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Permanent pacemaker implantation and left bundle branch block with self-expanding valves - a SCOPE 2 sub-analysis
Short title: Sub-analysis SCOPE 2 – Pacemaker and LBBB

Costanza Pellegrini, MD[1], Philippe Garot[2], MD, Marie-Claude Morice[2], MD, Corrado Tamburino[3], MD, PhD, Sabine Bleiziffer[4], MD, Holger Thiele[5], MD, Smita Scholtz[6], MD, Rene Schramm[4], MD, PhD, James Cockburn[7], MD, Michael Cunnington[8], MD, Alexander Wolf [9], MD, Marco Barbanti[10], MD, Didier Tchetché[11], MD, Paolo Pagnotta[12], MD, Martine Gilard[13], MD, Francesco Bedogni[14], MD, Eric Van Belle[15], MD, Mariuca Vasa-Nicotera[16], MD, Alaide Chieffo[17], MD, Kris Bogaerts[18], PhD, Christian Hengstenberg[19], MD, Davide Capodanno[3], MD, PhD, Michael Joner, MD[1,20]

1. Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technical University Munich, Germany
2. Institut Cardiovasculaire Paris-Sud, Hôpital Privé Jacques Cartier, Ramsay-Santé, Massy, France
3. Division of Cardiology Azienda Ospedaliera Universitaria "Policlinico-Vittorio Emanuele" University of Catania, Catania, Italy
4. Department of Thoracic and Cardiovascular Surgery, Heart-and Diabetes Center North Rhine-Westphalia, University Hospital, Ruhr-University Bochum, Bad Oeynhausen, Germany
5. Department of Cardiology, Heart Center Leipzig at University of Leipzig, Germany
6. Department of interventional Cardiology, Heart-and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany
7. Department of Cardiology, Brighton & Sussex University Hospitals NHS Trust, Brighton, United Kingdom
8. Department of Cardiology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
9. Department of Interventional Cardiology, Elisabeth Hospital Essen, Essen, Germany
10. Department of cardio-thoracic-vascular diseases and transplantation, Azienda Ospedaliero-Universitaria Policlinico “G. Rodolico-San Marco”, Catania, Italy
11. Groupe CardioVasculaire Interventionnel, Clinique Pasteur, Toulouse, France
12. Department of Cardiovascular Medicine, Humanitas Clinical and Research Center, Milano, Italy
13. Department of Cardiology, Brest University Hospital, Brest, France
14. Cardiology Department, IRCCS Policlinico San Donato, Milano, Italy
15. Department of Cardiology, University Hospital, Lille, France
16. Department of Cardiology, Goethe University Hospital Frankfurt, Frankfurt am Main, Germany
17. Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
18. KU Leuven, Faculty of Medicine, I-BioStat, Leuven, Belgium and UHasselt, I-BioStat, Hasselt, Belgium
19. Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
20. Deutsches Zentrum für Herz- und Kreislauf-Forschung (DZHK) e.V. (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

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Address for correspondence:
Prof. Dr. med Michael Joner
Klinik für Herz- und Kreislauferkrankungen
Deutsches Herzzentrum München, Munich, Germany
Telephone number: +49-(0)89 1218-4587
E-mail: joner@dhm.mhn.de

Conflict of interest

C.T. has received speaker fees from Medtronic.
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M.C. has received speaker and consultant fees from Medtronic.
A.W. is a proctor for Boston Scientific, Edwards Lifesciences, and Medtronic.
M.B. has received consultant fees from Edwards Lifesciences.
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Abstract

Background

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

Aims

To assess incidence and impact of new LBBB and PPI with self-expanding prostheses from a powered randomized comparison.

Methods

From the SCOPE 2 trial, 648 patients without 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 Evolut compared to ACURATE neo recipients (21.0% vs. 12.3%; p=0.004). Previous right bundle branch block (OR 6.11, 95% CI [3.19 - 11.73]; p<0.001) was associated with increased risk, and use of the ACURATE neo (OR 0.50, 95% CI [0.31 - 0.81]; p=0.005) with decreased risk of PPI at 30 days. 1-year mortality was similar in patients with and without new PPI.

9.4% of patients developed persistent LBBB at 30 days, with higher incidences in 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 Evolut recipients. The ACURATE neo valve was associated with 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.

Key words

ACURATE neo, CoreValve Evolut, randomized clinical trial, pacemaker implantation, left bundle branch block

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) 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 operators‘ experience, complication rates were 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) persisted as concerning complications [6]. While some studies showed no prognostic impact, recent investigations attributed them an increased risk of mortality or impaired recovery of left ventricular (LV) function [7–9].

Rates of new LBBB and PPI differ considerably across transcatheter heart valves (THV); yet randomized comparative evidence remains scarce to date. The SOLVE-TAVI randomized trial showed a trend towards higher PPI rates in CoreValve Evolut R (Medtronic Inc, Minneapolis, MN) versus SAPIEN 3 (Edwards LifeSciences, Irvine, CA) recipients [10], while the SCOPE I randomized trial showed similar PPI rates between the SAPIEN 3 and the ACURATE neo THVs (Boston Scientific, Marlborough, MA) [11]. The SCOPE 2 randomized trial was designed to compare the performance of the ACURATE neo and the CoreValve Evolut R (Evolut) THVs and was appropriately powered to detect a difference in PPI rates among these THVs at 30 days. The ACURATE neo THV was reported to exhibit significantly lower PPI rates as compared to the Evolut THV in this trial [12].

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

In this non-pre-specified sub-analysis of the SCOPE 2 randomized trial we aimed to i) assess independent predictors of new PPI after TAVR, focusing on clinical baseline characteristics, 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 at 1 year; iii) to establish whether new LBBB or PPI after TAVR have an impact on mortality at 1 year amongst two contemporary self-expanding THV prostheses.

Methods

Study design and definition of endpoints

The SCOPE 2 trial was a multicentre, randomized, parallel design, noninferiority, 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 or the Evolut THV. The primary endpoint was a composite of all-cause death or any stroke at 1 year powered for noninferiority 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 noninferiority). 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 updated Valve Academic Research Consortium [16] and an independent clinical events committee (CERC, Cardiovascular European Research Center, 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 sub-analysis from the SCOPE 2 trial, designed to specifically identify 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 adherence to their randomization 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 two 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. (ii) further, to analyse the incidence and impact of novel LBBB after TAVR, patients with missing or uninterpretable ECG at baseline, discharge or 30 days, as well as patients with prior LBBB were excluded. The remaining patients resulted in 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 as transient LBBB. Annular eccentricity was assumed for an eccentricity index > 0.25, calculated as: 1 − minimum diameter/maximum diameter [17,18].

Follow-up was conducted up to 1 year after TAVR and included assessment of all-cause mortality, development of New York Heart Association (NYHA) functional class and 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 Student's t-test or the Mann-Whitney U test, respectively. Categorical and ordinal variables are expressed as frequencies and proportions and were compared using the chi-square or Fisher exact test. Nominal logistic regression with computation of odds ratios (OR) and 95% confidence intervals (CI) was used to assess the association between type of THV and need for PPI at 30 days. To avoid overfitting, 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 potential effect on outcome as candidates. These included use

of the ACURATE neo THV, 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 postdilatation. Observations with missing data were excluded. As additional sensitivity analysis association between type of THV and need for PPI at 30 days was analysed in the ITT population. 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 $\leq$ 72mm), eccentric annuli (defined as EI > 0.25) and based on aortic valve and LVOT calcification (none/mild vs. $\geq$ 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. Comparison of cumulative event rates between these groups was performed by log-rank test. For comparison of LV function during follow-up matched paired Wilcoxon 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, SPSS Inc. Chicago, IL), JMP Version 13.0 software (SAS, Cary, NC) and R (Version 4.0.3, The R Foundation, Vienna, Austria) 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 patients to the Evolut THV. Applying the above-mentioned exclusion criteria (depicted in Figure 1), 648 patients formed the PPI 30 cohort, 333 of which were treated with the ACURATE neo and 315 with the Evolut THV. Furthermore, 426 patients formed the LBBB 30 cohort, 217 and 209 of which were treated with the ACURATE neo and the Evolut THV, respectively.

