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Comparison of transcatheter aortic valve replacement with the ACURATE neo2 versus Evolut PRO/PRO+ devices

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KEYWORDS

- aortic stenosis
- atrio-ventricular block
- conduction abnormalities
- MSCT
- paravalvular leak
- TAVI

Abstract

Background: The ACURATE *neo*2 (NEO2) and Evolut PRO/PRO+ (PRO) bioprostheses are new-generation self-expanding valves developed for transcatheter aortic valve replacement (TAVR).

Aims: We sought to compare the performance of the ACURATE *neo*2 and Evolut PRO/PRO+ devices.

Methods: The NEOPRO-2 registry retrospectively included patients who underwent TAVR for severe aortic stenosis with either the NEO2 or PRO devices between August 2017 and December 2021 at 20 centres. In-hospital and 30-day Valve Academic Research Consortium (VARC)-3 defined outcomes were evaluated. Propensity score (PS) matching and binary logistic regression were performed to adjust the treatment effect for PS quintiles. A subgroup analysis assessed the impact of aortic valve calcification.

Results: A total of 2,175 patients (NEO2: n=763; PRO: n=1,412) were included. The mean age was 82±6.2 years and the mean Society of Thoracic Surgeons score was 4.2%. Periprocedural complications were low, and both groups achieved high rates of technical success (93.1% vs 94.1%; p=0.361) and pre-discharge intended valve performance (96.0% vs 94.1%; p=0.056), both in the unmatched and matched analysis (452 pairs). Device success at 30 days was comparable (84.3% vs 83.6%; p=0.688), regardless of aortic valve calcification severity (p>0.05 for interaction). A suggestion for higher VARC-3 early safety in the NEO2 group was mainly driven by reduced rates of new permanent pacemaker implantation (7.7% vs 15.6%; p<0.001).

Conclusions: This retrospective analysis reports a similar short-term performance of the ACURATE *neo*2 platform compared with the new-generation Evolut PRO/PRO+ devices. Randomised studies are needed to confirm our exploratory findings.

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Abbreviations

aOR	adjusted odds ratio
AR	aortic regurgitation
CI	confidence interval
NEO2	ACURATE *neo*2
PPI	permanent pacemaker implantation
PRO	Evolut PRO/PRO+
PS	propensity score
TAVR	transcatheter aortic valve replacement
THV	transcatheter heart valve
VARC-3	Valve Academic Research Consortium-3

Introduction

Transcatheter aortic valve replacement (TAVR) is an established treatment in patients with severe aortic stenosis (AS)[1-6]. Transcatheter heart valve (THV) design has evolved to meet the high standards required for the application of TAVR in a younger and healthier population. Therefore, head-to-head comparisons of new-generation THV are useful to tailor device selection.

The ACURATE *neo*2 (NEO2) bioprosthesis (Boston Scientific) is a new-generation self-expanding THV which has been commercially available in Europe since September 2020. Its precursor, the ACURATE *neo* (NEO) device, despite encouraging results in observational studies, including the NEOPRO registry, did not meet non-inferiority to the Evolut R/PRO devices in the Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation 2 (SCOPE II) trial for the primary endpoint of all-cause death or stroke at 1 year. In addition, moderate or severe paravalvular aortic regurgitation (AR) was a major concern[7-13]. Therefore, the NEO2 design focused on improved sealing, with a 60% larger skirt compared to the first-generation NEO, to minimise paravalvular AR. Data from the ACURATE *neo*2 Conformité Européenne (CE) Mark Study were promising: procedural success was high with a low rate of moderate or severe paravalvular leak (PVL) at 1 year (2.5%)[14]. A recent analysis from the NEOPRO and NEOPRO-2 registries confirmed a significant reduction in predischarge moderate or severe PVL with the ACURATE *neo*2 device compared with its precursor (2% vs 5%; p<0.001)[15]. Since the new-generation Evolut PRO and PRO+ (PRO) bioprostheses (Medtronic) achieved high standards in terms of safety and efficacy, they represent the benchmark for self-expanding devices[16,17]. Therefore, the aim of our study was to compare TAVR with the latest-generation ACURATE *neo*2 and Evolut PRO and PRO+ bioprostheses in order to understand whether technology iteration impacts on device performance and short-term outcomes.

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Methods

STUDY POPULATION

NEOPRO-2 (A Multicenter Comparison of ACURATE NEO2 Versus Evolut PRO/PRO+ Transcatheter Heart Valves 2) was an international, observational, retrospective registry that included consecutive patients who underwent transfemoral TAVR for severe symptomatic aortic stenosis with either NEO2 or PRO devices between August 2017 and December 2021 at 20 centres[15]. A total of 2,175 patients were included in the registry: 763 patients (35.1%) treated with NEO2; 1,412 patients (64.9%) treated with Evolut PRO/PRO+ (n=158/1,412 [11.2%] with PRO+). The number of patients included from each participating centre is detailed in **Supplementary Table 1**. The treatment periods were September 2020 to December 2021 and August 2017 to October 2021 for the NEO2 and PRO groups, respectively.

Local multidisciplinary Heart Teams evaluated all cases and confirmed eligibility for transfemoral TAVR for symptomatic, severe stenosis of the native aortic valve (AV). All patients provided written informed consent for the procedure and subsequent data collection per local practice for retrospective data. Preprocedural screening was performed by means of clinical assessment (patient demographics, symptoms, comorbidities, laboratory examinations, and risk evaluation), echocardiography, and multidetector computed tomography (MDCT). AV and left ventricular outflow tract calcifications were classified and graded using a semiquantitative scoring system, as previously described[18]. The selection of prosthesis type and size was at the discretion of the treating physician at each centre.

DEVICE DESCRIPTION

The NEO2 device preserves several characteristics of its precursor, the ACURATE *neo* bioprosthesis, including a self-expanding nitinol frame with relatively low radial force, porcine pericardial leaflets in a supra-annular position, and self-aligning stabilisation arches with open-cell geometry[19]. In addition, it presents 2 new features: a 60% larger pericardial inner and outer skirt, to enhance sealing, and a radiopaque marker, for more precise positioning. Three sizes are available: small, medium, and large, which correspond to annular diameters up to 23, 25, and 27 mm, respectively. It is implanted using a delivery system inserted through a 14 Fr expandable sheath (iSleeve; Boston Scientific), as previously described[20].

The self-expanding supra-annular Evolut PRO bioprosthesis shares similar properties with the second-generation Evolut R THV, including an identical frame and inner tissue[21]. The principal design modification is the presence of an external pericardial wrap on the 23, 26, and 29 mm valves to enhance sealing with a 16 Fr delivery profile. The Evolut PRO+ device was developed to introduce the additional sealing skirt to the 34 mm valve and to reduce the dimension of the delivery sheath profile (14 Fr).

STUDY ENDPOINTS

The primary endpoint of the study was 30-day device success, defined according to Valve Academic Research Consortium-3 (VARC-3) criteria[22]. Secondary endpoints of interest included additional VARC-3-defined composite outcomes: technical success, predischarge intended performance of the valve, 30-day early safety, and the single components of these endpoints. Echocardiographic outcomes were evaluated predischarge and at

30 days; AR severity was assessed according to VARC-3 criteria and classified as none/trace, mild, moderate, and severe.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation and were compared using the unpaired Student's t-test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test.

