "modified PPI 30 cohort"

	Odds ratio	**95% Confidence interval**	**p-value**
Use of ACURATE *neo*	0.63	[0.41 - 0.96]	**0.002**
Right bundle branch block	4.75	[2.59 – 8.72]	**<0.001**
Left bundle branch block	0.46	[0.19 - 1.13]	0.091
Moderate to severe aortic calcification	1.64	[0.97 - 2.79]	0.066
Moderate to severe LVOT calcification	1.18	[0.66 – 2.10]	0.248

Logistic regression with computation of odds ratios (OR) and 95% confidence intervals (CI) was computed. For details, refer to method section. LVOT, left ventricular outflow tract.

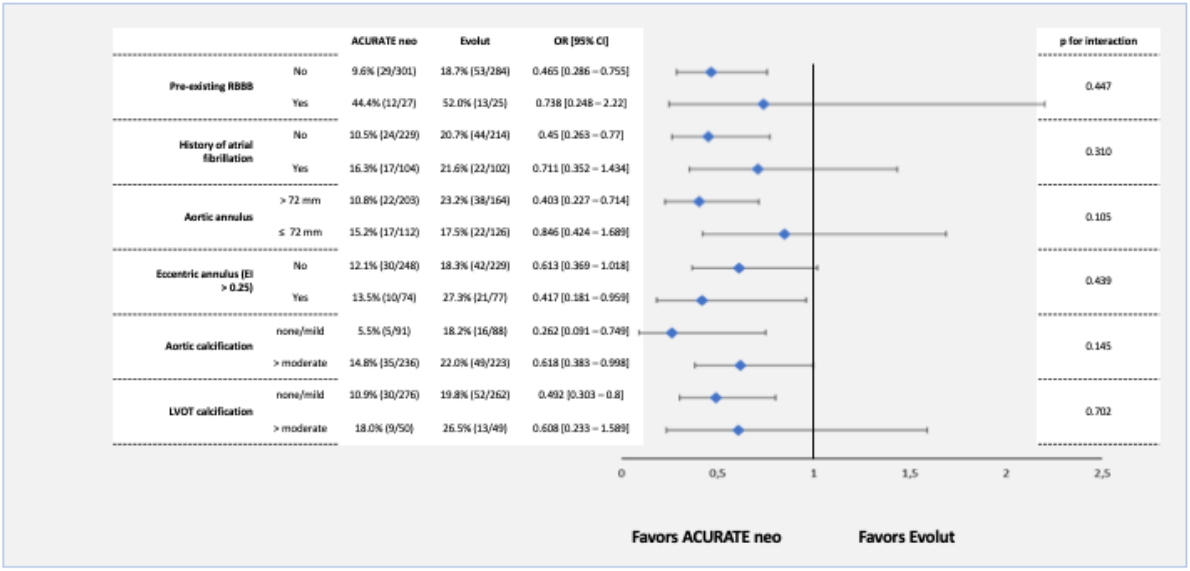
Supplementary Table 6. Baseline and procedural characteristics of the new LBBB 30 cohort according to implanted THV

	ACURATE *Neo* **n=217**	**CoreValve Evolut** **n=209**	**p-value**
Baseline characteristics			
Age, years	83.1±4.1	82.7±4.1	0.281
Female gender	147 (67.7)	153 (73.2)	0.217
Body mass index, kg/m^2	27.3±5.1	27.0±4.9	0.531
NYHA class III or IV	139 (64.1)	131 (62.7)	0.768
EuroScore I, %	11 [8 - 14] (n=204)	11 [8 - 14] (n=193)	0.813
STS Score, %	3 [2 -5] (n=214)	4 [3 - 5] (n=202)	0.925
Diabetes mellitus	55 (25.3)	52 (24.9)	0.912
Hypercholesterolaemia	99 (45.6)	101 (48.3)	0.576
Arterial hypertension	185 (85.3)	167 (79.9)	0.145
Coronary artery disease	92 (42.4)	74 (35.4)	0.139
Previous myocardial infarction	16 (7.4)	10 (4.8)	0.265
Peripheral artery disease	13 (6.0)	18 (8.6)	0.298
COPD	23 (10.6)	26 (12.4)	0.552
ECG			
History of atrial fibrillation	64 (29.5)	63 (30.1)	0.883
Bradycardia, beats/min	38/214 (17.8)	39/208 (18.8)	0.792
First degree atrio-ventricular block	43 (19.8)	19 (9.1)	**0.002**
QRS duration (ms)	96.83±21.56 (n=211)	97.75 ±19.87 (n=204)	0.653
MSCT			
Aortic annulus area, mm^2	428.24±51.94 (n=209)	411.22±55.52 (n=201)	**0.001**
Aortic annulus perimeter, mm	74.33±4.81 (n=205)	72.93±4.80 (n=194)	**0.004**
Moderate and severe aortic calcification	161/214 (75.2)	154/209 (73.7)	0.715
Moderate and severe LVOT calcification	25/213 (11.7)	29 (13.9)	0.511
Procedural characteristics			
Conscious sedation	185 (85.3)	179 (85.6)	0.909

Pre-dilatation	184 (84.8)	88 (42.1)	**<0.001**
Post-dilatation	98 (45.2)	74 (35.4)	**0.040**

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P-values are derived from chi-square or Fisher's exact tests for categorical variables and Student's t-tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given. COPD: chronic obstructive pulmonary disease; LVOT: left ventricular outflow tract; MSCT: Multi-Slice Computed tomography; NYHA: New York Heart Association functional class; PPI: permanent pacemaker implantation; STS score: Score of the Society of Thoracic Surgeons.