Permanent pacemaker implantation - predictors and impact on outcome

Overall, 16.5% (107/648) 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 after 30 days up to 1 year. A total of 79.4% of patients who required PPI at 30 days were implanted a dual chamber device, 17.8% a single chamber device and 1.9% a biventricular device (0.9% unknown). The indication for PPI at 30 days was AV-block II° Mobitz or AV-block III° in the vast majority of patients, showing no significant difference between ACURATE neo and Evolut recipients (78.0% vs. 75.8%; p=0.785). Infrequent indications comprising LBBB, AV-block I° etc are reported in Supplemental Table 1. Baseline characteristics of the PPI 30 cohort according to implanted THV are depicted in Supplemental Table 2 and showed no significant differences, except for a higher rate of first degree atrio-ventricular block (AV-block I°) and larger aortic annulus perimeter for patients receiving the ACURATE neo compared to the Evolut THV. Baseline characteristics according to need of 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 Evolut THV (21.0% (66/315); p=0.004) (Central Illustration). In a multivariable model, RBBB was associated with increased risk (OR 6.11, 95% CI [3.19 - 11.73]; p<0.001) and use of the ACURATE neo with decreased risk of PPI at 30 days (OR 0.50, 95% CI [0.31 - 0.81]; p=0.005) (Supplemental Table 3, Figure 2). Sensitivity analysis of the multivariable model in the ITT population confirmed RBBB to be associated with increased risk (OR 4.63, 95% CI [2.62 – 8.20]; p<0.001) and use of the ACURATE neo with decreased risk of PPI at 30 days (OR 0.56, 95% CI [0.37 - 0.85]; p=0.006) (Supplemental Table 4, 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) (Supplemental Figure 1).

There was no significant association between new PPI at 30 days and clinical outcome at 1 year: neither 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 (Supplemental 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 (Supplemental Figure 3A).

New left bundle branch block - development and impact on outcome

Overall, 16.9% (72/426) of patients developed postoperative LBBB, which persisted in only 9.4% (40/426) at 30 days (Figure 4). Baseline characteristics of the LBBB 30 cohort according to implanted THV are depicted in Supplemental Table 5 and showed no significant difference, except for AV-block I°, larger aortic annulus anatomies and higher rates of pre-and postdilatation for the ACURATE neo compared to the Evolut THV. 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 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 (Supplemental 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) (Supplemental Figure 3B).

Discussion

The results of this study can be summarized as follows: i) in an in-depth analysis of a randomized clinical trial, rates of new LBBB and new PPI at 30 days were significantly lower in patients treated with the ACURATE neo compared to the Evolut THV; ii) pre-existing RBBB was associated with increased, and use of the ACURATE neo THV with 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 need for PPI remain the most frequent complications after TAVR, despite improvement in THV technology and adapted implantation strategies [6]. While early randomized comparisons between THVs showed higher rates of conduction abnormalities and pacemaker rates with self-expanding design THVs compared to balloon-expandable THVs [18], more recent investigations showed favourable comparative results: 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 with the CoreValve and the Evolut THVs remained high with early generation devices, ranging from 17.4% to 25.9% [10,20,21]. However, the subsequent 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 clinical Study (NCT04091048) showed lower pacemaker rates of 8.8% at 30 days with the newest Evolut PRO and PRO+ THVs (Grubb K: An Optimized TAVR Care Pathway Using Evolut PRO and PRO+ Early Results from the Optimize PRO Study, SCAI 2021 conference).

The SCOPE 2 trial, the only contemporary randomized clinical trial comparing the ACURATE neo and the Evolut THVs, was powered to detect a difference in the key secondary endpoint of new PPI at 30 days, and the ACURATE neo THV was found superior, with an absolute reduction of 7.5% in the intention-to-treat population compared to the Evolut THV [12]. In the current sub-study, 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 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 delayed in time. Furthermore, no data were available on stimulation rates in patients requiring new PPI, as right ventricular pacing >40% has been associated with 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 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 changed over the years and resulted in more restrictive indications for PPI after TAVR. 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 vs. 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 hospitalization for heart failure at 3 years [25].

With the perspective of extending TAVR to lower risk and younger patients, it is paramount to reduce postprocedural PPI rates, especially in light of the expected longer survival. Against this background, THV selection should aim to lowest possible complication rates and THV choice tailored to patients' characteristics. In this analysis we found that 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 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 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 neo2 and the Evolut R PRO and PRO+ recently became available, with refinements addressing previous shortcomings and adapted implantation techniques, new randomized clinical trials are warranted to corroborate the current findings. The DOUBLE-CHOICE randomized clinical trial (NCT05036018) is set out to demonstrate non-inferiority of the ACURATE neo2 in comparison to the Evolut Pro/Pro+ THVs 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% to 22% for the SAPIEN 3 THV and 19% to 34% for the Evolut THV, while the highest rates up to 77% were described with the mechanically expanding Lotus (Boston Scientific, Marlborough, MA) THV [15,28–30]. However, another critical aspect to consider is the dynamic development of new LBBB over time: in the immediate postprocedural 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 and better characterize underlying conduction disturbances, and which of these are at risk to develop 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 two years from the TAVR procedure [7]. Similarly, a meta-analysis including >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 with 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 impact on mortality.

Limitations

The findings of this study need to be interpreted in the 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, participating centres had different level of experience in the implantation of the ACURATE neo THV, as in some countries the THV only became available with the participation in this study, possibly influencing results. Furthermore, a limited clinical follow-up of 1 year and incomplete, electrocardiographic and echocardiographic data during follow-up may preclude identification of significant long-term outcomes, especially in light of the current analysis regarding impact of new LBB 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 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, thus results have to be considered carefully as hypothesis generating statements.

Conclusions

In conclusion, in this in-depth analysis of the randomized SCOPE 2 clinical trial, we found that new conduction abnormalities and new PPI are significantly lower when using the ACURATE

neo compared to the 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

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 possible adverse prognostic impact. In this comparison from a randomized clinical trial, we performed a dedicated analysis of incidence and impact of new LBBB and PPI in two new-generation self-expanding devices, the ACURATE neo and the CoreValve Evolut R. Both, LBBB and PPI rates were significantly lower in ACURATE neo compared to Evolut recipients. Further, use of the ACURATE neo was associated with 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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Figures

Figure 1

Title: Study flow chart

Legend: Study flow chart showing exclusion criteria and the two adopted patient cohorts. Abbreviations: ECG, electrocardiogram; LBBB, left bundle branch block; PPI, permanent pacemaker implantation; TAVR, transcatheter aortic valve replacement.

Central Illustration

Title: A SCOPE 2 Sub-analysis – randomized comparison of Pacemaker and LBBB in the ACURATE neo and Evolut R

Legend: Comparison of the ACURATE neo and the Evolut R THVs from the randomized 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. Device illustrations reproduced with permission from Boston Scientific and Medtronic GmbH. Abbreviations: LBBB, left bundle branch block; PPI, permanent pacemaker implantation.

Figure 2

Title: Risk of PPI at 30 days according to THV in the designated PPI 30 cohort and in the ITT population

Legend: Risk of PPI at 30 days according to THV. Abbreviations: CI, confidence interval; ITT, intention-to-treat population; OR, Odds ratio.