Propensity score (PS) matching was used to adjust for differences in baseline characteristics, as previously described[23]. A PS was calculated for each patient to estimate the propensity toward belonging to a specific treatment group (NEO2 vs PRO). This was done by means of a non-parsimonious multivariate logistic regression including the following covariates: age, sex, body mass index, chronic obstructive pulmonary disease, estimated glomerular filtration rate, prior percutaneous coronary intervention, peripheral vascular disease, atrial fibrillation/flutter, New York Heart Association (NYHA) Functional Class III-IV, left ventricular ejection fraction (LVEF), European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, moderate-to-heavy AV calcification, and AV annulus perimeter. The C-statistic for the PS model was 0.65, indicating good discrimination. A 1-to-1 nearest neighbour matching algorithm without replacement (calliper 0.05) was performed to identify PS-matched pairs. The pseudo-R2 value was 0.0423 (p<0.0001) before matching and very low (0.005; p=0.953) after matching, thus confirming the adequate balancing of covariate distribution between the matched groups[24].

Prespecified primary and secondary endpoints were compared between the NEO2 and PRO groups in the overall and PS-matched cohorts. Binary logistic regression was performed to adjust the treatment effect for the PS quintiles in the overall cohort; results are presented as adjusted odds ratio (aOR) with 95% confidence interval (CI). In addition, we conducted a subgroup analysis of 30-day outcomes in patients grouped according to the severity of AV calcifications: none-mild (n=368 [23.7%]), moderate (n=709 [43.6%]), and heavy (n=550 [33.8%]).

All reported p-values are 2-sided, and a p-value <0.05 was considered as indicating statistical significance. All statistical analyses were performed using Stata version 13.0 (StataCorp).

Results

BASELINE CHARACTERISTICS

A total of 2,175 patients who underwent TAVR with either NEO2 (n=763) or PRO/PRO+ (n=1,412) THV from August 2017 to December 2021 were included. Baseline characteristics are summarised in **Table 1**. The mean age was 81.7±6.2 years, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score was 4.2±2.8%. Patients treated with PRO/PRO+ devices were more frequently males, had more frequently a history of prior cardiac surgery and more than mild mitral regurgitation, together with a lower LVEF and worse NYHA Class. Whereas patients in the NEO2 group more frequently reported a history of peripheral vascular disease, previous percutaneous coronary intervention, and atrial fibrillation/flutter. Similar annular perimeter was observed at MDCT between the groups, whereas moderate-to-heavy AV calcification was more frequent in the NEO2 group.

PROCEDURAL CHARACTERISTICS

As depicted in **Table 2**, most patients underwent TAVR under conscious sedation, with a significantly lower rate in the PRO group (86.1% vs 94.6%; p<0.001). Predilatation was more frequent in the NEO2 group (85.9% vs 44.3%; p<0.001), whereas post-dilatation rates were comparable between groups. Both groups achieved high rates of VARC-3 technical success (93.1% vs 94.1%; p=0.361) with no significant differences in periprocedural complications, except for higher vascular access complications in the PRO group (12.2% vs 8.5%; p=0.002), driven by minor vascular complications. Overall, procedural mortality occurred in 8 patients (0.4%); annular rupture was reported in 4 patients (0.2%) and all 4 cases underwent predilatation or post-dilatation.

EARLY ECHOCARDIOGRAPHIC OUTCOMES

Predischarge echocardiographic findings after TAVR are reported in **Table 2**. Both devices achieved high rates of VARC-3-defined intended performance of the valve (96.0% vs 94.1%; p=0.056). As depicted in **Figure 1**, AR after TAVR was mainly caused by PVL; moderate or severe AR was lower after a NEO2 implantation (1.7% vs 4.3%; p=0.003). The mean AV gradient was slightly higher in the NEO2 cohort (9.1±4.2 mmHg vs 7.7±4.0 mmHg; p<0.001); nevertheless, the proportion of patients with a mean AV gradient ≥20 mmHg was similar between the groups.

VARC-3-DEFINED OUTCOMES AT 30-DAY FOLLOW-UP

Information on 30-day survival status was available for 2,158 of 2,175 patients (99.2%), with 53 deaths reported (overall all-cause mortality rate 2.5%) and 18 patients lost to follow-up.

As reported in **Table 3**, 30-day all-cause death and stroke rates (including disabling and non-disabling strokes) were acceptable and similar between both groups. Despite higher rates of hospitalisation for cardiovascular reasons and myocardial infarction in the NEO2 group, no differences in cardiovascular mortality emerged. New permanent pacemaker implantation (PPI) at 30 days was more frequently needed in the PRO cohort (15.6% vs 7.7%; p<0.001). In addition, lower rates of any bleeding (11.5% vs 17.3%; p=0.001) and vascular complications (5.7% vs 12.7%; p<0.001) were observed in the NEO2 group, driven by a reduction in Type 1 bleeding and minor vascular complications, respectively. Nevertheless, patients in the NEO2 group more frequently developed stage 3 or 4 acute kidney injury (AKI) (2.5% vs 1.2%; p=0.020). Echocardiographic data at 30 days strengthened predischarge results **(Table 3)**. All other 30-day clinical outcomes were numerically low and similar in both groups.

VARC-3 device success (primary endpoint) was 83.8% in the overall cohort and similar in the NEO2 and PRO groups (84.3% vs 83.6%; p=0.688). The VARC-3 early safety composite endpoint

Table 1. Baseline patient characteristics.

	Overall (n=2,175)	ACURATE *neo2* (n=763)	Evolut PRO/PRO+ (n=1,412)	*p*-value
Clinical characteristics				
Age (years)	81.7±6.2	81.7±5.9	81.7±6.4	0.908
Male sex	809/2,175 (37.2)	251/763 (32.9)	558/1,412 (39.5)	0.002
BMI	27.1±5.2	27.2±5.0	27.1±5.2	0.927
COPD	320/2,171 (14.7)	125/762 (16.4)	195/1,409 (13.8)	0.108
Diabetes mellitus	656/2,169 (30.2)	220/763 (28.8)	436/1,406 (31.0)	0.292
Arterial hypertension	1,851/2,172 (85.2)	648/763 (84.9)	1,203/1,409 (85.4)	0.777
eGFR (ml/min/m^2)	60.8±27.0	63.6±28.6	59.2±25.9	<0.001
Dialysis	45/2,175 (2.1)	11/763 (1.4)	34/1,412 (2.4)	0.131
Prior PCI	498/2,172 (22.9)	213/763 (27.9)	285/1,409 (20.2)	<0.001
Prior cardiac surgery	180/2,171 (8.3)	53/763 (6.9)	127/1,408 (9.0)	0.005
Prior CABG	140/2,172 (6.5)	47/763 (6.2)	93/1,409 (6.6)	0.690
Peripheral vascular disease	275/2,171 (12.7)	115/763 (15.1)	160/1,408 (11.4)	0.013
Prior stroke	203/2,171 (9.4)	83/763 (10.9)	120/1,408 (8.5)	0.072
Atrial fibrillation/flutter	579/2,166 (26.7)	240/755 (31.8)	339/1,411 (24.0)	<0.001
PM or ICD	191/2,173 (8.8)	61/763 (8.0)	130/1,409 (9.2)	0.329
NYHA Class III or IV	1,293/2,164 (59.8)	417/761 (54.8)	876/1,403 (62.4)	0.001
STS-PROM (%)	4.2±2.8	4.2±3.1	4.2±2.7	0.602
EuroSCORE II (%)	4.5±4.2	4.3±3.9	4.7±4.4	0.060
Echocardiographic data				
AVA (cm^2)	0.70±0.20	0.71±0.26	0.70±0.17	0.533
LVEF (%)	56.9±10.4	57.9±10.0	56.3±10.5	<0.001
Moderate to severe MR	525/2,043 (25.7)	160/705 (22.7)	365/1,338 (27.3)	0.024
Moderate to severe TR	251/1,762 (14.3)	86/686 (12.5)	165/1,076 (15.3)	0.101
Severe pulmonary hypertension*	143/1,859 (7.7)	56/659 (8.5)	87/1,200 (7.3)	0.334
MDCT data				
Annular perimeter (mm)	73.5±5.8	73.7±5.1	73.4±6.1	0.211
Moderate to heavy AV calcification	1,259/1,627 (77.4)	444/629 (70.6)	815/998 (81.7)	<0.001
Any LVOT calcification	524/1,066 (49.2)	175/328 (53.4)	349/738 (47.3)	0.068
Moderate to severe LVOT calcification	220/1,066 (20.6)	61/328 (18.6)	159/738 (21.5)	0.272