Supplementary Figure 1

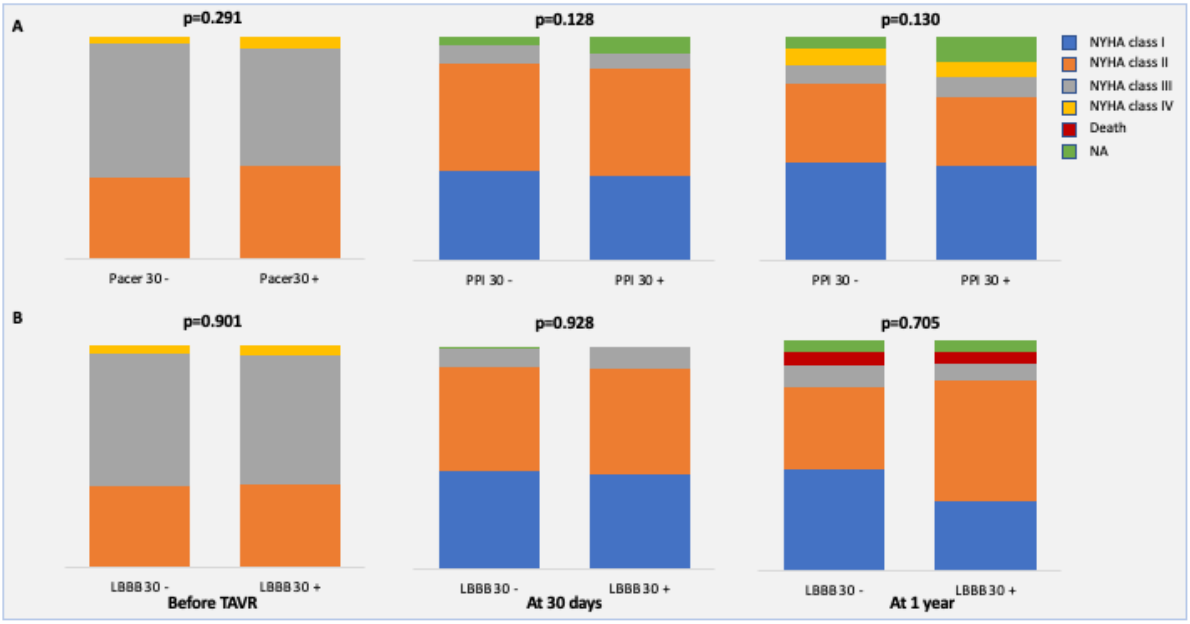


Supplementary Figure 1: Risk of PPI at 30 days according to THV in specific subgroups

Rates and odds ratios for PPI according to use of ACURATE *neo* or Evolut in specific subgroups.

CI: confidence interval; EI: Eccentricity index; LVOT: left ventricular outflow tract; OR: Odds ratio; RBBB: right bundle branch block.

Supplementary Figure 2

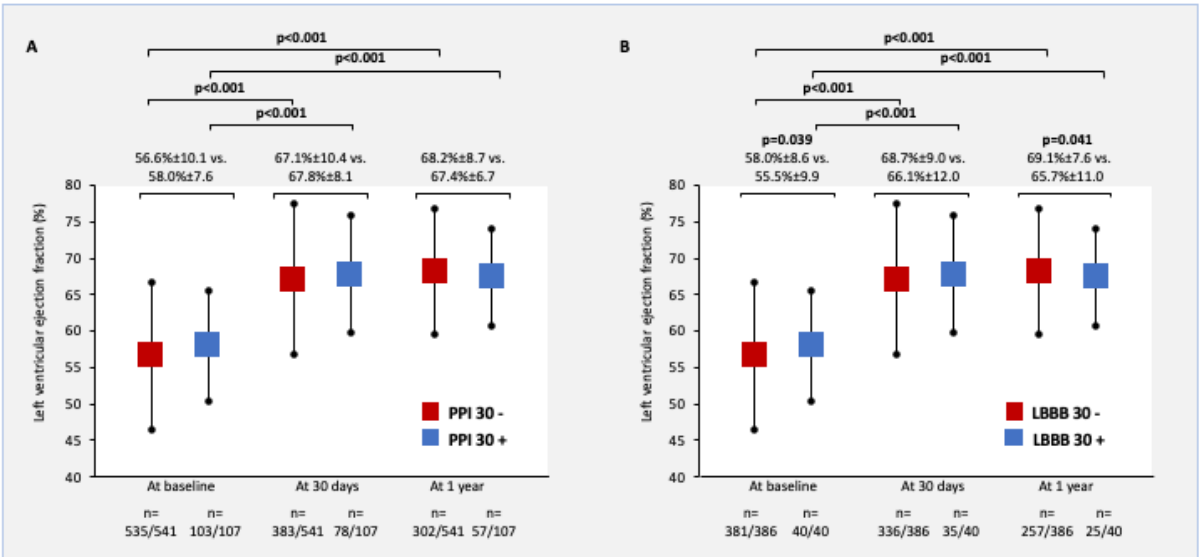


Supplementary Figure 2: Evolution of NYHA Functional Class over time according to new PPI at 30 days and new LBBB at 30 days.

A) new PPI at 30 days and B) new LBBB at 30 days.

LBBB: left bundle branch block; NA: not available; NYHA: New York Heart Association Functional Class; PPI: permanent pacemaker implantation; TAVR: transcatheter aortic valve replacement.

Supplementary Figure 3



Supplementary Figure 3: Evolution of left ventricular function over time according to new PPI at 30 days and new LBBB at 30 days

A) new PPI at 30 days and B) new LBBB at 30 days. Only significant p-values shown.

LBBB: left bundle branch block; PPI: permanent pacemaker implantation.