Figure 3

Title: Survival according to new PPI at 30 days (A) and new LBBB at 30 days (B)

Legend: Kaplan-Meier survival curves for all-cause mortality stratified for new PPI at 30 days (A) and new LBBB at 30 days (B).

Abbreviations: LBBB, left bundle branch block; PPI, permanent pacemaker implantation; TAVR, transcatheter aortic valve replacement.

Figure 4

Title: Evolution of LBBB over time

Legend: River plots showing dynamic evolution of LBBB at discharge, 30 days and 1 year.

Abbreviations: LBBB, left bundle branch block; NA, not available; PPI, permanent pacemaker implantation.

Tables

Table 1. Baseline characteristics of the PPI 30 cohort according to need of 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
Hypercholesterolemia	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 (10.03)	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 atrio-ventricular 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
Pre-dilatation	326 (60.3)	63 (58.9)	0.790
Post-dilatation	222 (41.0)	42 (39.3)	0.732

Abbreviations: 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.

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P values are derived from chi-square or Fisher exact tests for categorical variables and Student t tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given.

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

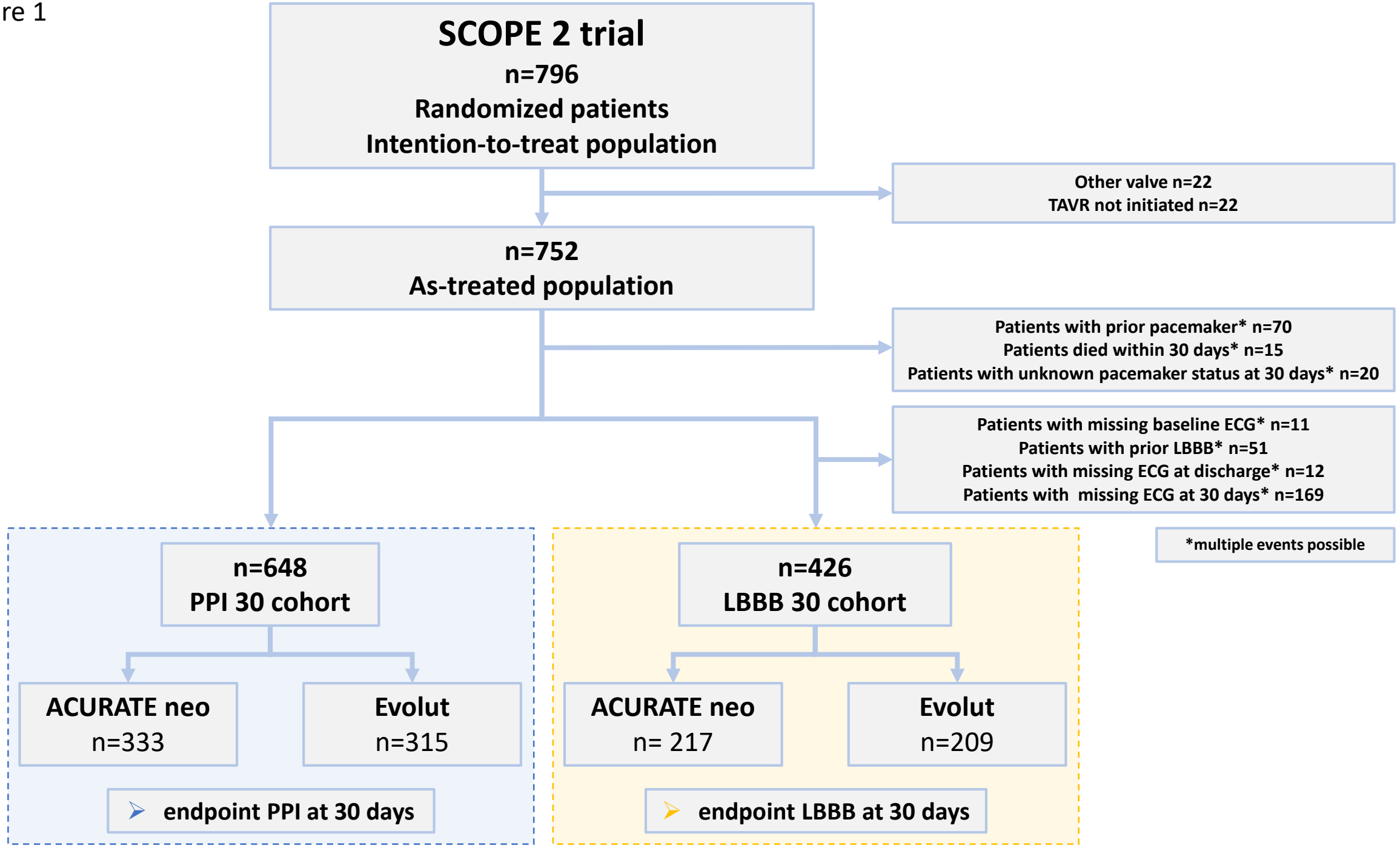
	LBBB 30 - n=386	LBBB 30 + n=40	p-value
Baseline characteristics			
Age, years	82.7±4.1	84.0±4.3	0.077
Female gender	274 (71.0)	26 (65.0)	0.430
Body mass index, kg/m^2	27.2±5.0	26.6±4.7	0.471
NYHA class III or IV	245 (63.5)	25 (62.5)	0.903
EuroScore I, %	11 [8-14] (n=360)	10 [8-15] (n=37)	0.500
STS Score, %	3 [2-5] (n=376)	4 [3-6] (n=40)	0.067
Diabetes mellitus	98 (25.4)	9 (22.5)	0.688
Hypercholesterolemia	186 (48.2)	14 (35.0)	0.112
Arterial hypertension	322 (83.4)	30 (75.0)	0.181
Coronary artery disease	152 (39.04)	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 atrio-ventricular 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
Pre-dilatation	246 (63.7)	26 (65.0)	0.874
Post-dilatation	160 (41.5)	12 (30.0)	0.160

Abbreviations: COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; LVOT, left ventricular outflow tract; MSCT, Multi-Slice Computed tomography; NYHA, New York Heart Association functional class; STS score, Score of the Society of Thoracic Surgeons.

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P values are derived from chi-square or Fisher exact tests for categorical variables and Student t tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given.

Figure 1


SCOPE 2 trial
n=796
Randomized patients
Intention-to-treat population
Other valve n=22
TAVR not initiated n=22
n=752
As-treated population
Patients with prior pacemaker* n=70
Patients died within 30 days* n=15
Patients with unknown pacemaker status at 30 days* n=20
Patients with missing baseline ECG* n=11
Patients with prior LBBB* n=51
Patients with missing ECG at discharge* n=12
Patients with missing ECG at 30 days* n=169
*multiple events possible
n=648
PPI 30 cohort
ACURATE neo
n=333
Evolut
n=315
endpoint PPI at 30 days
n=426
LBBB 30 cohort
ACURATE neo
n= 217
Evolut
n=209
endpoint LBBB at 30 days