Values are mean±SD or n/N (%). *Systolic pulmonary artery pressure on echocardiography >70 mmHg. AV: aortic valve; AVA: aortic valve area; BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MDCT: multidetector computed tomography; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PM: pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TR: tricuspid regurgitation

at 30 days was more frequently achieved after TAVR with the NEO2 device (78.7% vs 71.3%; p<0.001).

After adjustment for PS quintiles, the implanted valve did not have a significant impact on 30-day VARC-3 device success in the overall cohort (aOR 0.77, 95% CI: 0.55-1.07; p=0.121). As shown in **Supplementary Table 2**, after adjustment for PS quintiles, NEO2 implantation was associated with a higher risk of cardiovascular hospitalisations and stage 3 or 4 AKI and with a lower risk of any vascular complications and new PPI. A similar risk in VARC-3 early safety (aOR 1.29, 95% CI: 0.97-1.71; p=0.082) and VARC-3 intended performance of the valve (aOR 1.10, 95% CI: 0.59-2.07; p=0.766) was observed between the NEO2 and PRO groups.

After 1-to-1 PS matching (for the variables summarised in "Methods"), a total of 452 pairs were obtained from the overall cohort **(Supplementary Table 3)**. The PS-matched comparison substantially confirmed the results on procedural characteristics, periprocedural complications, and the predischarge haemodynamic outcomes that emerged in the overall population. Whereas there was no significant difference in terms of moderate or severe PVL between the matched NEO2 and PRO groups **(Supplementary Table 4)**, VARC-3 intended performance of the valve, VARC-3 device success, and VARC-3 early safety were similar between the matched NEO2 and PRO groups **(Supplementary Table 5)**. The lower rate of new PPI in the NEO2 group was also confirmed after PS matching.

SUBGROUP ANALYSIS ON AV CALCIFICATION

An exploratory subgroup analysis was performed to evaluate the main 30-day outcomes across different degrees of AV calcification in the overall cohort **(Supplementary Table 6)**. Trends towards

Table 2. Procedural characteristics and predischarge echocardiographic outcomes.

		Overall (n=2,175)	ACURATE *neo*2 (n=763)	Evolut PRO/PRO+ (n=1,412)	*p*-value
Procedural characteristics					
Conscious sedation		1,938/2,175 (89.1)	722/763 (94.6)	1,216/1,412 (86.1)	<0.001
Transfemoral TAVR		2,175/2,175 (100)	763/763 (100)	1,412/1,412 (100)	1.000
Valve size	23 mm (or S size)	–	185/763 (24.2)	49/1,233 (4.0)	–
	25 mm (or M size)	–	327/763 (42.8)	–	
	26 mm	–	–	468/1,233 (38.0)	
	27 mm (or L size)	–	252/763 (33.0)	–	
	29 mm	–	–	682/1,233 (55.3)	
	34 mm	–	–	34/1,233 (2.7)	
Predilatation		1,278/2,169 (58.9)	655/763 (85.9)	623/1,406 (44.3)	<0.001
Post-dilatation		587/2,039 (28.8)	233/761 (30.6)	354/1,278 (27.7)	0.159
Procedural death		8/2,175 (0.4)	2/763 (0.3)	6/1,412 (0.4)	0.549
Second THV implanted		19/2,172 (0.9)	6/762 (0.8)	13/1,410 (0.9)	0.748
Valve embolisation		23/2,172 (1.1)	8/762 (1.1)	15/1,410 (1.1)	0.976
Annular rupture		4/2,175 (0.2)	1/763 (0.1)	3/1,412 (0.2)	0.672
Pericardial tamponade		19/2,175 (0.9)	7/763 (0.9)	12/1,412 (0.9)	0.872
Aortic dissection		1/2,175 (0.1)	0/763 (0.0)	1/1,412 (0.1)	0.462
Coronary occlusion		10/2,175 (0.5)	2/763 (0.3)	8/1,412 (0.6)	0.317
Conversion to cardiac surgery		8/2,175 (0.4)	3/763 (0.4)	5/1,412 (0.4)	0.886
Vascular access complications	Minor	158/2,175 (7.3)	35/763 (4.6)	123/1,412 (8.7)	0.002
	Major	80/2,175 (3.7)	30/763 (3.9)	50/1,412 (3.5)	
VARC-3 defined technical success		2,038/2,175 (93.7)	710/763 (93.1)	1,328/1,412 (94.1)	0.361
Echocardiographic outcomes					
Total aortic regurgitation	None/trace	1,245/2,144 (58.1)	424/752 (56.4)	821/1,392 (59.0)	0.003
	Mild	826/2,144 (38.5)	315/752 (41.9)	511/1,392 (36.7)	
	Moderate	69/2,144 (3.2)	13/752 (1.7)	56/1,392 (4.0)	
	Severe	4/2,144 (0.2)	0/752 (0.0)	4/1,392 (0.3)	
Moderate or severe paravalvular aortic regurgitation		70/2,144 (3.3)	13/752 (1.7)	57/1,392 (4.1)	0.003
Mean gradient ≥20 mmHg		35/2,103 (1.7)	14/747 (1.9)	21/1,356 (1.6)	0.577
Mean gradient (mmHg)		8.2±4.1	9.1±4.2	7.7±4.0	<0.001
Max gradient (mmHg)		15.2±7.4	16.7±7.8	14.6±7.2	<0.001
Aortic EOA (cm^2)		1.86±0.51	1.79±0.46	1.94±0.54	<0.001
VARC-3 defined intended performance of the valve		2,001/2,112 (94.7)	719/749 (96.0)	1,282/1,363 (94.1)	0.056

Values are n/N (%) or mean±SD. EOA: effective orifice area; TAVR; transcatheter aortic valve replacement; THV: transcatheter heart valve; VARC-3: Valve Academic Research Consortium-3

lower VARC-3 early safety in the PRO group among patients with heavy AV calcification and a lower rate of moderate-severe PVL in the NEO2 group among patients with none-mild AV calcification were observed. However, no significant interaction between the type of implanted THV and AV calcification severity was observed for all evaluated endpoints (all p-values for interaction >0.05). Of note, the higher rate of new PPI in the PRO group was confirmed in all AV calcification subgroups.

Discussion

The NEOPRO-2 registry compared short-term VARC-3-defined outcomes in 2,175 patients undergoing transfemoral TAVR with the new-generation ACURATE *neo*2 and Evolut PRO/PRO+ bioprostheses in a contemporary, real-world, multicentre setting. The main findings of our study are as follows: 1) despite baseline heterogeneity in patient characteristics, periprocedural complications were numerically low, and both groups achieved high rates of VARC-3-defined technical success and predischarge intended performance of the valve; 2) 30-day VARC-3 device success was 83.8% in the overall cohort, similar between the NEO2 and PRO devices; 3) despite a different rate of short-term complications, a possible advantage for the NEO2 group in terms of VARC-3 early safety in the entire population did not reach statistical significance after adjustment for PS quintiles and PS matching; 4) TAVR with the NEO2 THV resulted in lower rates of PPI compared to the PRO/PRO+ devices with no differences per grade of AV calcification.

IN-HOSPITAL OUTCOMES

The patient population included in the registry was heterogeneous at baseline, suggesting a potential selection bias toward and operator

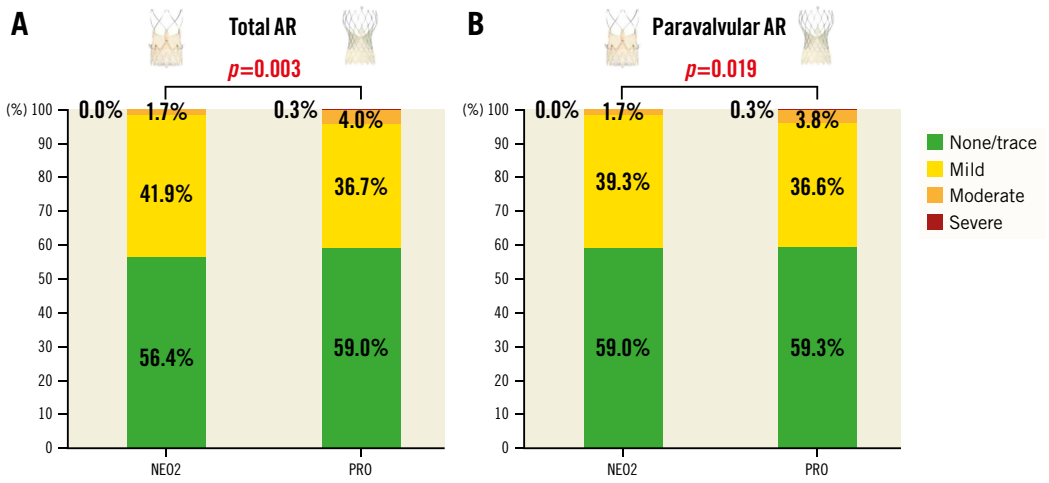


Figure 1. *Aortic regurgitation after transcatheter aortic valve replacement. Predischarge AR after TAVR. Comparison of predischarge total (A) and paravalvular (B) AR after implantation of NEO2 and PRO devices. AR: aortic regurgitation; NEO2: ACURATE neo2; PRO: Evolut PRO/PRO+; TAVR: transcatheter aortic valve replacement*

Table 3. 30-day outcomes.

		Overall (n=2,175)	ACURATE *neo2* (n=763)	Evolut PRO/PRO+ (n=1,412)	*p*-value
Clinical outcomes					
All-cause mortality		53/2,158 (2.5)	22/760 (2.9)	31/1,398 (2.2)	0.332
Cardiovascular mortality		43/2,158 (2.0)	17/760 (2.2)	26/1,398 (1.9)	0.549
Stroke		60/2,102 (2.9)	20/709 (2.8)	40/1,393 (2.9)	0.597
Cardiac hospitalisation*		61/2,103 (2.9)	30/709 (4.2)	31/1,394 (2.2)	0.010
MI		2/2,103 (0.1)	2/709 (0.3)	0/1,394 (0.0)	0.047
VARC-3 bleeding	Type 1	181/2,103 (8.6)	39/709 (5.5)	142/1,394 (10.2)	0.001
	Type 2	94/2,103 (4.5)	23/709 (3.2)	71/1,394 (5.1)	
	Type 3	45/2,103 (2.1)	18/709 (2.5)	27/1,394 (1.9)	
	Type 4	3/2,103 (0.1)	2/709 (0.3)	1/1,394 (0.1)	
Vascular complications	Minor	140/2,103 (6.7)	18/709 (2.5)	122/1,394 (8.7)	<0.001
	Major	78/2,103 (3.7)	23/709 (3.2)	55/1,394 (4.0)	
Access non-vascular complications		0/2,103 (0.0)	0/709 (0.0)	0/1,394 (0.0)	1.000
Permanent PM implantation**		249/1,929 (12.9)	51/663 (7.7)	198/1,266 (15.6)	<0.001
Valve dysfunction requiring repeat intervention (BAV, TAVR, SAVR)		6/2,117 (0.3)	2/723 (0.3)	4/1,394 (0.3)	0.686
Valve embolisation/migration		6/2,117 (0.3)	3/723 (0.4)	3/1,394 (0.2)	0.412
Endocarditis		3/2,117 (0.1)	0/723 (0.0)	3/1,394 (0.2)	0.212
THV thrombosis		3/2,117 (0.1)	2/723 (0.3)	1/1,394 (0.1)	0.235
Intervention for cardiac structural complication		6/2,117 (0.3)	4/723 (0.5)	2/1,394 (0.2)	0.093
AKI stage 3 or 4		34/2,117 (1.6)	18/723 (2.5)	16/1,394 (1.2)	0.020
NYHA Class III or IV		41/1,078 (3.8)	11/326 (3.4)	30/752 (4.0)	0.628
Valve performance and VARC-3 defined outcomes					
Moderate or severe total aortic regurgitation		72/2,135 (3.4)	17/750 (2.3)	55/1,385 (4.0)	0.037
Moderate or severe paravalvular aortic regurgitation		72/2,135 (3.4)	17/750 (2.3)	55/1,385 (4.0)	0.037
Mean gradient >20 mmHg		36/2,094 (1.7)	16/745 (2.2)	20/1,349 (1.5)	0.262
VARC-3 device success		1,748/2,085 (83.8)	606/719 (84.3)	1,142/1,366 (83.6)	0.688
VARC-3 early safety		1,547/2,095 (73.8)	566/719 (78.7)	981/1,376 (71.3)	<0.001
VARC-3 intended performance of the valve		2,001/2,107 (95.0)	714/747 (95.6)	1,287/1,360 (94.6)	0.340

Values are n/N (%). *Including hospitalisation for valve-related symptoms or other cardiovascular reason **Excluding patients with pacemaker at baseline. AKI: acute kidney injury; BAV: balloon aortic valvuloplasty; MI: myocardial infarction; NYHA: New York Heart Association; PM: pacemaker; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; THV: transcatheter heart valve; VARC-3: Valve Academic Research Consortium-3

preference for the use of the Evolut platform in more challenging anatomies with a higher burden of AV calcification. Nevertheless, both devices achieved high rates of VARC-3-defined technical success both in the unmatched (NEO2 93.1%, PRO 94.1%; p=0.361) and matched populations. The higher proportion of patients undergoing general anaesthesia for TAVR with the PRO devices may reflect both the different time period analysed for the 2 groups and a centre-specific protocol, instead of a clinical need, since most of these procedures were performed in the same centres. The higher percentage of valve predilatation in the NEO2 group may reflect both the manufacturer's recommendation for a systematic use, the low radial force of the valve, and the considerable proportion of patients with significant AV calcification in this group[20]. Nevertheless, the effect of predilatation is uncertain and its application did not have a significant impact on short-term adverse events in a subanalysis of the NEOPRO population[10]. Periprocedural complications were acceptable and similar in both groups. The higher proportion of minor vascular access complications in the PRO group may be partly explained by the different dimensions of the introducer sheaths between the PRO and NEO2 devices.