Central Illustration

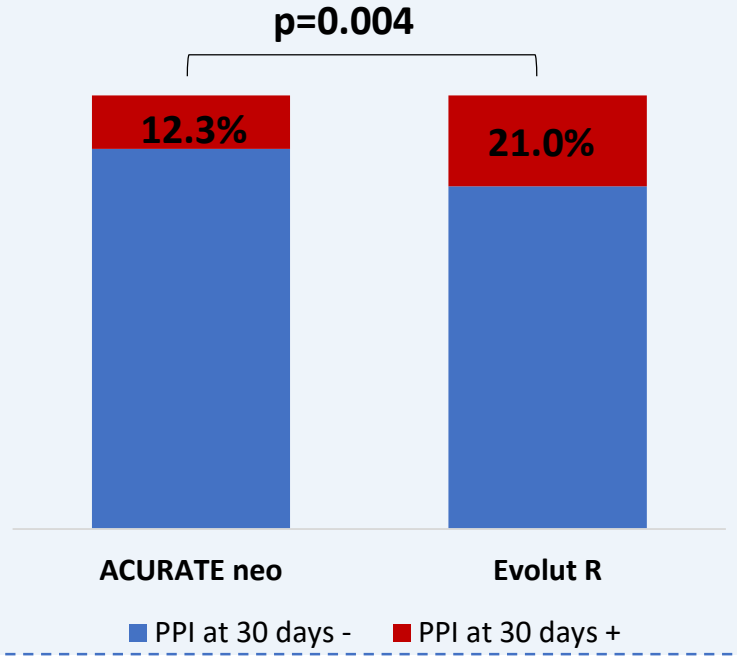
SCOPE 2 trial
n=796
Randomized patients

ACURATE neo

CoreValve Evolut R

PPI 30 cohort

endpoint PPI at 30 days



LBBB 30 cohort

endpoint LBBB at 30 days

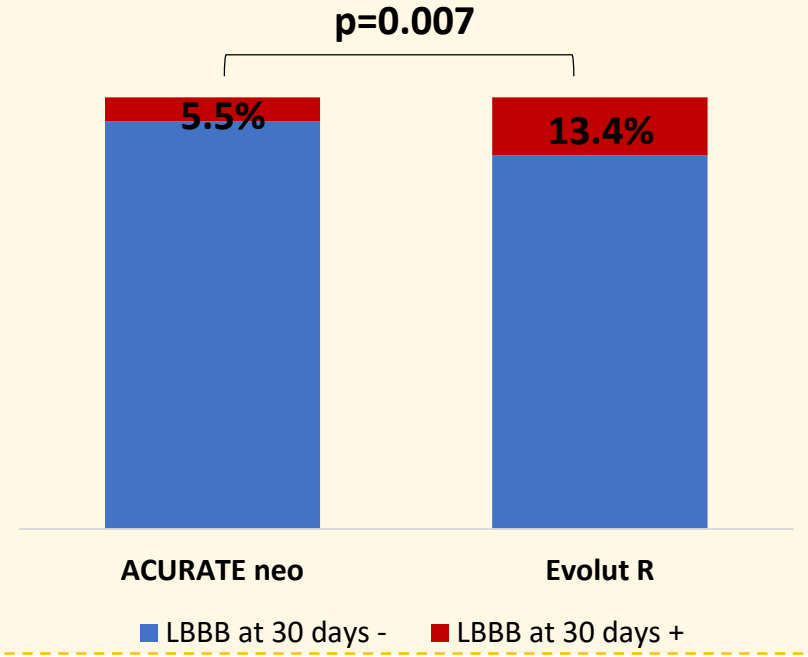


Figure 2

	OR [95% CI]	p-value
PPI 30 cohort		
Univariable analysis	0.53 [0.35 – 0.81]	0.003
Multivariable analysis	0.50 [0.31 – 0.81]	0.005
ITT population		
Univariable analysis	0.53 [0.35 – 0.81]	0.003
Multivariable analysis	0.56 [0.37 – 0.85]	0.006
Modified PPI 30 cohort		
Univariable analysis	0.54 [0.36 – 0.83]	0.004
Multivariable analysis	0.63 [0.41 – 0.96]	0.002

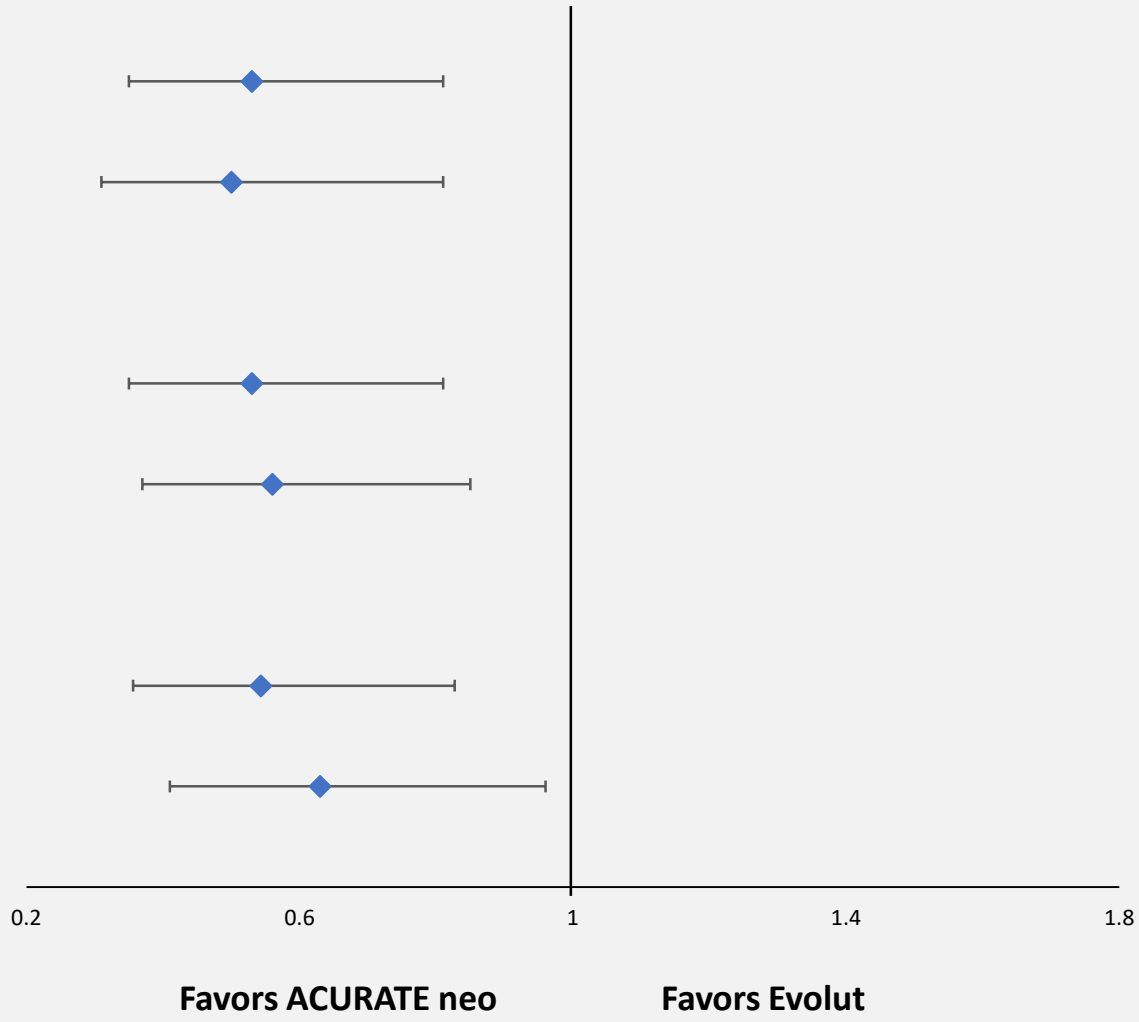
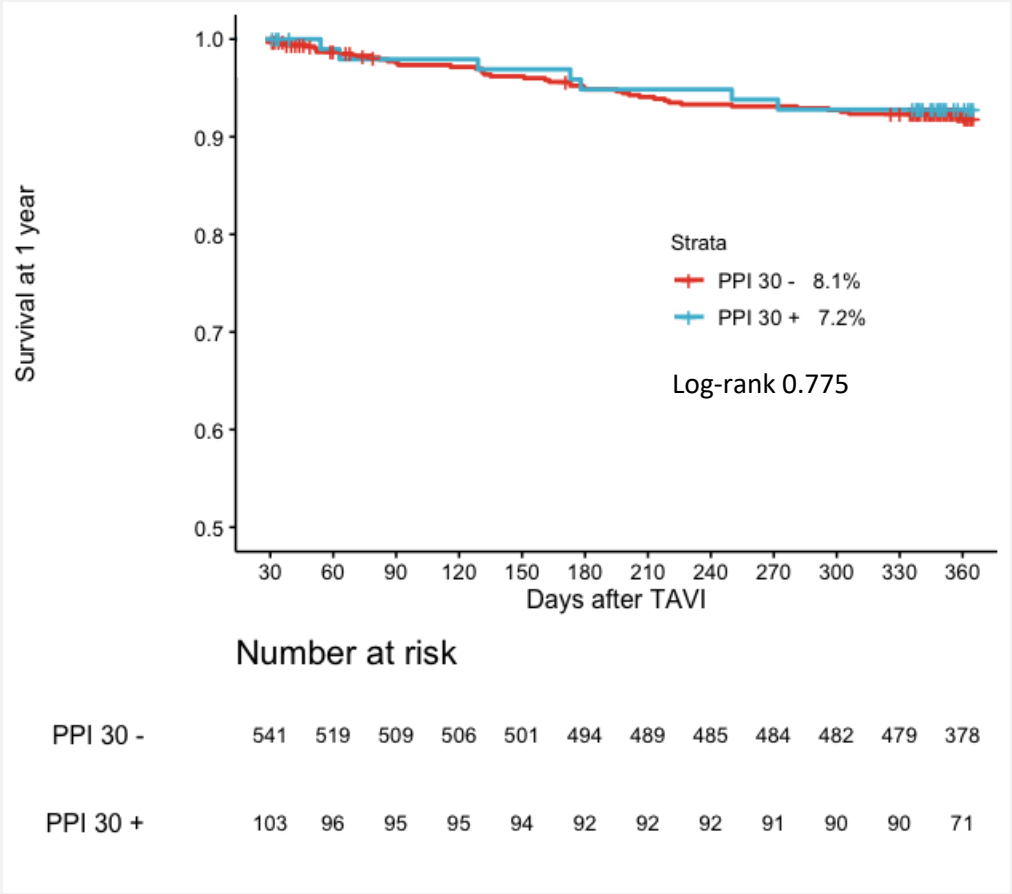


Figure 3

A


Survival at 1 year
1.0
0.9
0.8
0.7
0.6
0.5
Strata
PPI 30 - 8.1%
PPI 30 + 7.2%
Log-rank 0.775
30 60 90 120 150 180 210 240 270 300 330 360
Days after TAVI
Number at risk
PPI 30 - 541 519 509 506 501 494 489 485 484 482 479 378
PPI 30 + 103 96 95 95 94 92 92 92 91 90 90 71

B

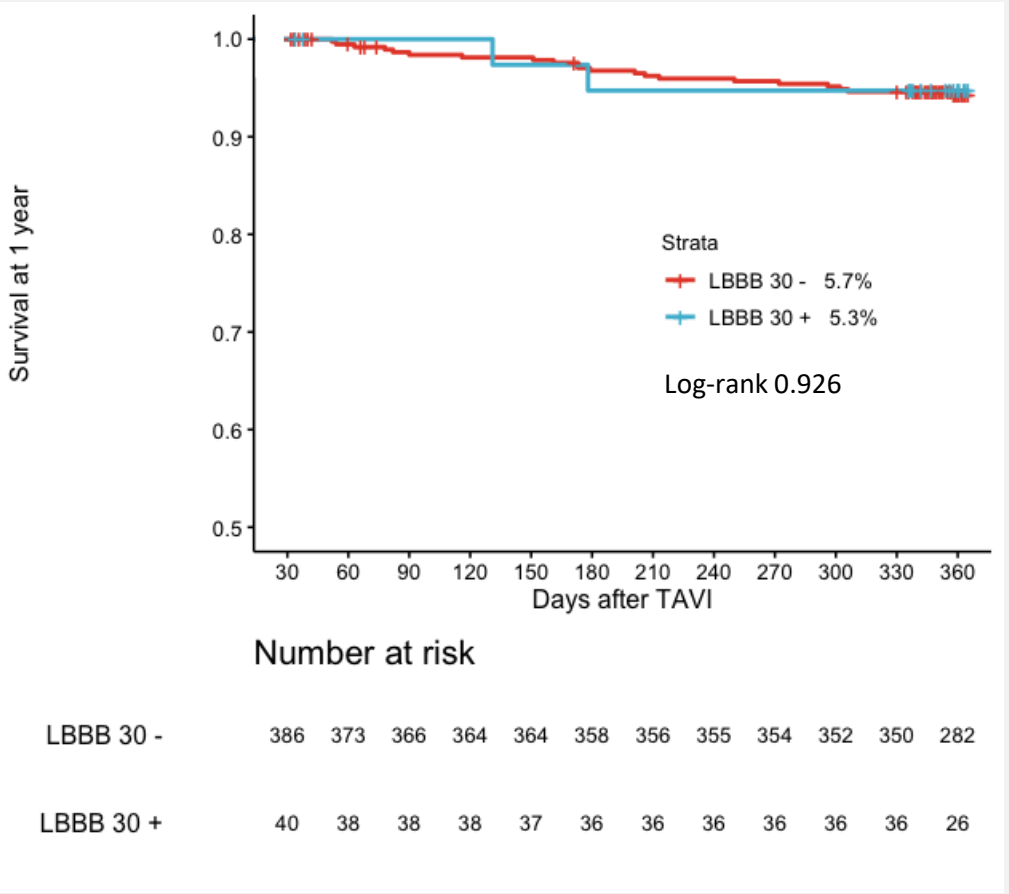