Both groups achieved high rates of predischarge VARC-3-defined intended performance of the valve (96.7% vs 96.3%; p=0.780). Moderate or severe PVL was a relevant concern in TAVR with the ACURATE *neo* bioprosthesis, with reported rates of up to 10%[7,8,25]. In our study, the predischarge moderate or severe PVL rate after a NEO2 implantation was low (1.7%), with no reported cases of severe PVL, confirming the preliminary experiences with this device[14]. Concerning the Evolut devices, the rate of moderate or severe PVL has been progressively reduced from 8%-10% with the first-generation CoreValve to 0%-6% with the latest-generation Evolut PRO and PRO+ devices, which is in line with our results (4.1%)[4,8,17,26]. A lower residual moderate or severe PVL in the NEO2 group in the overall population did not reach statistical significance after matching (2.0% vs 3.1%; p=0.281), indicating a comparable sealing performance of these devices after adjustment for baseline heterogeneity. Residual mild PVL was frequent (up to 39% in both groups). Since this has been associated with worse prognosis, we hope that future studies will further evaluate this issue[27]. The slightly lower mean gradients of the Evolut PRO bioprosthesis have been previously reported and may partly be explained by the more frequent use of the 29 mm device[7]. Nevertheless, the difference was not clinically relevant.

VARC-3 DEVICE SUCCESS

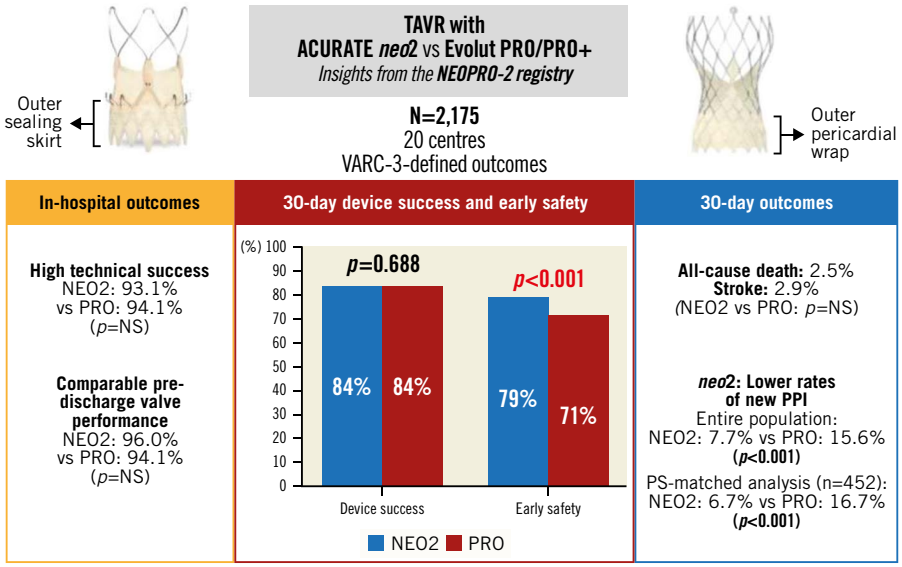
VARC-3 device success at 30-day follow-up was acceptable in both groups (NEO2 84.3%, PRO 83.6%; p=0.688) **(Central illustration)**. This finding was confirmed after adjustment for PS quintiles, in the PS-matched pairs, and was not influenced by AV calcification severity. Focusing on the 4 single components of the endpoint, the 30-day mortality rate was 2.5%, similar in the 2 groups and comparable with current reports; technical success was high, as previously discussed[14,16]. In the overall population, few patients needed repeat intervention for valve dysfunction or cardiac structural complications. Nevertheless, patients undergoing TAVR with the PRO device more frequently experienced post-procedural vascular complications (12.7% vs 5.7%; p<0.001). This potential disadvantage was confirmed after adjustment for PS quintiles and in the matched pairs **(Supplementary Table 2, Supplementary Table 5)**. This result may be partly explained by the low proportion of PRO+ devices in our registry (11.2% of the PRO group), which are delivered through a 2 Fr smaller sheath, and the higher AV calcification burden and NYHA Class in the PRO group, which may be a marker of overall frailty. Most of the difference was driven by minor vascular complications not requiring interventions, therefore not affecting device success. Finally, VARC-3-defined intended performance of the valve was high in both groups **(Table 3)**.

To the best of our knowledge, the NEOPRO-2 registry is the first study comparing 30-day VARC-3-defined device success between the ACURATE *neo*2 and Evolut PRO/PRO+ devices. Our data are similar to the 30-day results from the Early Neo2 registry and the ACURATE *neo*2 CE Mark Study[14]. Considering the Evolut bioprostheses, the Medtronic TAVR 2.0 US Clinical Study reported 100% implant success and low 30-day mortality rates (1.7%) with the Evolut PRO device[17]. Satisfactory short-term outcomes emerged also in the FORWARD PRO study and in the STS/ACC TVT registry[16,28]. Pending the results of ongoing trials (ClinicalTrials.gov: NCT03735667; NCT05036018), there is a lack of randomised data comparing the performance of these self-expanding THV. In this context, our study reports a similar rate of VARC-3 device success between the latest-generation NEO2 and PRO valves, also after adjustment for a range of baseline variables that may affect procedural outcomes.

VARC-3 EARLY SAFETY COMPOSITE ENDPOINT

The VARC-3 early safety composite endpoint at 30-day follow-up was achieved in 73.8% of patients, with higher rates after NEO2 implantation in the overall population (78.7% vs 71.3%; p<0.001) **(Central illustration)**. Despite not achieving statistical significance, a trend towards higher 30-day early safety in the NEO2 group was observed after adjustment for PS quintiles (aOR 1.29, 95% CI: 0.97-1.71; p=0.082) and in the PS-matched cohort (77.1% vs 72.2%; p=0.095). This result was mainly driven by a lower incidence of new PPI at 30 days in the NEO2 group (overall population: 7.7% vs 15.6%; p<0.001), regardless of the degree of AV calcification, a finding that was confirmed also after adjustment for PS quintiles and in the PS-matched analysis. Therefore, our data confirm the favourable profile of the NEO2 device in terms of conduction disturbances, due to the reduced radial force and limited protrusion into the left ventricular outflow tract, compared to its precursor[7,8,29]. With regard to the Evolut platform, the proportion of new PPI at 30 days in our registry (15.6%) is consistent with previous experiences, and we should acknowledge the absence of data on preprocedural conduction system diseases and implantation techniques[7,8,17]. An "optimised" self-expanding valve (SEV) TAVR care pathway, including the cusp-overlap technique, is currently under evaluation in the ongoing Optimize PRO Study (ClinicalTrials.gov: NCT04091048).