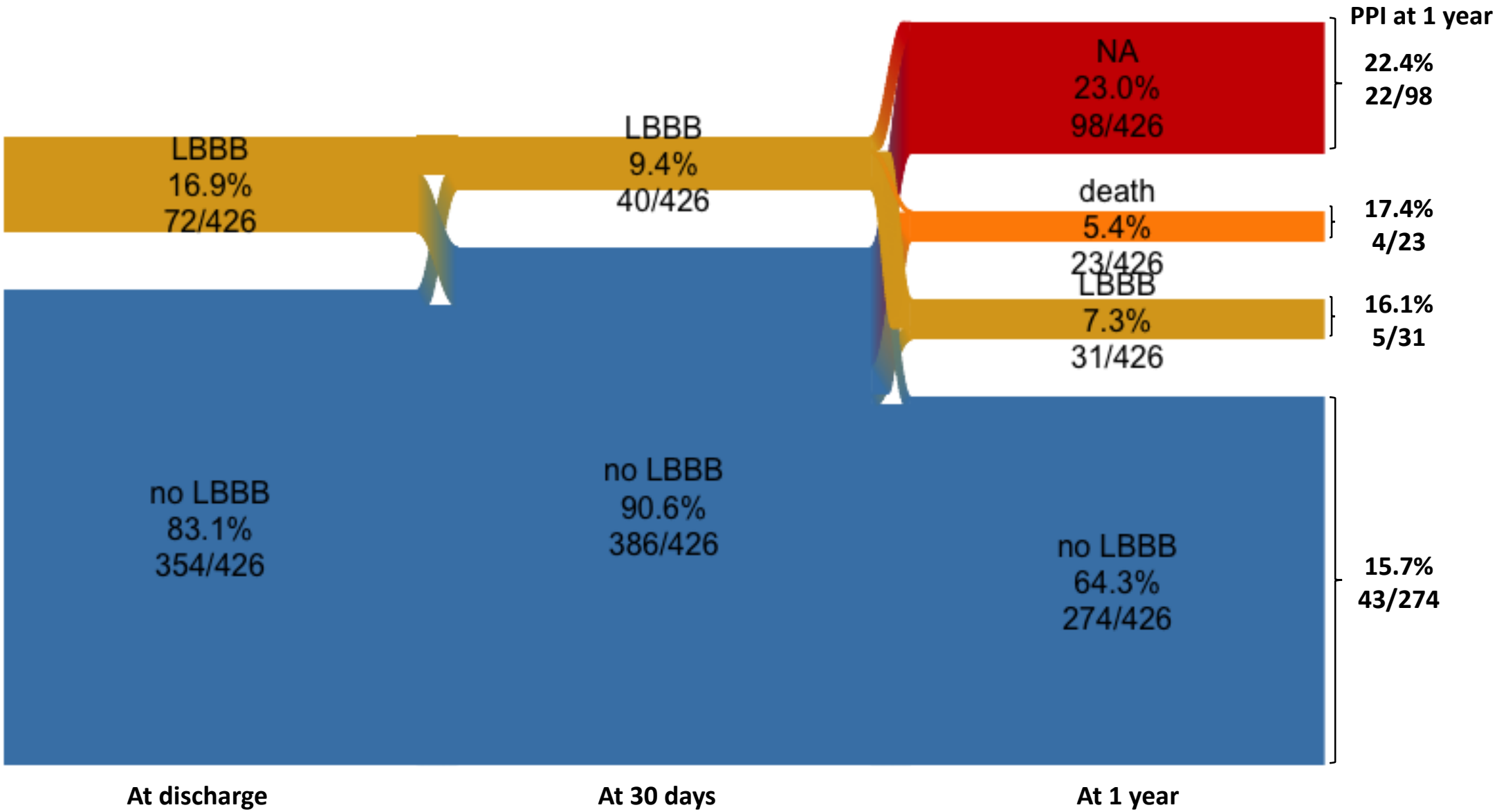
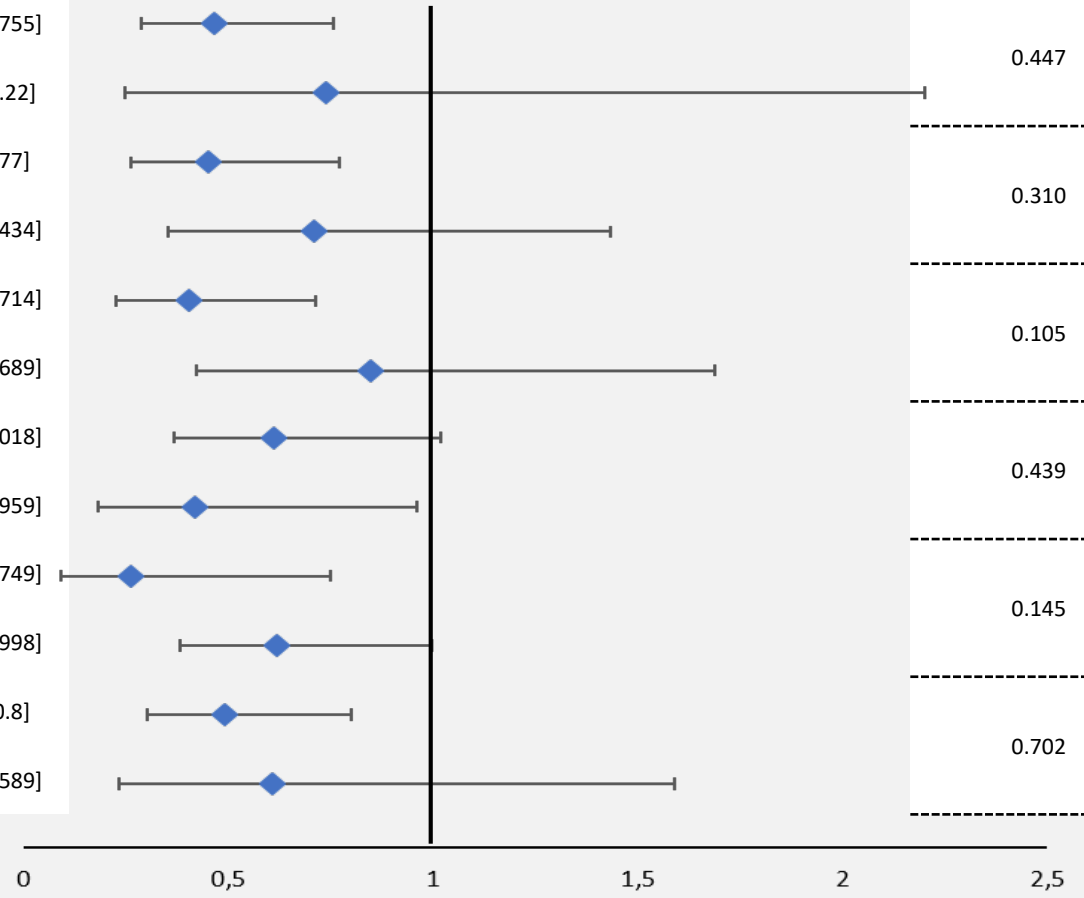

Survival at 1 year
1.0
0.9
0.8
0.7
0.6
0.5
Strata
LBBB 30 - 5.7%
LBBB 30 + 5.3%
Log-rank 0.926
30 60 90 120 150 180 210 240 270 300 330 360
Days after TAVI
Number at risk
LBBB 30 - 386 373 366 364 364 358 356 355 354 352 350 282
LBBB 30 + 40 38 38 38 37 36 36 36 36 36 36 26