CENTRAL **ILLUSTRATION** **TAVR with NEO2 versus PRO/PRO+ devices in the NEOPRO-2 registry.**



Comparison of NEO2 and PRO/PRO+ devices for design characteristics, VARC-3-defined composite outcomes, and relevant single endpoints including all-cause death, stroke and new PPI. NEO2: ACURATE neo2; NS: not significant; PPI: permanent pacemaker implantation; PRO: Evolut PRO/PRO+; PS: propensity score; TAVR: transcatheter aortic valve replacement; VARC: Valve Academic Research Consortium

Since the TAVR period analysed for the PRO group started in 2017, our results may be influenced by a limited use of these novel approaches. In addition, 30-day data in the overall population suggested a reduced occurrence of moderate or severe PVL, vascular complications and bleedings in the NEO2 group. Potential explanations have been previously discussed for in-hospital outcomes.

Limitations

Our study had a retrospective, observational design, with no core laboratory analysis of echocardiographic data or independent adjudication committee for clinical events. Follow-up data at 30 days were not available for all patients and hard events were numerically low. We performed PS adjustment, PS-matched comparison and a subgroup analysis based on the severity of AV calcification to overcome differences in baseline characteristics and potential confounders. However, a latent impact of unknown or unmeasured confounding factors cannot be excluded, including missing data on post-procedural medical therapy. We acknowledge that many centres contributed with nearly exclusively 1 valve type to the registry, adding potential selection and centre-specific bias which may not have been completely mitigated despite PS-matched and multivariable regression analyses. Furthermore, the different sample sizes between the NEO2 and PRO groups in the overall cohort may have influenced the study results. In addition, since the TAVR period analysed for the PRO group started in 2017, our results may not completely reflect the current performance of the PRO/PRO+ devices. Whether restriction of the comparison to a more recent time period may translate into different results is debatable. Finally, comparison with previous studies is complex, due to the heterogeneous populations included and the different endpoint definitions used and follow-up period assessed.

Conclusions

In our multicentre, contemporary, real-world registry, transfemoral TAVR with the ACURATE *neo*2 bioprosthesis achieved a short-term performance comparable with the Evolut PRO/PRO+ THV in terms of VARC-3-defined outcomes, reflecting current TAVR standards with new-generation self-expanding devices. A tendency for higher VARC-3 early safety in the NEO2 group was mainly driven by reduced rates of new PPI. Randomised studies are needed to confirm our exploratory findings.

Impact on daily practice

In the real-world, multicentre NEOPRO-2 registry, transfemoral TAVR with the new-generation ACURATE *neo*2 (NEO2) bioprosthesis achieved a short-term performance similar to the Evolut PRO/PRO+ platform in terms of VARC-3-defined outcomes and low rates of predischarge more-than-mild paravalvular leak (1.7%), meeting current TAVR standards with self-expanding devices. Our data may suggest a higher VARC-3 early safety in the NEO2 group, driven mainly by reduced rates of new permanent pacemaker implantation. While randomised studies are needed to confirm our exploratory analysis, these real-world results may be considered as a further step towards tailoring valve selection in TAVR candidates.

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Guest editor

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W-K. Kim is a proctor for Boston Scientific and Abbott Vascular; and has received personal fees from Abbott Laboratories, Boston Scientific, Edwards Lifesciences, Medtronic, and Meril outside the submitted work. M. Barbanti has served as a consultant for Edwards Lifesciences. M. Adamo has received consultation and speaker fees from Abbott Vascular and Medtronic. R. Estévez-Loureiro has served as a consultant for Abbott Vascular, Boston Scientific, and Edwards Lifesciences. F. De Marco has served as a proctor for Boston Scientific and Kardia. S. Toggweiler is a proctor and consultant for Boston Scientific, Medtronic, and Biosensors/NVT; is a proctor for Abbott Vascular; and is a consultant for Medira, Shockwave, Teleflex, AtHeart, VeoSource, and Equity in Hi-D Imaging. V. Veulemans has received lecture fees and travel support from Medtronic and Edwards Lifesciences. D. Mylotte is a proctor for Medtronic and Microport. B. Reimers has received speaker honoraria from Boston Scientific. L. Sondergaard has received consultant fees and/or institutional research grants from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and SMT. A. Wolf is a proctor for Medtronic and Boston Scientific. A. Latib has served on advisory boards or as a consultant for Medtronic, Boston Scientific, Philips, Edwards Lifesciences, and Abbott Vascular. A. Mangieri has received a research grant (to the institution) from Boston Scientific; and has served on a medical advisory board for Boston Scientific. The Guest Editor reports lecture fees paid to his institution from Amgen, Bayer Healthcare, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Ferrer, Pfizer, and Novartis; consultancy fees paid to his institution from Boehringer Ingelheim; and grant support from Bayer Healthcare, Boston Scientific, Biotronik, Edwards Lifesciences, GlaxoSmithKline, Medtronic, and Pfizer. The other authors have no conflicts of interest to declare relevant to the contents of this paper.

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Supplementary data

Supplementary Table 1. Number of patients included from each participating centre.

Supplementary Table 2. Binary logistic regression of 30-day outcomes adjusted for propensity score quintiles.

Supplementary Table 3. Baseline patient characteristics after propensity score matching.

Supplementary Table 4. In-hospital outcomes after propensity score matching.

Supplementary Table 5. 30-day outcomes after propensity score matching.

Supplementary Table 6. 30-day outcomes stratified per aortic valve calcification grade.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00498

Supplementary data

Supplementary Table 1. Number of patients included from each participating centre.

Centre, city, country	Number of included patients		
	Overall (n=2175)	**Acurate *neo2* (n=763)**	**Evolut PRO/PRO+ (n=1412)**
Kerckhoff Heart and Lung Center, Bad Nauheim, Germany	262	261	1
University of Catania, Catania, Italy	249	24	225
Spedali Civili di Brescia, Brescia, Italy	214	16	198
Carmel Medical Center, Haifa, Israel	183	0	183
Complejo Hospitalario Universitario de Vigo, Vigo, Spain	183	4	179
Policlinico San Donato, Milan, Italy	168	77	91
Lucerne Cantonal Hospital, Luzern, Swiss	143	49	94
University Hospital Düsseldorf, Düsseldorf, Germany	96	7	89
Galway University Hospital, Galway, Ireland	91	4	87
Montefiore Medical Center, New York, United States	88	0	88
Rigshospitalet, Copenaghen, Denmark	82	81	1
Fondazione Poliambulanza, Brescia, Italy	70	40	30
Maria Cecilia Hospital, Cotignola, Italy	69	16	53
Elisabeth-Krankenhaus Essen, Essen, Germany	59	39	20

Rabin Medical Center, Petah Tikva, Israel	49	49	0
Policlinico San Matteo, Pavia, Italy	47	0	47
Istituto Clinico S. Ambrogio, Milano, Italy	45	44	1
Humanitas Research Hospital, Rozzano-Milano, Italy	41	41	0
Albertinen-Krankenhaus, Hamburg, Germany	25	0	25
AZ Sint-Jan AV Hospital, Brugge, Belgium	11	11	0

Supplementary Table 2. Binary logistic regression of 30-day outcomes adjusted for propensity score quintiles.

Binary regression analysis of 30-day outcomes in the unmatched population			
	ORadj	**95% CI**	**p value**
All-cause death	1.59	0.74 – 3.42	0.231
Cardiovascular death	1.01	0.43 – 2.39	0.977
Cardiac hospitalisation*	2.25	1.14 – 4.41	**0.019**
Stroke	0.81	0.42 – 1.56	0.521
Any bleeding	0.89	0.64 – 1.25	0.511
AKI stage 3 or 4	4.45	1.75 – 11.38	**0.002**
Any vascular complication	0.53	0.35 – 0.79	**0.002**
Major vascular complications	1.43	0.76 – 2.70	0.267
Intervention for cardiac structural complications	1.17	0.53 – 2.57	0.692
AV reintervention	1.52	0.14 – 17.01	0.733
Moderate or severe AR	0.53	0.24 – 1.13	0.102
Permanent PM implantation**	0.40	0.26 – 0.63	**<0.001**
VARC-3 device success	0.77	0.55 – 1.07	0.121
VARC -3 early safety	1.29	0.97 – 1.71	0.082
VARC -3 intended valve performance	1.10	0.59 – 2.07	0.766

Data are presented as adjusted odds-ratio (ORadj) and 95% confidence interval (95% CI), and associated p value. *Including hospitalisation for valve-related symptoms or other cardiovascular reason. **Excluding patients with pacemaker at baseline.

AKI: acute kidney injury; AR: aortic regurgitation; AV: aortic valve; PM: pacemaker; VARC-3:Valve Academic Research Consortium-3

Supplementary Table 3. Baseline patient characteristics after propensity score matching.

Baseline patient characteristics after propensity-score matching				
	Overall (n=904)	**ACURATE *neo*2 (n=452)**	**Evolut PRO/PRO+ (n=452)**	**p-value**
Clinical characteristics				
Age (years)	81.8 ± 5.7	81.9 ± 5.7	81.6 ± 5.8	0.435
Male sex	284/904 (31.4)	149/452 (33.0)	135/452 (29.9)	0.316
BMI	27.4 ± 5.1	27.4 ± 4.9	27.4 ± 5.4	0.869
COPD	110/904 (12.2)	54/452 (12.0)	56/452 (12.4)	0.839
Diabetes mellitus	287/904 (31.8)	147/452 (32.5)	140/452 (31.0)	0.617
Arterial hypertension	786/904 (87.0)	394/452 (87.2)	392/452 (86.7)	0.843
eGFR (ml/min/m^2)	63.7 ± 27.4	63.0 ± 27.6	64.3 ± 27.2	0.469
Dialysis	16/904 (1.8)	8/452 (1.8)	8/452 (1.8)	1.000
Prior PCI	260/904 (28.8)	124/452 (27.4)	136/452 (30.1)	0.378
Prior cardiac surgery	64/904 (7.1)	36/452 (8.0)	28/452 (6.2)	0.226
Prior CABG	51/904 (5.6)	32/452 (7.1)	19/452 (4.2)	0.061
Peripheral vascular disease	93/904 (10.3)	47/452 (10.4)	46/452 (10.2)	0.913
Prior stroke	89/904 (9.9)	49/452 (10.8)	40/452 (8.9)	0.315
Atrial fibrillation/flutter	294/904 (32.5)	140/452 (31.0)	154/452 (34.1)	0.320
PM or ICD	96/904 (10.6)	49/452 (10.8)	47/452 (10.4)	0.829
NYHA class III or IV	529/904 (58.5)	266/452 (58.9)	263/452 (58.2)	0.840
STS-PROM (%)	3.9 ± 2.7	3.8 ± 2.5	4.0 ± 2.8	0.332
EuroSCORE II (%)	4.2 ± 3.7	4.2 ± 3.9	4.3 ± 3.5	0.667
Echocardiographic data				
AVA (cm^2)	0.71 ± 0.2	0.71 ± 0.3	0.71 ± 0.2	0.975
LVEF (%)	57.7 ± 9.4	57.9 ± 9.7	57.5 ± 9.2	0.453

Moderate to severe MR	228/891 (25.6)	104/451 (23.1)	124/440 (28.2)	0.080
Moderate to severe TR	99/766 (12.9)	49/434 (11.3)	50/332 (15.1)	0.123
Severe pulmonary hypertension*	59/884 (6.7)	36/450 (8.0)	23/434 (5.3)	0.108
MDCT data				
Annular perimeter (mm)	73.6 ± 5.4	73.6 ± 5.2	73.5 ± 5.6	0.839
Moderate to heavy AV calcification	683/904 (75.6)	347/452 (76.8)	336/452 (74.3)	0.395
Any LVOT calcification	219/583 (37.6)	94/228 (41.2)	125/355 (35.2)	0.143
Moderate to severe LVOT calcification	97/583 (16.6)	40/228 (17.5)	57/355 (16.1)	0.638

Values are mean ± SD or n/N (%). *Systolic pulmonary artery pressure on echocardiography >70 mmHg.

AV: aortic valve; AVA: aortic valve area; BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MDCT: multidetector computed tomography; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PM: pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TR: tricuspid regurgitation

Supplementary Table 4. In-hospital outcomes after propensity score matching.

Procedural characteristics and pre-discharge echocardiographic outcomes after propensity-score matching				
	Overall (n=904)	**ACURATE *neo*2 (n=452)**	**Evolut PRO/PRO+ (n=452)**	**p-value**
Procedural characteristics				
Conscious sedation	828/904 (91.6)	452/452 (100.0)	376/452 (83.2)	**<0.001**
Transfemoral TAVR	904/904 (100.0)	452/452 (100.0)	452/452 (100.0)	1.000
Valve size				-
23 mm (or S size)	-	112/452 (24.8)	8/452 (1.9)	
25 mm (or M size)	-	188/452 (41.6)	-	
26 mm	-	-	162/452 (37.6)	
27 mm (or L size)	-	152/452 (33.6)	-	
29 mm	-	-	255/452 (59.1)	
34 mm	-	-	6/452 (1.4)	
Pre-dilatation	556/901 (61.7)	392/452 (86.7)	164/449 (36.5)	**<0.001**
Post-dilatation	242/898 (26.9)	137/451 (30.4)	105/447 (23.5)	**0.020**
Procedural death	3/904 (0.33)	0/452 (0.0)	3/452 (0.7)	0.083
Second THV implanted	10/904 (1.1)	4/452 (0.9)	6/452 (1.3)	0.525
Valve embolisation	10/904 (1.1)	5/452 (1.1)	5/452 (1.1)	1.000
Annular rupture	3/904 (0.3)	1/452 (0.2)	2/452 (0.4)	0.563
Pericardial tamponade	11/904 (1.2)	6/452 (1.3)	5/452 (1.1)	0.762
Aortic dissection	0/904 (0.0)	0/452 (0.0)	0/452 (0.0)	1.000
Coronary occlusion	3/904 (0.33)	0/452 (0.0)	3/452 (0.7)	0.083
Conversion to cardiac surgery	4/904 (0.4)	1/452 (0.2)	3/452 (0.7)	0.316
Vascular access complications				**0.003**