Figure 4

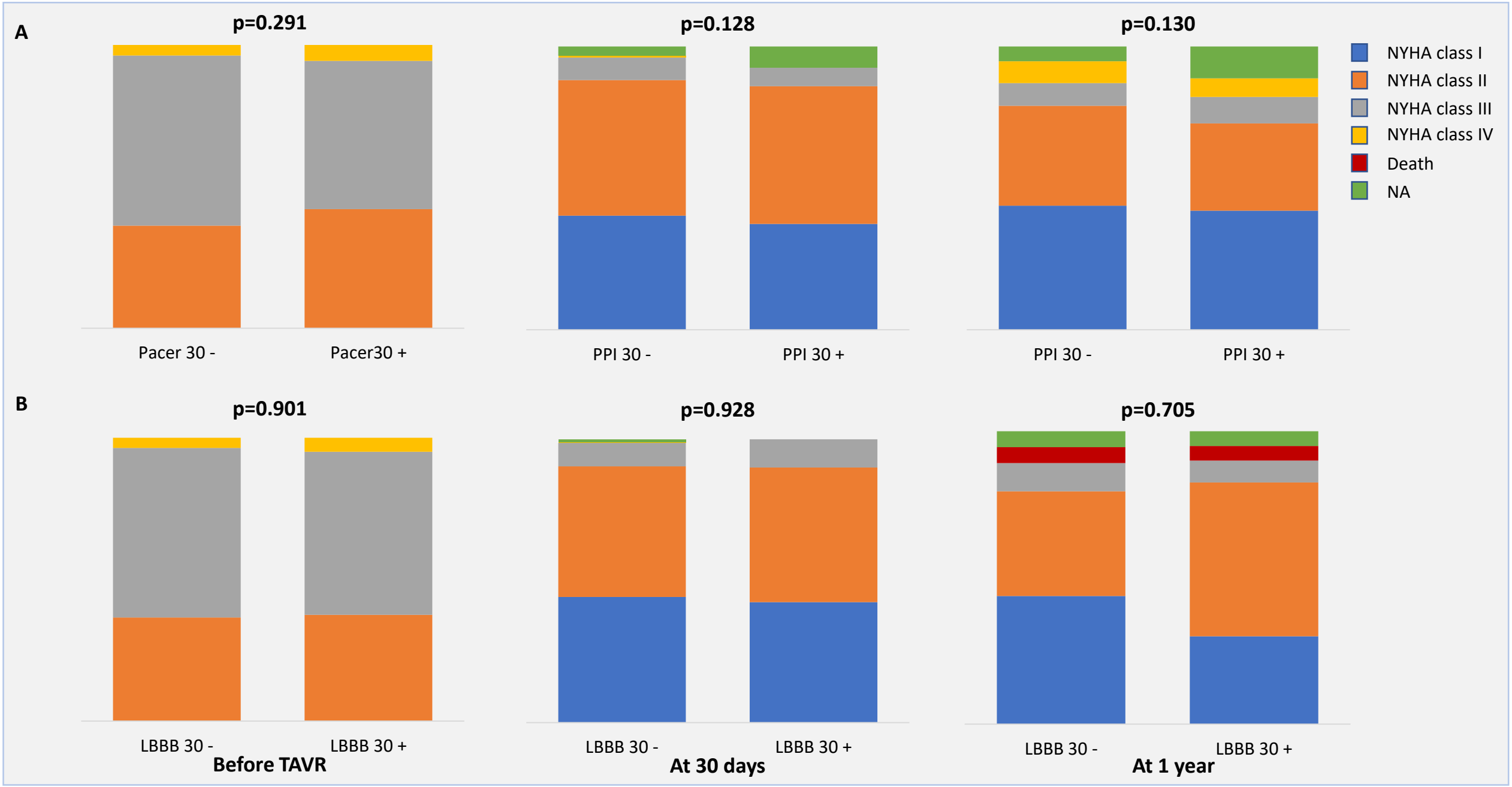

PPI at 1 year
LBBB
16.9%
72/426
no LBBB
83.1%
354/426
LBBB
9.4%
40/426
no LBBB
90.6%
386/426
NA
23.0%
98/426
22.4%
22/98
death
5.4%
23/426
17.4%
4/23
LBBB
7.3%
31/426
16.1%
5/31
no LBBB
64.3%
274/426
15.7%
43/274
At discharge
At 30 days
At 1 year

Supplemental Figure 1

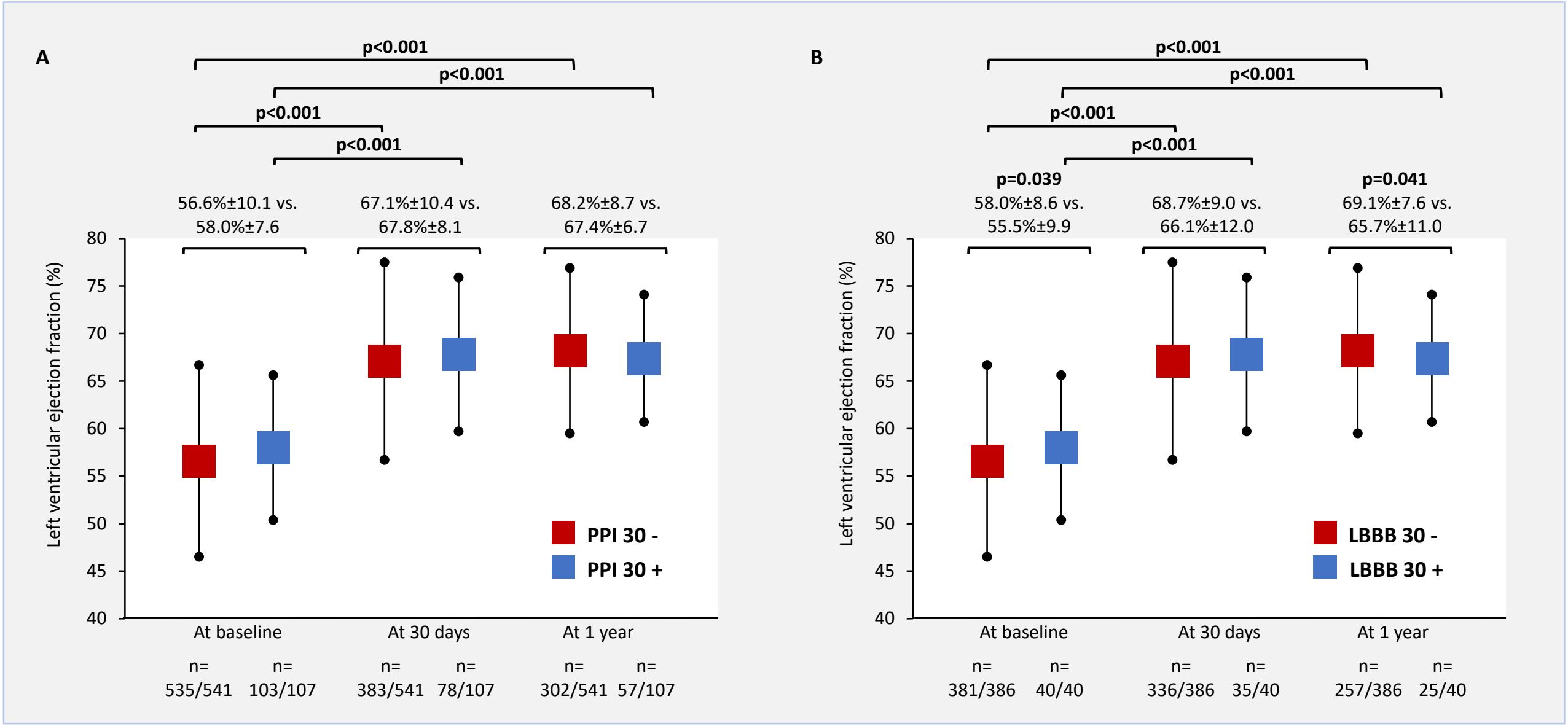
		ACURATE neo	Evolut	OR [95% CI]	p for interaction
Pre-existing RBBB	No	9.6% (29/301)	18.7% (53/284)	0.465 [0.286 – 0.755]	0.447
	Yes	44.4% (12/27)	52.0% (13/25)	0.738 [0.248 – 2.22]	
History of atrial fibrillation	No	10.5% (24/229)	20.7% (44/214)	0.45 [0.263 – 0.77]	0.310
	Yes	16.3% (17/104)	21.6% (22/102)	0.711 [0.352 – 1.434]	
Aortic annulus	> 72 mm	10.8% (22/203)	23.2% (38/164)	0.403 [0.227 – 0.714]	0.105
	≤ 72 mm	15.2% (17/112)	17.5% (22/126)	0.846 [0.424 – 1.689]	
Eccentric annulus (EI > 0.25)	No	12.1% (30/248)	18.3% (42/229)	0.613 [0.369 – 1.018]	0.439
	Yes	13.5% (10/74)	27.3% (21/77)	0.417 [0.181 – 0.959]	
Aortic calcification	none/mild	5.5% (5/91)	18.2% (16/88)	0.262 [0.091 – 0.749]	0.145
	> moderate	14.8% (35/236)	22.0% (49/223)	0.618 [0.383 – 0.998]	
LVOT calcification	none/mild	10.9% (30/276)	19.8% (52/262)	0.492 [0.303 – 0.8]	0.702
	> moderate	18.0% (9/50)	26.5% (13/49)	0.608 [0.233 – 1.589]	



Supplemental Figure 2



Supplemental Figure 3



Supplementary material

Supplemental Figures

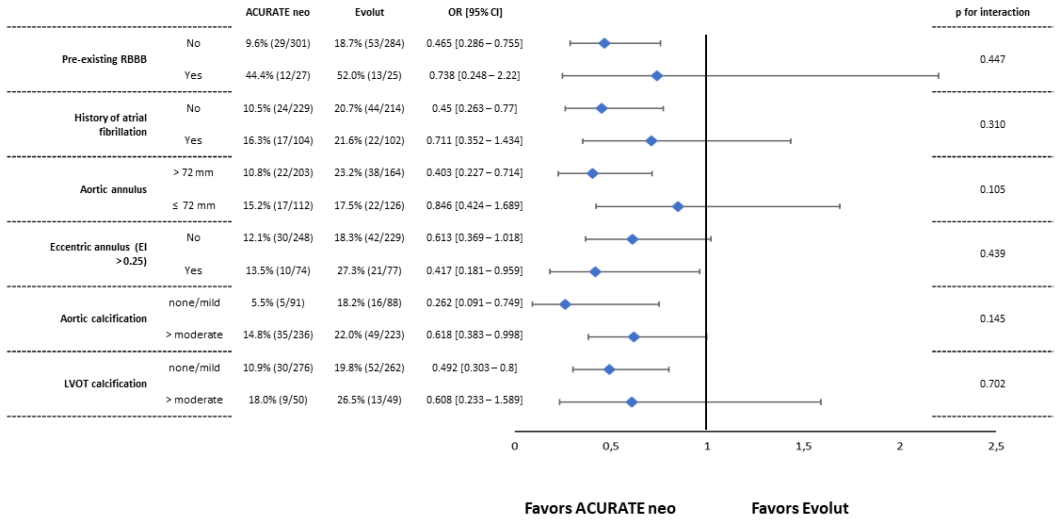
Supplemental Figure 1

Title: Risk of PPI at 30 days according to THV in specific subgroups

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

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

Supplemental Figure 1



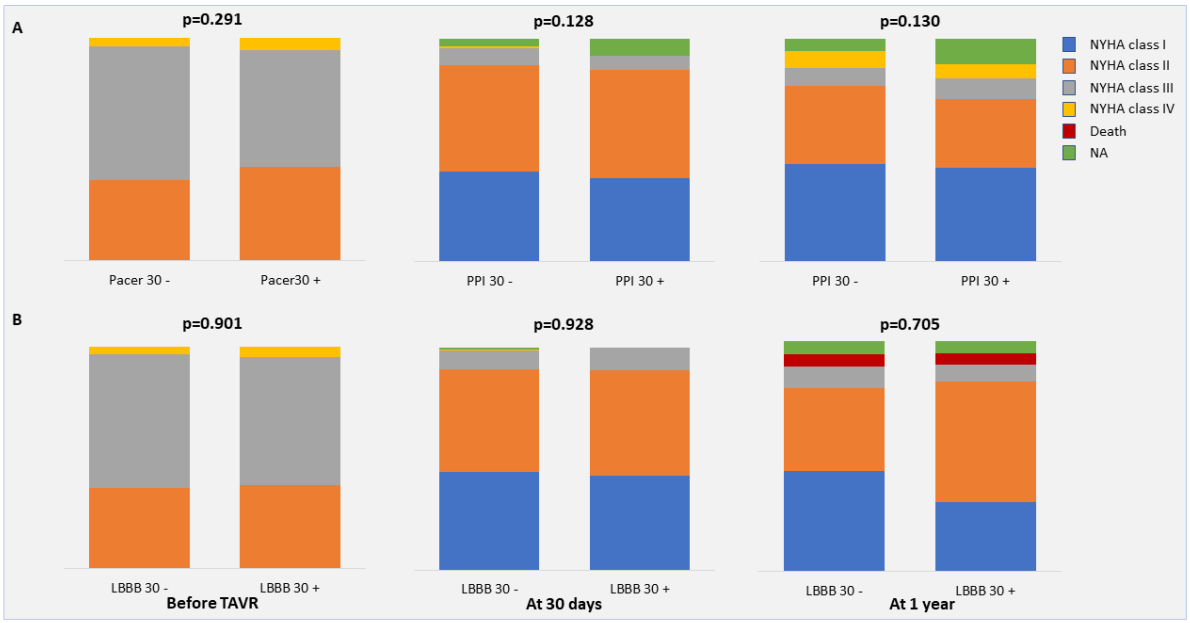
Supplemental Figure 2

Title: Evolution of NYHA functional class over time according to new PPI at 30 days (A) and new LBBB at 30 days (B)

Legend: Evolution of NYHA functional class over time according to new PPI at 30 days (A) and new LBBB at 30 days (B).

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

Supplemental Figure 2



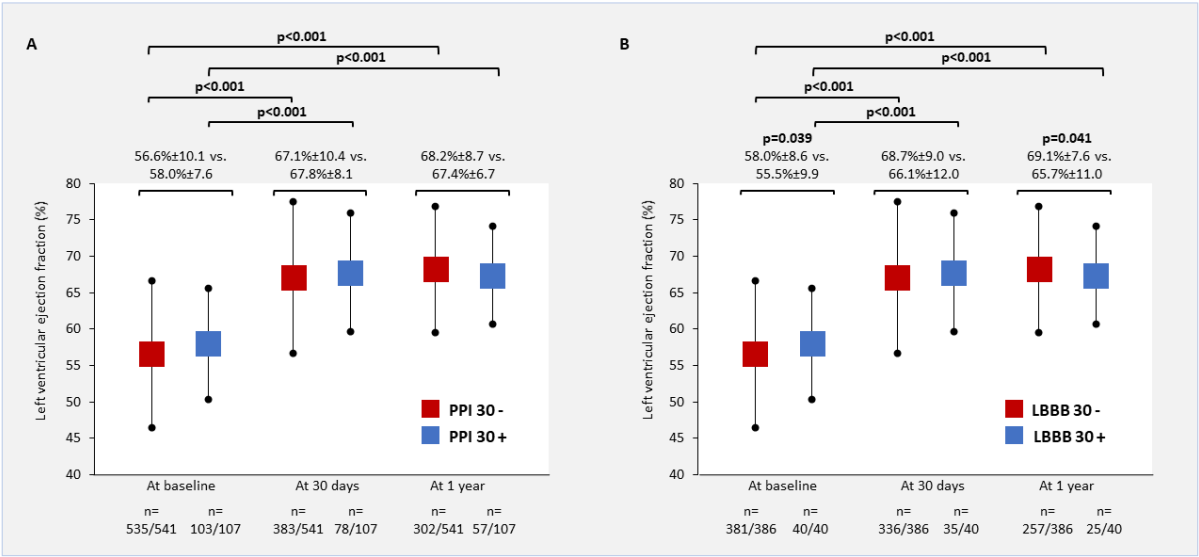
Supplemental Figure 3

Title: Evolution of left ventricular function over time according to new PPI at 30 days (A) and new LBBB at 30 days (B)

Legend: Evolution of left ventricular function over time according to new PPI at 30 days (A) and new LBBB at 30 days (B). Only significant p-values shown.

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

Supplemental Figure 3



Supplemental Tables

Supplemental 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

Abbreviations: AV-block, atrio-ventricular block.

All data are absolute number (percentage). P values are derived from chi-square or Fisher exact tests for categorical variables

Supplemental 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
Hypercholesterolemia	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**

Abbreviations: 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.

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P values are derived from chi-square or Fisher exact tests for categorical variables and Student t tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given.

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

	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
Pre-dilatation	1.26	[0.78 - 2.05]	0.348

Abbreviations: LVOT, left ventricular outflow tract.

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

Supplemental 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

Abbreviations: LVOT, left ventricular outflow tract.

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

Supplemental Table 5. 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
Hypercholesterolemia	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**

Abbreviations: 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.

All data are mean ± standard deviation, median [interquartile range] or absolute number (percentage). P values are derived from chi-square or Fisher exact tests for categorical variables and Student t tests or Wilcoxon rank-sum tests for continuous variables. In case of missing data, numbers of available measurements are given.