Minor	70/904 (7.7)	22/452 (4.9)	48/452 (10.6)	
Major	30/904 (3.3)	18/452 (4.0)	12/452 (2.7)	
VARC-3 defined technical success	845/904 (93.5)	418/452 (92.5)	427/452 (94.5)	0.226
Echocardiographic outcomes				
Total aortic regurgitation				0.559
None/trace	521/896 (58.1)	263/450 (58.4)	258/446 (57.9)	
Mild	352/896 (39.3)	178/450 (39.6)	174/446 (39.0)	
Moderate	23/896 (2.6)	9/450 (2.0)	14/446 (3.1)	
Severe	0/896 (0.0)	0/450 (0.0)	0/446 (0.0)	
Moderate to severe paravalvular aortic regurgitation	23/896 (2.6)	9/450 (2.0)	14/446 (3.1)	0.281
Mean gradient ≥20 mmHg	9/879 (1.0)	6/449 (1.3)	3/430 (0.7)	0.347
Mean gradient (mmHg)	8.4 ± 4.0	9.0 ± 4.0	7.7 ± 4.0	**<0.001**
Max gradient (mmHg)	15.0 ± 6.9	15.9 ±7.0	14.4 ± 6.7	**0.008**
Aortic EOA (cm2)	1.79 ± 0.4	1.75 ± 0.4	1.91 ± 0.5	**<0.001**
VARC-3 defined intended performance of the valve	852/883 (96.5)	434/449 (96.7)	418/434 (96.3)	0.780

Values are n/N (%) or mean ± SD.

EOA: effective orifice area; NYHA: New York Heart Association; TAVR: transcatheter aortic valve replacement: THV: transcatheter heart valve; VARC-3: Valve Academic Research Consortium–3;

Supplementary Table 5. 30-day outcomes after propensity score matching.

30-day outcomes in the propensity-score matched population				
	Overall (n=904)	**ACURATE *neo*2 (n=452)**	**Evolut PRO/PRO+ (n=452)**	**p-value**
Clinical outcomes				
All-cause mortality	19/891 (2.1)	12/450 (2.7)	7/441 (1.6)	0.265
Cardiovascular mortality	15/891 (1.7)	7/450 (1.6)	8/441 (1.8)	0.764
Stroke	31/858 (3.6)	14/420 (3.3)	17/438 (3.9)	0.667
Cardiac hospitalisation*	33/858 (3.9)	22/420 (5.2)	11/438 (2.5)	**0.038**
MI	0/858 (0.0)	0/420 (0.0)	0/438 (0.0)	1.000
VARC-3 bleeding				0.062
Type 1	69/858 (8.0)	26/420 (6.2)	43/438 (9.8)	
Type 2	41/858 (4.8)	19/420 (4.5)	22/438 (5.0)	
Type 3	17/858 (2.0)	12/420 (2.8)	5/438 (1.1)	
Type 4	2/858 (0.2)	2/420 (0.5)	0/438 (0.0)	
Vascular complications				**0.001**
Minor	64/858 (7.5)	17/420 (4.0)	47/438 (10.7)	
Major	32/858 (3.7)	17/420 (4.0)	15/438 (3.4)	
Access non-vascular complications	0/858 (0.0)	0/420 (0.0)	0/438 (0.0)	1.000
Permanent PM implantation**	91/767 (11.9)	25/372 (6.7)	66/395 (16.7)	**<0.001**
Valve dysfunction requiring repeat intervention (BAV, TAVR, SAVR)	3/858 (0.3)	2/420 (0.5)	1/438 (0.2)	0.539
Valve embolisation/migration	4/858 (0.5)	3/420 (0.7)	1/438 (0.2)	0.296
Endocarditis	0/858 (0.0)	0/420 (0.0)	0/438 (0.0)	1.000
THV thrombosis	1/858 (0.1)	1/420 (0.2)	0/438 (0.0)	0.307

Intervention for cardiac structural complication	4/858 (0.5)	4/420 (0.9)	0/438 (0.0)	**0.041**
AKI stage 3 or 4	16/858 (1.9)	14/420 (3.3)	2/438 (0.5)	**0.002**
NYHA class 3 or 4	12/367 (3.3)	3/171 (1.8)	9/196 (4.6)	0.127
Valve performance and VARC-3 defined outcomes				
Moderate to severe total aortic regurgitation	25/894 (2.8)	10/448 (2.2)	15/446 (3.4)	0.305
Moderate to severe paravalvular aortic regurgitation	23/986 (2.6)	9/450 (2.0)	14/446 (3.1)	0.281
Mean gradient > 20 mmHg	10/877 (1.1)	8/447 (1.8)	2/430 (0.5)	0.065
VARC-3 device success	715/850 (84.1)	346/420 (82.4)	369/430 (85.8)	0.171
VARC-3 early safety	635/851 (74.6)	324/420 (77.1)	311/431 (72.2)	0.095
VARC-3 intended performance of the valve	848/880 (96.4)	430/447 (96.2)	418/433 (96.5)	0.788

Values are n/N (%).

*Including hospitalisation for valve-related symptoms or other cardiovascular reason

**Excluding patients with pacemaker at baseline.

AKI: acute kidney injury; BAV: balloon aortic valvuloplasty; MI: myocardial infarction; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; THV: transcatheter heart valve; VARC-3: Valve Academic Research Consortium–3

Supplementary Table 6. 30-day outcomes stratified per aortic valve calcification grade.

30-day outcomes stratified per aortic valve calcification grade										
	None or Mild Calcification			**Moderate Calcification**			**Heavy Calcification**			
	NEO2 (185)	**PRO (183)**	**p-value**	**NEO2 (311)**	**PRO (398)**	**p-value**	**NEO2 (133)**	**PRO (417)**	**p-value**	**p-value for interaction**
All-cause death	6/185 (3.2)	4/180 (2.2)	0.550	9/309 (2.9)	4/392 (1.0)	0.065	2/133 (1.5)	7/413 (1.7)	0.880	0.441
VARC 3 – Device Success	150/178 (84.3)	145/175 (82.9)	0.720	244/294 (83.0)	340/389 (87.4)	0.105	100/118 (84.8)	324/393 (82.4)	0.559	0.260
VARC 3 – Early Safety	142/178 (79.8)	128/178 (71.9)	0.083	223/293 (76.1)	283/388 (72.9)	0.348	97/119 (81.5)	275/401 (68.6)	**0.006**	0.207
VARC 3 – Valve Performance	178/183 (97.3)	163/175 (93.1)	0.067	290/305 (95.1)	376/388 (96.9)	0.218	125/131 (95.4)	366/393 (93.1)	0.350	0.088
New PM implantation *	11/164 (6.7)	21/137 (15.3)	**0.016**	23/267 (8.6)	58/357 (16.3)	**0.005**	6/104 (5.8)	65/381 (17.1)	**0.004**	0.625
Moderate or severe PAR	2/183 (1.1)	10/180 (5.6)	**0.017**	8/306 (2.6)	9/396 (2.3)	0.770	4/131 (3.1)	26/405 (6.4)	0.145	0.114

Values are n/N (%).

*Excluding patients with pacemaker at baseline.

PAR: paravalvular aortic regurgitation; PM: pacemaker; VARC-3: Valve Academic Research Consortium–3